Hospitals & Asylums

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Convention on Pandemic Treatment

Preamble

Recognizing that since February 2020 everyone on the planet has probably been exposed to, and at one time or another, contracted the highly contagious COVID-19 disease, that begins with an infected nose that can descend down the airways and cause death when the lungs fill with fluid.

Recognizing the World Health Organization (WHO) has declared the official name of the coronavirus disease as COVID-19, and named the virus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Recalling as of July 26, 2020 there have been an estimated 16.1 million confirmed cases, 9.27 million recovered and 645,000 deaths from COVID-19.

Recalling that the invention of the antibiotic streptomycin in 1946 and tuberculosis drug isoniazid (INH) in the 1950s eliminated demand for the historical Tubercular Hospital at Fort Bayard under 24USC§19, nine months of the combination of INH and rifampin chemotherapy will result in roughly 95% cure rates, therapy with INH, rifampin and ethambutol helps avoid the complication of drug resistance with non-tubercular mycobacterial disease, the addition of pyrazinamide can reduce treatment time to six months, but is toxic.

Resenting the futile preventative vaccine propaganda in response to pandemics that have already begun and must be cured with the right drugs, the trade in live viruses, their loss, theft and abuse, that there is officially no treatment for coronavirus, that the Ozone Secretariat has not exempted corticosteroid inhalers from the Montreal Protocol to cure the coronavirus and achieve 2020 goals and most of all that WHO pandemic response does not prescribe hydrocortisone creme, or to avoid Cushing's disease side-effect, essential oil of eucalyptus, lavender and peppermint aromatherapy to cure coronavirus and mold allergies and prescription Oseltamivir (Tamiflu), Zanamivir (Relenza) and Amantadine (Symmetrel) to cure influenza.

Resolving to wear a clean face mask in contagious places to reduce the risk of transmission by an estimated 95%.

Recognizing that coronavirus and influenza are disabilities for which everyone has the equal right to voluntary curative treatment to fully enjoy all their right and freedoms pursuant to the Convention on the Rights of Persons with Disabilities (2007).

Resolving to respond to the coronavirus pandemic and any future influenza pandemics by prioritizing the immediate prescription of curative medicines.

Believing health = eucalyptus, lavender and peppermint

Art. 1 Essential oils of eucalyptus, lavender and peppermint

1. Essential oils of eucalyptus, lavender and peppermint cure coronavirus and mold allergies. A drop is topically applied with the index finger to the exterior of the nose and upper lip.

2. The aroma should cause the nasal irritation to immediately go down, and contagiousness and infection is believed to be instantly cured. The nasal irritation congeals into boogers. The alcohol in the essential oil mixture also sterilizes fingers probing inside the nostrils to prevent infection, careful to avoid injury to the sensitive mucosal membrane. When the gold boogers are removed, without injury, nasal irritation is completely eliminated. The patient is cured.

3. Scientific, before and after treatment, diagnostic testing is needed to determine the cure rate and speed, and other particulars regarding these essential oils, before children risk their lives returning to schools that have been closed since the beginning of the COVID-19 pandemic.

Art. 2 Aromatherapy

To sterilize popular indoor social environments, such as schools, against the highly contagious and potentially lethal coronavirus, aromatherapy using essential oils of eucalyptus, lavender and peppermint is advised to be dispensed by humidifier. These humidifiers should be placed at the entrance to ensure everyone is treated as they enter the building. The public must be informed that these essential oils are non-toxic and non-allergenic by nature, they cure both coronavirus and mold allergies.

Art. 3 Soaps, Cleansers and Other Medicinal Herbs

Public restrooms must sanitized with eucalyptus, lavender and peppermint soaps and cleaners. The social solution to end the pandemic may be to reopen public restrooms stocked with soaps containing essential oils of eucalyptus, lavender or peppermint for people to wash their nose, face, hands and chest. Oral echinacea preparations have been effective at curing fluid filled lungs, but relief is not instant. Many other natural remedies for pulmonary conditions may cure coronavirus, and are due publicity if they work or don't. The public must trust eucalyptus, lavender and peppermint.

Art. 4 Hydrocortisone crème

1. Corticosteroids are the definitive medical treatment for coronavirus and mold allergies. Cushing's disease is a non-life threatening side-effect of excessive life-saving corticosteroid use, its symptoms are fragile bones and puffy cheeks, and may a be a lead culprit in the high rates of total knee and hip replacement surgeries in industrialized nations. The non-prescription of corticosteroid inhalers to first time asthma patients is certain to be a leading cause of the dramatic rise in asthma and allergy patients over the past few decades.

2. Hydrocortisone crème is a corticosteroid that is accessible over-the-counter, for as little as a dollar a tube. When a dab is applied topically to the exterior of the nose, hydrocortisone creme instantly cures coronavirus and allergic rhinitis due to mold. A dab of hydrocortisone crème can also be applied to the chest to treat the potentially lethal fluid filled lungs exhibited in severe acute respiratory syndrome (SARS) from coronavirus, the carcinogenic lung nodules of pulmonary aspergillosis and the coronavirus and mold triggers of asthma attacks for as fast a cure as a rescue inhaler and lower-cost and risk of potentially lethal malicious mold contamination than more expensive oral, inhaled and intravenous corticosteroids. The dose of

corticosteroid in hydrocortisone crème is much lower than other corticosteroid preparations and should be below the threshold of Cushing's disease, despite chronic use.

3. Because essential oil of eucalyptus, lavender and peppermint aromatherapy is equally curative with corticosteroids, without any potentially harmful side-effects, and can be used to sterilize environments, they are the primary medicines to be promoted to cure the COVID-19 pandemic. Nonetheless, no law shall be allowed to prohibit, limit or control the use of prescription and over-the-counter corticosteroids to cure coronavirus and mold allergies and treat asthma and chronic obstructive pulmonary disorder.

Art. 5 Corticosteroid inhaler exemption

1. It is a crime that there is said to be no official treatment for coronavirus although corticosteroids are the definitive medical treatment for coronavirus, and that the Ozone Secretariat has not exempted corticosteroid inhalers from their failed 2020 prohibition agenda to inform the public that corticosteroids cure COVID-19. Ozone is a form of air pollution and its defenders do not have the standing to prohibit life-saving corticosteroid inhalers, or any other, dangerously less-effective, fluorocarbon propelled inhaler, a smarter physician would want to prohibit, for that matter, because asthma patients may want to treat ozone inhalation. Wherefore corticosteroid inhalers are to be exempted from the 1987 Montreal Protocol on Substances that Deplete the Ozone Layer, and 1990 London Amendment, 1992 Copenhagen Amendment, 1997 Montreal Amendment, 1999 Beijing Amendment, and 2016 Kigali Amendment thereto, by the Ozone Secretariat.

Art. 6 Prescription influenza drugs

1. WHO must respond to influenza pandemics by prioritizing the prescription of Oseltamivir (Tamiflu), Zanamivir (Relenza) and Amantadine (Symmetrel) to cure influenza. Amantadine (Symmetrel) is cheapest and is also indicated to cure the potentially lethal extra-pyramidal facial tic side-effect of antipsychotic drugs by the Food and Drug Administration (FDA).

2. WHO influenza pandemic response has been crazy for as long as anyone can remember. It involves espionage-like publicity regarding the sending of live virus samples around the globe for vaccine development although flu vaccine effectiveness is often abysmal and it is prescription flu drugs that are wanted. WHO must primarily prescribe and provide life-saving prescription flu drugs, second ensure the public is informed of the use of masks and safety protocols to prevent the spread of contagious airborne disease and third develop a more effective vaccine for the next flu season.

Art. 7 Ratification

The Secretary-General of the United Nations, and Director-Generals of the World Health Organization and Ozone Secretariat shall equally be the depositary of the present Convention. The Arabic, Chinese, English, French, Russian and Spanish texts of the present Convention shall be equally authentic. A State Party may denounce the present Convention by written notification to the Secretary-General or Director-Generals. Any State Party may propose an amendment to the present Convention and submit it to the Secretary-General, or Director-Generals. Reservations incompatible with the object and purpose of the present Convention shall not be permitted, and may be withdrawn. The present Convention shall be open for signature by all States as of 28 July 2020 and shall enter into force after the thirtieth day after the deposit of its twentieth instrument of ratification.

I. Oxygen

I.1 Hydrocortisone, Eucalyptus, Lavender and Peppermint

Since February 2020 everyone on the planet has been exposed to and probably contracted the highly contagious COVID-19 disease. Worldwide, as of July 26, 2020 there have been an estimated 16.1 million confirmed cases, 9.27 million recovered and 645,000 deaths from COVID-19. In the United States there have been an estimated 4.25 million confirmed cases, 1.28 million recovered and 149,000 deaths. Everyone, especially the World Health Organization (WHO) and those responsible for editing the medical literature, must be informed, although coronavirus disease is potentially fatal if the infection descends down the airways from the nose and the lungs fill with fluid, "coronavirus is the only cold with a cure - hydrocortisone creme, and essential oils of eucalyptus, lavender and peppermint . Hydrocortisone creme, or to avoid the fragile bones and puffy cheeks of the corticosteroid side-effect Cushing's disease - essential oil of lavender, peppermint and eucalyptus are highly effective and safe cures for both coronavirus and mold allergies if applied topically as a "nose sanitizer" to the location of infection, in aromatherapy with a humidifier to free an indoor environment from coronavirus, or in soaps and cleansers (Sapeika '63). To get the message across in August 2020, after consolidating two books on the heart and lungs into this book on the Chest in April, failed, and the popular and ride reliant Pacific Crest Trail (PCT) was ill-advised due to resupply point closures, I hiked a thousand miles on the American Discovery Trail and Continental Divide Trail (CDT), in nearly compete solitude, from the Seville orange grove at the California State capitol in Sacramento, where the signs with inaccurate legal citation prohibiting orange picking have not been removed as requested, to the historical Tubercular Hospital at Fort Bayard, New Mexico, at the edge of the Gila National Forest, pronounced with a guttural Spanish g that sounds like "h" somewhere between heal-a and kill-a, pursuant to 24USC§19. Do not be dissuaded from camping in the wilderness by campground closures, copious amounts of sweat alone, can completely cure a mild COVID-19 infection, until re-exposed, because coronavirus is so highly contagious, complete solitude is necessary. Unlike vitamin C, rumored to cure colds if used in high doses at the beginning of the disease, essential oils of lavender, peppermint and eucalyptus and hydrocortisone creme definitively and instantly cure COVID-19 and mold allergies when applied to the nose and/or chest. The nasal irritation turns to boogers that can be picked out and eaten, in private, similar to the chemical process for extracting gold from ore.

It remains for diagnostic tests on consenting human test subjects presenting with common, everyday COVID-19 symptoms of the nose, before and after application of hydrocortisone creme, essential oils of lavender, peppermint and eucalyptus, to determine the cure rate and length of time after application of these cheap, safe, effective and essential medicines, that the infection is scientifically cured. The contagion seems to be instantly eliminated and irritation ends when the congealed boogers are cleaned out, without injury. Environmental hygiene is essential, water works, but the Food and Drug Administration (FDA) has advocated for the use of Lysol, active ingredient - essential oil of eucalyptus. The FDA is highly advised to approve hydrocortisone crème and essential oils of eucalyptus, lavender and peppermint as topical nose sanitizers that cure coronavirus and mold allergies and endorse studies regarding non-toxic and non-allergenic aromatherapy treatments using humidifiers at the school doors, to create a healing indoor environment without any coronavirus or mold infections, that might otherwise be harbored in its airways, in an orderly fashion, as the people enter and exit the building, before the 2020-2021 school year and snot nosed child deaths begin. When the FDA considers whether or not to approve a new medication, other than cost, whereby the objective is to advocate for the

cheapest, safe and effective remedy, two issues are paramount: 1. Do the results of well-controlled studies provide substantial evidence of safety and effectiveness? 2. Do the results show the product is safe; do the drug's benefits appear to outweigh its risks? Pursuant to the Food Drug and Cosmetic Act (FD&CA) under 21USC§355.

Essential oils of **lavender, peppermint and eucalyptus**, are the most highly advised treatment to be used as nose sanitizers, and as the active ingredient in environmental cleansers, soap and aromatherapy that could be administered to an informed public, in enclosed spaces by a humidifier, to make public spaces, such as bars, churches, hospitals, libraries, restaurants, schools and stores safe to congregate in again despite the pandemic raging outside, and pleasant smelling, without any known side-effects, allergies or toxic risks. Otherwise, **face masks** will have to be worn in contagious public places, to reduce airborne transmission by 95%, and hopefully walk out without an infected nose. Face masks must be replaced or washed after eight hours and a dirty mask is certain to harbor the disease. Mask use is psychologically contagious. Although face masks do not indicate a coronavirus patient, they do indicate that someone suspects the environment is contagious. If someone is wearing a mask it is best to also wear a mask. It is legally necessary to adhere to mask protocols at establishments who claim to be successful enough at containing the virus to remain open to the public, with a face mask policy. **Corticosteroids**, such as hydrocortisone creme, as well as essential of lavender and eucalyptus have long been known to cure mold allergies in certain medical texts (Sapeika '63), but not all. With the global population being required, under penalty of death, to learn to use these, and other safe and effective corticosteroid and natural remedies, such as echinacea, to cure coronavirus and mold allergies, incidence of asthma and allergies, and Cushing's disease from excessive corticosteroid use, should decline dramatically. That which doesn't kill us makes us stronger. Essential oils of lavender and eucalyptus, cost ten times more than a $1 tube of hydrocortisone creme, but just a dab to the nose suffices. A $10 bottle of essential oil of eucalyptus, lavender or peppermint, should safely get an individual or family through the duration of the pandemic, without causing Cushing's disease or any unpleasant side-effects.

The World Health Organization (WHO) has announced the official names of the virus responsible for COVID-19 (previously known as "2019 novel coronavirus" or 2019 nCOV) and the disease it causes. The official name of the coronavirus disease is COVID-19, and the virus is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). WHO pandemic response to influenza outbreaks is however notoriously ineffective at administering curative prescription drugs Oseltamivir (Tamiflu), Zanamivir (Relenza) and Amantadine (Symmetrel), that also cures the potentially fatal extra-pyramidal syndrome facial tic side-effect of antipsychotic drugs, due to vaccine propaganda, and seeming propensity to capitalize on, or derive some sort of enjoyment from abusive and repressive social controls, such as quarantines and requiring the use of masks, that would be completely unnecessary if essential curative medicines were prescribed right away. Henbane exposure is suspected in COVID-19 quarantine related domestic violence where insomnia was not an issue. Dirty masks may harbor coronavirus infection and masks do not prevent severely infected patients, who should be prescribed medication and quarantined in solitude at home, ventilated hospital room or in the wilderness, from spreading the disease in public places. Generally, these pandemics tend to continue until State intervention provides the effective medicine that WHO has denied the public knowledge of. Masks are not a gag order, they are the response to gag orders regarding the safe and effective cures for pandemics. To swiftly end the COVID-19 pandemic and any future influenza pandemics WHO and national health agencies must resolve to prescribe the public hydrocortisone creme, essential oils of lavender, peppermint and eucalyptus nose sanitizer to treat coronavirus, mold allergies and

asthma and Oseltamivir (Tamiflu), Zanamivir (Relenza) and Amantadine (Symmetrel) to treat influenza pandemics.

Coronavirus disease spreads primarily through contact with an infected person when they cough or sneeze. It also spreads when a person touches a surface or object that has the virus on it, then touches their eyes, nose, or mouth. Reports have documented that HCoVs are involved in a wide spectrum of clinical presentation in upper and lower respiratory tract illnesses, as well as being a contributor to exacerbations of chronic obstructive pulmonary disease and among patients presenting cystic fibrosis. The median time for hospitalized CoV- infected patients to be discharged was 12 days (range, 5–30 days). Coronaviruses display the marked seasonality typical of other respiratory viruses, with high detection frequencies in the winter months but few or no detections in the summer (Cabeca '13). The effectiveness of summer heat at sterilizing coronavirus pandemics has been disproven in the summer of 2020 when coronavirus outbreaks were noticed at every relaxation of quarantine regulations when many people tested positive for coronavirus after attending social gatherings. To effectively describe the symptoms of the pandemic, COVID-19 must be remembered as the most highly contagious disease ever encountered, more contagious than any other cold virus or other infection. COVID-19 instantly leaps from nose to nose, to varying degrees depending on proximity to site of infection, inside a building or within about six feet of an infected person or place. The infection can descend into the lungs and cause death when the lungs fill with fluid. Face masks help to reduce transmission and contraction of SARS by an estimated 95% but must be discarded or washed after eight hours to prevent the mask from being the primary source of coronavirus contamination, and do not entirely eliminate nasal infection by COVID-19 in contaminated places, as a fancy humidifier administering essential oil of lavender, peppermint and eucalyptus to informed public in an enclosed building, might.

Hospitals could be more forthwith regarding the prescription for corticosteroids. A hospital infectious disease specialist from Gallup, New Mexico, who treats COVID-19 patients with corticosteroids was overjoyed to learn of the effectiveness of over-the-counter hydrocortisone creme, essential oil of lavender, peppermint and eucalyptus as a nose sanitizer. He defended the extraordinarily totalitarian weekend closures of all commerce, including all gas stations and grocery stores, on the Navajo Reservation, where infection rates are reported to be second only to New York City, although total commerce closure might be life-threatening to desert highway pedestrians and cyclists, as being the only method that has so far proven to be effective at reducing COVID-19 incidence. The reason for the high incidence of COVID-19 on the Navajo Reservation is believed to be that they know everyone, are highly social, unlikely to seek medical help and in regard to the pandemic their friendliness and generosity is as a great as a fault as overcrowding and mold contaminated corticosteroids in New York City.

There are several myths regarding COVID-19 that must be neutralized. The foremost dangerous myth is that there is no treatment for coronavirus. Corticosteroids are the definitive medical treatment for coronavirus, asthma and mold allergies. The literature has been confused on this topic. At its best it states: Normally there is no treatment for coronaviruses other than a caution to wash hand and keep clean. For Severe Acute Respiratory Syndrome (SARS), a coronavirus, the inpatient treatment with no fatalities was to ventilate the patient and medicate with the antibiotic levofloxacin (Levaquin), and corticosteroids methylprednisolone IV and then prednisone (Kit-Ying ’06). From this hospital bill the effectiveness of hydrocortisone creme as a nose sanitizer was quickly extrapolated, with completely curative effect, as must so often be done with medical literature. Nonetheless, there is a widespread medical conspiracy to prescribe

first time asthmatic patients ineffective and dangerous salbuterol inhalers, indicated to exacerbate, possibly fatally, asthma attacks, in an untreated population with skyrocketing rates of asthma and allergies, that must be prohibited. A dab of hydrocortisone creme applied to the nose or chest is an extremely cheap and effective cure for coronavirus and mold allergies, but high dose or prolonged use of corticosteroids can cause the fragile bones and puffy cheeks of Cushing's disease. Fear of Cushing's disease is probably the unspoken reason underlying this life-threatening corticosteroid phobia exhibited by the medical profession in their treatment of first-time asthma patients. Excessive corticosteroid exposure may be a major reason for the high rates of total knee and hip replacement surgeries. Corticosteroids are however life-saving medicines that must exempted from the Montreal Protocol on Substances that Deplete the Ozone of 1987 to achieve 2020 goals, while salbuterol inhalers are prohibited, to get the message regarding the effectiveness of corticosteroids across. There will be no more denying first time asthma patients their corticosteroid inhalers. Nonetheless, it is essential that the medical profession and, to respond to the COVID-19 pandemic, world-population in general, are instructed in the use of essential oils of lavender and eucalyptus as nose sanitizers to quickly cure coronavirus, mold allergies, and asthma. Essential oil of lavender and of eucalyptus are to be applied to the nose and upper lip to quickly treat the irritated nose from COVID-19 or mold allergies or to the chest to treat the fluid filled lungs of coronavirus or painful nodules of a mold infected lung, as in aspergillosis. Peppermint is thought to be slightly less effective and easily confused with other mint species, but it would be nice to prescribe peppermint candy as curative treatment. Certain essential oils used in aromatherapy can treat and cure allergy and asthma symptoms where conventional medicine has failed – essential oils of lavender, peppermint and eucalyptus are particularly curative of allergic rhinitis (Sapeika '63).

The second dangerous myth regarding COVID-19 is that it exhibits flu-like symptoms of a cough and other ever more far-fetched symptoms. It was not until July, four months after the beginning of the pandemic in February, that a runny nose was even officially considered a symptom of COVID-19, and it was lumped in with other symptoms, such as diarrhea, that are absolutely not indicative of coronavirus. Taking an entire season to touch one's nose does not pass the drunk driving test. The people must instantly nose COVID-19 symptoms. The initial description of COVID-19 symptoms as being flu-like, obviously began with hospitalized patients with Severe Acute Respiratory Syndrome (SARS) and neglected to identify the nose as the immediate sensor of infection, giving rise to a dangerous paranoia regarding asymptomatic patients. The myth of the asymptomatic patient led to the wrongful quarantining of health professionals, passively exposed to patients with a positive diagnosis, and also of traveller's subjected to three week to month-long quarantines at the international border and propaganda regarding self-quarantining in interstate travel and social activity. The mistake regarding the flu-like symptoms of SARS caused many people, including health professionals, to not immediately know that they had contracted coronavirus, or were in a contagious place, by the inflamed nose. There is no such thing as an asymptomatic COVID-19 patient, the nose becomes instantly infected and irritated when exposed to coronavirus. Untreated the infection can descend to the lungs and the alveoli become filled with fluid until the lungs are totally saturated, the patient cannot breathe and dies without the right readily available prescription, over-the-counter or homeopathic treatment.

Coronavirus (COVID-19) pandemic, alleged to have originated from the Wuhan market in China, has been declared a world-wide pandemic since February 2020. Tens of millions of people have confirmed diagnosis and hundreds of thousands have died with a diagnosis or because their lungs filled with fluid and they asphyxiated directly as the result of the easily cure coronavirus infection because the official story is that there is no treatment. Many state

governments have engaged quarantine protocols, dramatically reducing travel, trade and employment, causing extraordinary economic damage to reduce coronavirus exposure, without properly using their authority to prescribe curative hydrocortisone creme, essential oil of eucalyptus, lavender and peppermint treatment, like the isoniazid tuberculosis treatment that put the tubercular hospitals completely out of business, although it takes six months to effect a cure, in cases uncomplicated by non-tubercular mycobacterial disease, requiring special treatment. It is alarming that since the beginning of the global COVID-19 pandemic in February 2020, the United States has exhibited the fastest growing rates of infection and consequential economic failure. Nonetheless, Canada and a few other nations have also initiated massive relief Acts. Canada is noted for paying COVID-19 disabled workers $1,000 a month, just like my father's retirement payment to his son, disabled before age 22.

It is not known what the ultimate outcome the COVID-19 pandemic shall have on mortality statistics, whereas there is a two year delay in the production of mortality statistics, in the United States. Will overall mortality go up, stay the same or decline? How will NCHS account for statistically significant coronavirus pandemic deaths? What shall the coroner rule as their cause of death, if they tested positive for coronavirus, but died from some other fatal ailment? As of July 16, in the United States 149,000 people have died with a COVID-19 diagnosis in the year 2020. This is dramatically more than 55,672 influenza and pneumonia death in 2017. A novel 'pandemic pneumonia' category should probably be reserved for people who died because their lungs filled up with fluid from coronavirus, flu or pneumococcal complication. An estimated 200,000 deaths might be categorized pandemic pneumonia in 2020, 150,000 more than the previous year. The developing wisdom from Wuhan, Washington, and Italy—has been that older people and sicker people are substantially more likely to suffer severe illness or die from COVID-19 than their younger, healthier counterparts. Older people are much more likely than young people to have lung disease, kidney disease, hypertension, or heart disease, and those conditions are more likely to transform a coronavirus infection into something nastier. But what happens when these assumptions don't hold up, and the young people battling the pandemic share the same risks? The reason snot nosed children have not been dying in as massive numbers, as their grandparents, is that schools have been closed since the beginning of the pandemic. The President has ordered that schools be reopened for the new school year, but without eucalyptus, lavender and peppermint essential oil aromatherapy and hydrocortisone creme, to treat the infected, the protocol is widely considered unsatisfactory. Homeschooling may be the best choice, if the pandemic remains untreated. It might eliminate coronavirus from the social environment, if the entrance, where all the children and staff enter, in the beginning of the day, and exit from at end of the day, was misted with a large humidifier to provide essential oil of eucalyptus, lavender or peppermint aromatherapy. School nurses will have to be prepared to treat children with snot noses with essential oils of eucalyptus, lavender and peppermint, with hydrocortisone creme as a last resort before calling their parents to take them to a doctor to permit sick leave.

The most recent 2020 National Center for Health Statistics (NCHS) mortality statistics are from 2017. A total of 2,813,503 resident deaths were registered in the United States in 2017. The 10 leading causes accounted for 74.0% of all deaths in the United States in 2017. Causes of death are ranked according to number of deaths. In 2017, the 10 leading causes of death (heart disease, cancer, unintentional injuries, chronic lower respiratory diseases, stroke, Alzheimer disease, diabetes, influenza and pneumonia, kidney disease, and suicide) remained the same as in 2016. Causes of death are ranked according to number of deaths. The 10 leading causes accounted for 74.0% of all deaths in the United States in 2017. From 2016 to 2017, age-adjusted death rates

increased for 7 of 10 leading causes of death and decreased for 1. The rate increased 4.2% for unintentional injuries, 0.7% for chronic lower respiratory diseases, 0.8% for stroke, 2.3% for Alzheimer disease, 2.4% for diabetes, 5.9% for influenza and pneumonia, and 3.7% for suicide. The rate decreased 2.1% for cancer. Rates for heart disease and kidney disease did not change significantly (Murphy et al '17). 793,840 people died of heart and cerebrovascular disease, 28%, and 215,873 people died of chronic lower respiratory disease, influenza and pneumonia, 7.7% of 2,813,503 total deaths in 2017, not including 150,000 primary lung cancer diagnosis, that would bring the respiratory death toll to 365,873, 13% of total and 25% of malignant neoplasms. Will NCHS rename the influenza and pneumonia cause of death category - pandemic pneumonia?

Leading Causes of Death 2017

Rank	Cause	ICD-10 Code	Total	%	Per 100,000
	All		2,813,503	100.0	863.8
1	Diseases of the Heart	(I00-I09,I11,I13,I20-I51)	647,457	23.0	198.8
2	Malignant Neoplasms	(C00-C97)	599,108	21.3	183.9
3	Accidents: (Unintentional Injuries)	(V01-X59,Y85-Y86)	169,936	6.0	52.2
4	Chronic lower respiratory disease	(J40-J47)	160,201	5.7	59.2
5	Cerebrovascular diseases	(I60-I69)	146,383	5.2	44.9
6	Alzheimer disease	(G30)	121,404	4.3	37.3
7	Diabetes mellitus	(E10-E14)	83,564	3.0	25.7
8	Influenza and Pneumonia	(J09-J18)	55,672	2.0	17.1
9	Nephritis	(N00-N07, N17-N19, N25-N27)	50,633	1.8	15.5
10	Intentional self-harm (suicide)	(U03,X60-X84,Y87.0)	47,173	1.7	14.5

	All other causes	(residual)	731,972	26.0	224.7

Source: Heron, Melony. National Vital Statistics Reports, Vol. 68, No. 6, June 24, 2019 - Table 1. Deaths, percentage of total deaths, and death rates for the 10 leading causes of death in selected age groups, by race and Hispanic origin and sex: United States, 2017, pg. 17

Above all else, guard your heart, for it is the wellspring of life (Proverbs 4:23). Heart attack is a leading killer of both men and women in the United States. Of the estimated 50 million, 166 out of 1,000, with unhealthy levels of lipoprotein in their blood, 7 million Americans feel angina (23 in 1,000), 1.5 million will suffer an acute myocardial infarction (heart attack) for which 550,000 will be hospitalized (1.8 out of 1,000) and of the 2.4 million people who died in 2004, 666,000 died from heart disease (2.2 out of 1,000) and 150,000 from stroke. Only severe ischemia, with blood flow of 10% or less of normal, lasting at least 20 to 40 minutes or longer leads to irreversible damage (necrosis) of some cardiac myocytes. After the onset of an acute ischemic event, sudden cardiac death (SCD) may occur within 1 to 2 hours in 20% of patients (Schoen ’94: 528, 537 539). 90 percent of heart disease involves the deposition of fat in coronary artery disease, as the result of excessive lipid consumption, insufficient exercise, carbon monoxide and/or cardio-toxin. Besides trans-fats, an invisible dye can contaminate the laundry making therapeutic cardiovascular exercise counterproductive to lethal, because it is activated by water, ie. Sweat, and the heart is stressed by the exertion. Carbon monoxide also causes angina. Treatment of heart disease involves, fresh air, fabric and vegan diet, no trans-fats; antibiotics cure endocarditis, statins reduce cholesterol, Hawthorn is the supreme herb for the heart, sage help digest fats. Patients must run the minimum three miles of the Marine Corp Physical Fitness Test (PFT) daily rather than 1 ½ mile run perpetuating the struggle with the Army Weight for Height Chart. Endocarditis is most frequently caused by *Streptococcus pyogenes* and can be caused by *Bactroides fragilis* treated with metronidazole, and most dangerously by *Staphyloccus aureus* with a 50% mortality on hospital admission better treated with doxycycline or clindamycin for pregnant women and children under age 8. Do not let the blood be contaminated by fatty foods, that should normally be less than 30% of caloric intake, whereas unlike other macronutrients, carbohydrates and protein, that are detoxified by the liver, fats go directly to the heart via the little-understood lymphatic system (Enders '15: 50-54). Though the strong eat whatever they want, the weak eat only vegetables (Romans 14:2). Test your servants for 10 days. Give us nothing but vegetables to eat and water to drink (Daniel 1:12).

Chronic obstructive pulmonary disease and influenza and pneumonia are leading causes of death. With some exceptions, such as the Spanish flu of 1918 and novel coronavirus infection pneumonia (NCIP), respiratory infections tend to be extremely common and not very life-threatening. The major inconvenience regarding respiratory infections is their contagiousness, requiring self-quarantine. More than half of all visits to doctor's offices are for ear, nose and throat problems (Lucente & Har-el '04). In the average year, colds are responsible for a loss of 440 million workdays and 62 million school days (Rosin '98: 14-16). Seasonal influenza affects up to 30% of the population, killing on average 30,000 a year in the US or 350,000 globally (Biddle ’95: 79-85). While influenza viruses circulate year-round, most of the time flu activity peaks between December and February, but activity can last as late as May. In addition to flu viruses, several other respiratory viruses also circulate during the flu season and can cause symptoms and illness similar to those seen with flu infection. These respiratory viruses include rhinovirus (one cause of the “common cold”) and respiratory syncytial virus (RSV), which is the most common cause of severe respiratory illness in young children as well as a leading cause of death from respiratory illness in those aged 65 years and older. An influenza pandemic is a

global outbreak of a new influenza A virus previously unrecognized by vaccine manufacturers. Pandemics happen when new (novel) influenza A viruses emerge which are able to infect people easily and spread from person to person in an efficient and sustained way. The United States did not experience an influenza pandemic. Flu season happens annually and usually peaks between December and February and was low 2019-2020.

Pandemic flu is an outbreak of a novel type A influenza, and rarely happens, three times in 20th century 1918, 1957, and 1968. The 1918 Spanish flu caused an estimated 600,000 death in the US alone, 218.4 deaths per 100,000 Americans, and between 40 and 60 million worldwide, two to three times as many as the 22 million who died in WWI. The 1918 Spanish Flu killed the greatest number of people over such a period of time of any natural or man made calamity. The 1957 Asian flu, caused 2 million lives globally, 22 deaths per 100,000 population; and 1968 Hong Kong flu, took 1 million lives globally, 13.9 deaths per 100,000 population. During the 2018-19 flu season, about 35 million people in the US contracted the flu and about 34,000 died, according to the Centers for Disease Control and Prevention, a 0.1% chance of dying. During the 2019-2020 flu season, it was estimated 32 million people got the flu, with 310,000 hospitalizations and 18,000 deaths, a 0.6% chance of dying. The World Health Organization estimates that worldwide, annual influenza epidemics result in about 3-5 million cases of severe illness and about 250,000 to 500,000 deaths, an 8-10% chance of dying, of severe influenza, worldwide. Relative historical effectiveness of the flu vaccine often eclipses necessary information regarding prescription flu medicines Oseltamivir (Tamiflu), Zanamivir (Relenza) and Amantadine (Symmetrel).

It remains to be seen if the total death rate increases due to the COVID-19 pandemic, or if it merely took susceptible people. To definitively end the COVID-19 pandemic, as isoniazid ended the tuberculosis, so everyone could take off the face masks and freely associate in public places again, there can be no more gag orders in regards to informing the public of the safety and effectiveness of hydrocortisone crème, essential oil of lavender, peppermint and eucalyptus at curing coronavirus and mold allergies (Sapeika '63). NCHS is advised to include 2020 COVID-19 deaths in the influenza and pneumonia category, with a footnote, or changing the name of the category to pandemic pneumonia. An advance report January 1, 2020 to January 1, 2021 would nice. It is alarming that the 2020 Annual Report of the Board of Trustees of the Federal Old Age Survivor Trust Fund and Disability Insurance Trust Fund reported that since 2010 under age 65 mortality has increased. During this same period overall mortality and over age 65 mortality continued the inexorable decrease since 1900. SSA's disability population reduction agenda is a lead culprit, whereas disability applicants have been subjected to monoclonal antibody to the back contaminated disability questionnaires treated with an Epsom salt bath, and B&E. The death rate of disability beneficiaries 243 per 100,000 is slightly lower than 253 per 100,000 for all under age 65 deaths. There are many insults to the working age and juvenile population that one must beware of, for instance the child welfare fraudulent population pyramid busting statistics of SSA and Census bureau. Reducing under age 65 mortality in response the COVID-19 pandemic, seems to be mostly about SSA having a balance available to pay disabled workers and poor children benefits, without any disability questionnaires, via Social Security Online under 31USC§1502.

The law of perversity is that the least is known about the most common diseases. The only other disease so cheap to cure, and so important to know how to treat is hospital, community and cow acquired methicillin resistant *Staphylococcus Aureus* (MRSA) skin, spinal and other internal lesions. MRSA lesions cause extremely painful **toxic shock syndrome**, when also exposed to

Streptococcus spp. and 50% mortality rate on admissions of MRSA caused heart attacks to hospitals. MRSA is cured by an Epsom salt, chlorine or salt water swimming pool or ocean bath. In regards to MRSA hospitals are conspicuous in that they are not known to even have bathtubs, nor necessarily prescribe an **Epsom salt bath** nor use saline solution in their sponge baths nor any procedure, but surgery. It is also egregious that hospitals prescribe months of intravenous (IV) treatment with penicillin to treat MRSA although the name indicates that neither penicillin nor metronidazole, the usual drugs for dealing with the problem of antibiotic resistance, above the neck and below the ribs, respectively, work, doxycycline and clindamycin for children under age 8 and pregnant are the most highly indicated drugs for the treatment of MRSA but they pale by comparison to the instant curative power of a half hour soak in an Epsom salt bath, leaving the uninfected lesions to shrivel away, in a week. Health professionals must know to take Epsom salt baths or swim in a chlorine or salt-water pool, salt-water lake or ocean, if they are to be free of MRSA, clean and non-offensive.

The International Court of Justice held, killings, rape and other forms of sexual violence, torture, beatings, cruel treatment, and for the destruction of or denial of access to food, shelter and other essentials of life, all with the intent to destroy the ... group, in whole or in part in the Application of the Convention on the Prevention and Punishment of the Crime of Genocide (*The Gambia v. Myanmar*) Summary 2020/1 23 January 2020. Although the crime of genocide weighs heavily upon WHO and greedy medical professionals in general, due the cheapness of the COVID-19 cures, without accurate public information, physicians don't necessarily know the safe and effective treatment either and are equally or more likely to get sick and die untreated, than laymen. It was unequally a crime of genocide for the unaccountably unjust US President to cut or terminate WHO contributions, without himself informing the public of cheap, safe and effective coronavirus cures. It is held, to defend medicine-less WHO pandemic response against well-founded allegations of the crime of the genocide, and torture, that WHO influenza and coronavirus pandemic response fails to prescribe corticosteroids, essential oils of eucalyptus, lavender and peppermint to cure coronavirus and Oseltamivir (Tamiflu), Zanamivir (Relenza) and Amantadine (Symmetrel) to cure influenza and this constitutes discrimination against disability, for which WHO must make reasonable accommodation for in their pandemic response , whereas persons disabled by coronavirus or influenza have the right to life on an equal basis with persons who know to use effective remedies despite the apparent ignorance of public health authorities under Arts. 1 and 10 of the Convention on the Rights of Persons with Disabilities CRPD) (2007). To prevent the perpetuation of this exploitation, violence and abuse, the United Nations must hold WHO pandemic response responsible to the independent monitoring of Hospitals & Asylums (HA), who advised calcium supplementation for postmenopausal women to prevent osteoporosis to WHO *Essential Nutrition Actions: Mainstreaming Nutrition Through the Life-Course* (2019), hydrocortisone crème, essential oils of eucalyptus, lavender and peppermint to cure the COVID-19 pandemic and Oseltamivir (Tamiflu), Zanamivir (Relenza) and Amantadine (Symmetrel) to cure influenza pandemics under Art. 16(3) of the CRPD.

States Parties must recognize that persons with pulmonary disabilities due to coronavirus or influenza, have the right to the enjoyment of the highest attainable standard of health without discrimination on the basis of disability. Wherefore States Parties shall: Provide those health services needed by persons with disabilities specifically because of their disabilities, including early identification and intervention as appropriate, and services designed to minimize and prevent further disabilities, including among children and older persons under Art. 25(b) of the CRPD. Negligent WHO influenza and pandemic response must free itself from allegations of torture, cruel, inhuman or degrading treatment, so that no one shall be subjected without his or

her free consent to medical or scientific experimentation in vaccine propaganda and untreated pandemics with safe, effective and affordable cures under Art. 15 of the CERD. Recognizing the importance of accessibility to the physical, social, economic and cultural environment, to health and education and to information and communication, in enabling persons with disabilities to fully enjoy all human rights and fundamental freedoms in (v) of the Preamble of the CRPD: It is medically necessary that WHO respond to influenza and coronavirus pandemics by henceforth, immediately informing the public to prescribe tried and true corticosteroids, in particular cheap and accessible over-the-counter hydrocortisone creme, warned of the Cushing's disease side-effect from excessive use, to emphasize the utility of essential oil of eucalyptus, lavender and peppermint aromatherapy to cure coronavirus and prescription Oseltamivir (Tamiflu), Zanamivir (Relenza) and Amantadine (Symmetrel) to cure influenza.

To do the global COVID-19 pandemic justice it will be necessary to exempt life-saving corticosteroid inhalers from the Montreal Protocol on Substances that Deplete the Ozone Layer of 1987. It is true that asthma patients using corticosteroid inhalers, might avoid puffy cheeks and serious cartilaginous and skeletal complications from Cushing's disease, with the same curative outcomes, by learning to using eucalyptus, lavender and peppermint essential oils, on their nose and chest, in bath soaps and as environmental aromatherapy. The failed, and un-exempted as requested, attempt to prohibit international trade in corticosteroid inhalers is however held to be probable cause for the global COVID-19 pandemic in 2020, the year the Montreal Protocol had hoped to totally ban all ozone depleting fluorocarbon inhalers. Ozone is considered an official air pollutant and inhalers using fluorocarbons may be curative of ozone in their own right, whereby the Ozone Secretariat does not have the standing to prohibit corticosteroid inhalers, or any other inhaler. It would be nice to liberate first time asthma patients from their dangerously ineffective salbuterol inhaler and get the word out that corticosteroid rescue inhalers save lives, but misinformed doctors, without chronic asthma, fill up their medical cabinets with nearly useless salbuterol inhalers\, the Ozone Secretariat does not have the standing to do so. Although the Ozone Secretariat has declared that they have not achieved their 2020 goals, I have resolved, for several years now, to legalize corticosteroids inhalers and not other inhalers by this deadline. The UN must require the misbehaving Ozone Secretariat to publicly extend their laboratory exemption to legalize corticosteroid inhalers to help cure the COVID-19 pandemic. Current metered dose inhalers (MDIs) contain chlorofluorocarbon (CFC) propellants, a new propellant HFA134a, with no effect on ozone, may be a suitable alternative (Jenkins '10). However, the Ozone Secretariat will have to cooperate with the corticosteroid inhaler producers they have wronged, or they shall not meet the 2020 goals. Legalizing “corticosteroid inhalers” under the 1987 Montreal Protocol on Substances that Deplete the Ozone Layer, 1990 London Amendment, 1992 Copenhagen Amendment, 1997 Montreal Amendment, 1999 Beijing Amendment, and 2016 Kigali Amendment does the COVID-19 pandemic and Chronic Obstructive Pulmonary Disease (COPD) justice. Corticosteroids are the first and best medical treatment for fluid filled lungs. Consignments of corticosteroid medical supplies, as well as essential oil of eucalyptus, lavender and peppermint to treat the coronavirus pandemic shall be allowed free passage under Art. 23 of the Fourth Geneva Convention Relative to the Protection of Civilians in Times of War (1949). States, including all states party to the UN Ozone Secretariat, must remove any impediments arising to the free exportation of goods required for humanitarian needs, such as (i) medicines and medical devices..., specifically essential oils of eucalyptus, lavender and peppermint and corticosteroids to treat the coronavirus pandemic pursuant to paragraph 98 of Alleged violations of the 1955 Treaty of Amity, Economic Relations, and Consular Rights (*Islamic Republic of Iran v. United States of America*) No. 175 3 October 2018.

Consistent with WHO pandemic response reform obligations, to avoid health care fraud allegations, it seems necessary to proceed with the understanding that coronavirus is a medical disability and the determination of whether an impairment substantially limits a major life activity shall be made without regard to the ameliorative effects of mitigating measures such as medication pursuant to Sec. 3(4)(E)(i)(I) of the Americans with Disabilities Act (ADA) of 1990 under 42USC§12102(4)(E)(i)(I). WHO, health professionals, public officials and contagious patients responsible for the coronavirus, influenza and other pandemics must be held to the higher standard of informing the public of the safety and effectiveness of ameliorative measures provided by hydrocortisone creme, essential oils of lavender, peppermint and eucalyptus nose sanitizer in curing the coronavirus and mold allergies and Oseltamivir (Tamiflu), Zanamivir (Relenza) and Amantadine (Symmetrel) to cure influenza and to a lesser extent the need to wear face masks to prevent 95% of transmission pursuant to *Sutton v. United Air Lines, Inc.*, 527 U.S. 471 (1999) and *Toyota Motor Manufacturing, Kentucky, Inc. v. Williams*, 534 U.S. 184 (2002). The Department of Justice and/or FBI, is the only agency who has actually been witnessed, by three people, including the petitioning lawyer herself, to have intentionally spread COVID-19 virus when they obsessively B&E Attorney General petitioners. FBI and Department of Justice health care fraud enforcement is believed to be responsible for the widespread dumbing down of the medical profession, its economic incompetence and most significantly their wrongful requirements for ineffective treatments seeming to aim for the expensive surgeries, armed forces apparently sympathize with. Essentially, due to the economic collapse resulting from excessive bailouts and store closures, everyone out of work due to the COVID-19 pandemic, will be entitled to disability insurance if the pandemic is not cured and economic depression averted, when their unemployment compensation expires, and they must all be informed of the treatment and cured of the COVID-19 disease, whereas the term "qualification standards" may include a requirement that an individual shall not pose a direct threat to the health or safety of other individuals in the workplace in Title I Sec. 103(b) of the ADA under 42USC§12113(b).

Olmstead v. LC No. 98-536 (1999) held, Title II of the American Disabilities Act (ADA) of 1990, which proscribes discrimination in the provision of public services, specifies, *inter alia,* that no qualified individual with a disability shall, by reason of such disability, be excluded from participation in, or be denied the benefits of, a public entity's services, programs, or activities or be subjected to discrimination by such entity under 42USC§12132. The "reasonable-modifications regulation," requires public entities to "make reasonable modifications" to avoid "discrimination on the basis of disability," but does not require measures that would "fundamentally alter" the nature of the entity's programs. 28CFR§35.130(b)(7). Discrimination in compensation occurs when a discriminatory compensation decision or other practice is adopted, when an individual becomes subject to a discriminatory compensation decision or other practice, or when an individual is affected by application of a discriminatory compensation decision or other practice, including each time wages, benefits, or other compensation is paid, resulting in whole or in part from such a decision or other practice. In addition to any relief, liability may accrue and an aggrieved person may obtain relief, including recovery of back pay for up to two years preceding the filing of the charge pursuant to Sec. 107 of the ADA under 42USC§12117 as referenced to Sec. 706(e)(3) of the Civil Rights Act of1964 under 42USC§2000-(e)(3)(A)(B) and 29USC§794a.

Despite the fact that the 33 mile marker was removed from the CDT Gila River Alternate trail southern road section, Congress must heed this lesson when passing unlawfully expensive and ineffective relief Acts, *ultra-vires* statutory authority, other than a propensity for prior error

barely remembered due to senility, high on speed (ephedrine) derived from ephedra (Mormon tea) harvested in or near the Great Basin National Park, by heading their bills with a prescription for hydrocortisone creme, essential oil of lavender, peppermint and eucalyptus aromatherapy. Like the three day panic attack and six month recovery from severe mental illness after Dimethoxymethylamphetamine (DOM) exposure if unwashed, ephedrine is not listed as a controlled substance, wherefore its extraordinarily unwitting and un-dismissed abuse by the three branches of the federal government should not be prosecuted as a crime but treated as a constitutional disability pursuant to Sec. 510 of the ADA under 42USC§12210 and the XXV Amendment. Although the judicial remedy is the same, disability is a better way to B&E than abetting the hypocritical criminal enforcement of treason under Arts. 2(4) and 3(3) of the US Constitution. To restore the public to health, sanction abuse must be accurately redressed by aiming to abolish the B&E perpetrator from the Attorney General's office, the only believed to abuse the coronavirus, FBI (not just norovirus anymore), DEA, ICE, Interagency Drug and Crime Enforcement and US Sentencing Commission (to judge US doctors subjected against their will to ineffective and wrongful regulations and sanctions under penalty of health care fraud enforcement) under Art. 54 of the Fourth Geneva Convention Relative to the Protection of Civilians in Times of War (1949).

The COVID-19 pandemic initially caused a 30% decline in the US stock market, before they shifted to computerized trading at my recommendation and is still struggling with a wide-spread store closures, work stoppages, closures, and bankruptcy, in fear of the $1.5 trillion and possibly mounting cost of the special issue bonds for coronavirus relief, six times more than legitimate federal unemployment payments, and equal amount of loans to state unemployment compensation programs, threatening to be withdrawn from the stock market, if the US dollar is not devaluated to compensate for the corticosteroid counterfeit by October 1, 2020. Pandemic circumstance were estimated in 2005 to reduce the economy by up to 5% and this time, due to the extraordinary contagiousness of COVID-19 in comparison with influenza, the UN has estimated a 10% economic decline for the duration of the pandemic. Although the official unemployment rate in the US is estimated to be around 10% and have been as high 12% more than 17% of the workforce are out of work, as of July 2020. This is the highest unemployment rate since the Great Depression, significantly higher than the Great Recession.

An estimated 32 million persons will lose their $600 weekly supplement July 31. There are about 22 million receiving regular state unemployment benefits and 8 million receiving special pandemic compensation they didn't have to contribute to from the CARES Act. The yard signs in Utah put Republicans under the influence of Mormon tea (ephedrine) and the Heroes Act prevailed upon Congress but Republicans have introduced an Act of their own. The Republicans propose to finance non-toxic payroll tax relief for the people who definitely don't need it, and the General Fund will be held liable for damages by the Social Security Administration for no good reason. The Heroes act has not agreed upon a more reasonable federal payment rate based on contribution. All these Relief acts seem to legislated under the influence of speed. For instance the discontinued $666 billion Payroll Paycheck Program, initially disguised as a legitimate federal payroll loan guarantee program for private investors, mysteriously paid 100% by the federal government, to keep certain small businesses open for business, without a prescription for hydrocortisone creme, essential oils of lavender, peppermint and eucalyptus aromatherapy. The hypocrisy of the medicine-less WHO and national influenza and coronavirus pandemic response and definitely fits the description of “affluenza”, whereas the hold-up with prescribing essential medicines is hypothetically - the coronavirus cure is so cheap. For the privilege to legislate coronavirus relief they must begin with a prescription for hydrocortisone creme,

essential oils of eucalyptus, lavender and pepperming. Hydrocortisone creme can be purchased for $1 at the dollar store, and if everyone put a dab on their nose and chest at the same time the pandemic would theoretically be over. But the public communication regarding the cure for coronavirus has been so poor it is highly advised to prevent the Cushing's disease side-effect of corticosteroids overuse by prescribing $10 bottles of essential oil of eucalyptus, lavender and peppermint aromatherapy to cure COVID-19.

The Center for Disease Control (CDC) recommended that for 8 weeks, from March 15 to May 15, organizers (whether groups or individuals) cancel or postpone in-person events that consist of 50 people or more throughout the United States. On 3/11/2020 Rep. Lowey, Nita M. [D-NY-17] introduced H.R. 6201 Families First Coronavirus Response Act that passed on 3/18/2020 to become Public Law No. 116-127. This bill responds to the COVID-19 (i.e., coronavirus disease 2019) outbreak by providing paid sick leave, tax credits, and free COVID-19 testing; expanding food assistance and unemployment benefits; and increasing Medicaid funding. On 3/19/2020 Sen. McConnell, Mitch [R-KY] introduced S.3548 Coronavirus Aid, Relief and Economic Security Act or the CARES Act to the 116th Congress (2019-2020). On 3/21/2020 Sen Perdue, David [R-GA] introduced S. Amdt. 1563 to suspend Federal payroll taxes for 2020 was referred to the Committee on Finance. Congress.gov reports that Rep. Courtney, Joe [D-CT-2] introduced the CARES Act, that passed in the Senate on 3/25/2020, on the impossible date of 1/24/2019. The CARES Act is reported to have passed on 3/27/2020 to become Public Law No: 116-136. The CARES Act addresses economic impacts of, and otherwise responds to, the COVID-19 (coronavirus) outbreak. The bill authorizes emergency loans to distressed businesses, including air carriers, and suspends certain aviation excise taxes. With respect to small businesses, the bill establishes, and provides funding for, forgivable bridge loans; and provides additional funding for grants and technical assistance. $1,200 tax rebates to individuals, with additional $500 payments per qualifying child. The rebate begins phasing out when incomes exceed $75,000 (or $150,000 for joint filers). With $250 billion for the tax rebate, $250 billion for the $600 a week unemployment compensation until July 31, $250 billion loans to state unemployment compensation programs and $666 billion for the Payroll Protection Program (PPP) the total cost of the CARES Act is estimated at $1.4 trillion to be filed as a special issue treasury bond in the Relief Acts category of Treasury mandatory programs. The lesson from the Great Recession is that the excessive federal spending must stop for the stock market to recover. Congress must realize neither new Act prescribes curative drugs, are both excessive . SSA Ticket to Work program might have better luck informing the COVID-19 disable worker population of the cure for the coronavirus than the Labor Department. Both agencies must inform the public of their right to $1 hydrocortisone creme, and $10 essential oils of eucalyptus, lavender and peppermint to cure coronavirus.

The Treasury and Customs Commissioner must decide the devaluate the dollar 10-12% by the beginning of the new fiscal year October 1, 2020 pursuant to the Marshall Lerner Condition under 19USC§4421 and 22USC§5301. Unless the Treasury and Customs Commissioner decide the devaluate the dollar by the beginning of the new fiscal year October 1, 2020 the $1.4 trillion cost of the special issue bond and about $500 billion - $800 billion regular t-bonds will withdraw $2.2 trillion from the stock market. Neither Heroes Act, nor Republican counter-revolution, should pass. The devaluation is sealed by ensuring there is $250 billion to $350 billion balance available for the disability insurance trust fund and supplemental security income program to insure workers disabled by the COVID-19 pandemic, and children growing up in poverty, at Social Security Online pursuant to the Anti-Deficiency Act of 1982 under 31USC§1502. Unless the Treasury and Customs Commissioner decide the devaluate the dollar by the beginning of the

new fiscal year October 1, 2020 the $1.4 trillion cost of the special issue bond and about $500 billion - $800 billion regular t-bonds will withdraw $2.2 trillion from the stock market. To insure the incomes of workers disabled by the COVID-19 pandemic, more cost-effectively and relieve the high costs and legislative chaos of unemployment compensation, it is advised for pandemic compensation beneficiaries to pass the pillars of Epsom salt guarding the social security disability program backpay (pain) with a monoclonal antibody to the spine that becomes infected by methicillin resistant *Staphylococcus aureus* (MRSA) lesions treated to an Epsom salt bath. Congress must accept their free half year of disability insurance from devaluating to offset the cost of the CARES Act and any subsequent Act to redress insufficiencies in this bill by resolving to tax the rich and state employees the full 12.4% Old Age Survivor Disability Insurance tax on all their income FY 22 by amending the Adjustment to Contribution Base in Sec. 230 of the Social Security Act under 42USC§430 by:

Hydrocortisone, Eucalyptus, Lavender and Peppermint (HELP) Act

To provide for all workers disabled by the COVID-19 pandemic and their families aiming to end child poverty by 2020 and all poverty by 2030.

To prescribe all unemployment compensation beneficiaries and disability applicants HELP - Hydrocortisone creme and essential oil of Eucalyptus, Lavender and Peppermint aromatherapy to cure coronavirus and mold allergies.

Be it enacted in the House and Senate Assembled

(a) The Treasury and Customs Commissioner must decide the devaluate the dollar 10-12% to offset the cost of the special issue bonds from Relief acts and regular t-bonds sold to pay for the federal deficit by the beginning of the new fiscal year October 1, 2020 pursuant to the Marshall Lerner Condition under 19USC§4421 and 22USC§5301.

(1) To relieve the high cost of unemployment compensation relief acts the +/- $250 billion balance available of funds unspent by the Relief Acts after devaluation will be used to provide impoverished COVID-19 disabled workers disability insurance (DI), and all neglected children growing up in poverty a supplemental security income (SSI) benefit at no cost to taxpayers until January 1, 2020 when the tax loophole for the rich and state employee legislated as Adjustment to Contribution Base in Sec. 230 of the Social Security Act under 42USC§430 shall be repealed and amended:

(b) Regardless of the fact that coronavirus and mold allergies are cured with nose sanitizing hydrocortisone creme, and essential oil of lavender, peppermint or eucalyptus aromatherapy, everyone out of work due to the COVID-19 pandemic shall be considered disabled pursuant to Sec. 3(4)(E)(i)(I) of the Americans with Disabilities Act (ADA) of 1990 under 42USC§12102(4)(E)(i)(I). The term "disability" means the inability to engage in any substantial gainful activity by reason of any medically determinable physical or mental impairment which can be expected to result in death or which has lasted or can be expected to last for a continuous period of not less than 12 months pursuant to Sec. 223 of the Social Security Act under 42USC§423.

(1) To protect the workforce from contagious disease, it must be required that all applicants are informed hydrocortisone creme, essential oil of lavender, peppermint and eucalyptus nose sanitizer cures coronavirus and mold allergies pursuant to Sec. 103(b) of the ADA under 42USC§12113(b). All disability applicants shall be prescribed HELP by the Ticket to Work

Program - hydrocortisone creme and essential oil of eucalyptus, lavender and peppermint aromatherapy – to at least medically treat COVID-19 pandemic disabled workers and workplaces who might be bankrupted by the cost of the Relief Acts pursuant to the higher standards of *Sutton v. United Air Lines, Inc.*, 527 U.S. 471 (1999) and *Toyota Motor Manufacturing, Kentucky, Inc. v. Williams*, 534 U.S. 184 (2002).

(c) To defend the public against contagious airborne disease and pollutants pursuant to Sec. 103(e)(4) of the ADA under 42USC§12113(e)(4) is commonly appended: The Secretaries of Health and Human Services, and Environmental Protection Agency, (who list six air pollutants 2019), not later than October 1, 2020, shall review all airborne pollutants, infectious and communicable diseases of concern to respiratory health in the workplace and disseminate this information to the public, along with information on the best available medical treatment.

I.2 Air Pollution

Air is composed of nitrogen 78.1%, oxygen 20.9%, water vapor 0.4% (1-4% near earth's surface), argon 0.9%, carbon dioxide 0.038%, neon 0.002%, helium 0.0005%, methane 0.0002%, krypton 0.0001%, hydrogen 0.00005%, nitrous oxide 0.00003%, ozone 0.000004%, carbon monoxide trace (Hamilton ’10: 66-67). "Dry" air refers to the gaseous constituents of the Earth's atmosphere - with the exception of water vapor. This is not included because, unlike the gases that occur in fixed amounts, water vapor is highly variable in concentration. Water vapor resides at lower levels, mainly within the first few miles of the atmosphere, because it originates at the Earth's surface. In addition to its gaseous constituents, the air within the lower levels of the atmosphere (the troposphere) contains solid and liquid water in the form of ice, water droplets, clouds and precipitation. Very small particles, known as aerosol, also occur in the same layer; they comprise a suspension of solid and liquid particles with very low settling velocities and small diameters (Reynolds '05: 10). UN Environment Global Environment Outlook. GEO-6. Healthy Planet, Healthy People published by Cambridge University Press in 2019 provides a comprehensive and expanding list of air pollutants, far beyond the 6 air pollutants studied by the Environmental Protection Agency.

Complex scientific studies of tobacco smoke, pepper spray, prohibited chemical weapons and infectious airborne diseases must be included to restore the epidemiological reason underlying the government response to air pollution, undermined by rhetoric regarding a 2º C global warming ostensibly “caused” by CO_2 emissions, since the beginning of the Industrial Revolution by the end of the century, in the UN Framework Convention on Climate Change (1992), alarming to smoke inhalation victims scorched by the triple digit heat of forest fires 1,000ºF. California Governor Gavin Newsom (D) took office in January 2019 and Pacific Gas and Electric (PG&E) has already gone bankrupt for inability to pay many arson claims. The cold winter and heavy snow pack of 2018-2019 is attributed the Polar Code of 1 January 2017 totally eliminating artificial warming of the Arctic Ocean from fall of 2018 until relapsing in June 2019. Although the normalization of Arctic sea surface temperature was noted by the Australian Bureau of Meteorology, the full global National Oceanic and Atmospheric Administration (NOAA) sea surface temperature (SST) map of the polar region was whited out for this brief first time there was no artificial warming of the Arctic Ocean since records began to be kept. With Newsom's election there is high hope that the drought is over and California will live in harmony with nature by 2030. The cold weather in March 2020 proved Governor Newsom has consciously mobilized State of California military-industrial resources, to further his climate change victory, to make his temporary injunction against all artificial warming of Arctic ocean

waters, a law of nature. Hypothetical finder's keeper's: California oil refineries should be prepared to convert self-combusting hydrocarbons, such as styrene, to a more stable hydrocarbon, on short notice; oil tankers or war ships must cable self-igniting styrene railcars out of the ocean, after extinguishing the styrene for three months with 15 parts per million of 4-tertiary-butyl-catechol (TBC).

Air pollution is the most important environmental contributor to the global burden of disease, leading to an estimated 6 million to 7 million premature deaths annually. Of those deaths, 2.6 million to 3.8 million deaths have been attributed to burning wood, coal, crop residue, dung and kerosene for cooking, heating and lighting. Another 3.2 million to 3.5 million deaths have been attributed to other sources of ambient air pollution. People who are elderly, very young, sick and poor are more susceptible to air pollution, which can exacerbate pre-existing illnesses or conditions. The study of air pollution needs to be rededicated to respiratory health after incompetently associating carbon dioxide with causing global warming. Fire causes smoke. Oxygen is a flammable waste-product of carbon dioxide consuming photosynthetic plants. Carbon dioxide is a waste-product of oxygen breathing animals and fuel combustion. The false association of carbon dioxide emissions with "causing" climate change, negligently defined as a 2ºC increase over pre-industrial temperatures this century, in the 1992 United Nations Framework Convention on Climate Change (UNFCCC), 1997 Kyoto Protocol, 2012 Doha Amendment, and 2016 Paris Agreement, is incompetent to redress genuine causes of global warming, especially, forest fires, and oceanic hydrocarbon heating pumps, over 1,000ºC. Despite being misled regarding the whole planet being as polluted by fossil fuel emissions as 3% of the land warmed 5ºC by cities; national transportation and electricity providers are highly encouraged to comply with treaty fossil fuel emissions reductions targets and also to plant shade trees, grass and shrubs for a net increase in ground level oxygen for breathing and definitive net decrease in carbon dioxide. Carbon dioxide as cause of global warming stands out with marijuana prohibition as one the Generals of the United Nations (GUN) greatest errors. It is grievous that global warming continues unabated because the UNFCCC is incompetent to extinguish the forest fores and oceanic hydrocarbon heating pumps, that actually causes global warming. Falsely associating carbon dioxide with global warming, wastes precious breath, whether it is disputed or virally propagated world-wide as an urban myth. The implications of the 2017 withdrawal of the United States, the second-largest emitter, and very large forest, from the Paris Agreement are mixed, because the withdrawal does not preclude individual American states' policies to support innovation friendly with the environmentally ill Paris temperature goals and global emissions could begin to fall by 2020.

Success replenishing stratospheric ozone in Antarctica by banning ozone depleting aerosol chemicals may have been so intoxicating, by 1992 climate scientists had falsely associated a similarly unlikely causative connection between carbon dioxide and global warming, that fails to extinguish the carbon dioxide emitting forest fires and oceanic hydrocarbon heating pumps, that actually cause global warming. Stratospheric O_3 depletion has been treated by the 1985 Vienna Convention for the Protection of the Ozone Layer, 1987 Montreal Protocol on Substances that Deplete the Ozone Layer, 1990 London Amendment, 1992 Copenhagen Amendment, 1997 Montreal Amendment, 1999 Beijing Amendment, and 2016 Kigali Amendment. Emissions of ozone-depleting substances (ODSs) have decreased dramatically as a result of the Montreal Protocol. New studies provide robust evidence that hole in the stratospheric ozone over Antarctica has started to recover. Persistent bioaccumulative toxic chemicals (e.g. POPs and Hg) have been regulated by the 1989 Basel Convention on the Control of Transboundary Movements of Hazardous Wastes and their Disposal, 1998 Rotterdam Convention on the Prior Informed

Consent Procedure for Certain Hazardous Chemicals and Pesticides in International Trade, 2001 Stockholm Convention on Persistent Organic Pollutants, and 2013 Minamata Convention on Mercury. The Climate and Clean Air Coalition for Reduction of Short-Lived Climate Pollutants (CCAC) is an example of a coordinated effort to make near- term progress focused on specific pollutants and sectors (CCAC 2015). Environmental concentrations of persistent organic pollutants (POPs) have been reduced in Europe, North America, Asia and the Pacific, and the Arctic. United Nations International agreements have been successful in addressing specific chemicals, but new chemical risks are emerging (UN Environment '19; 108)

The Clean Air Act requires EPA to set National Ambient Air Quality Standards (NAAQS) for six "criteria" pollutants in outdoor air - carbon monoxide, lead, ground-level ozone, nitrogen dioxide, particulate matter, and sulfur dioxide. Breathing air with a high concentration of CO reduces the amount of oxygen that can be transported in the blood stream to critical organs like the heart and brain. At very high levels, which are possible indoors or in other enclosed environments, CO can cause dizziness, confusion, unconsciousness and death. Very high levels of CO are not likely to occur outdoors. However, when CO levels are elevated outdoors, they can be of particular concern for people with some types of heart disease. These people already have a reduced ability for getting oxygenated blood to their hearts in situations where the heart needs more oxygen than usual. They are especially vulnerable to the effects of CO when exercising or under increased stress. In these situations, short-term exposure to elevated CO may result in reduced oxygen to the heart accompanied by chest pain also known as angina. CO must be in the differential diagnosis for angina, particularly that experienced by athletes, when talking with CO_2 producing O_2 breathing animal, to prevent false accusation of endocarditis against the CO emitting stressed out car-driving talker by the over-exerted listener. Ozone in the air we breathe can harm our health. People most at risk from breathing air containing ozone include people with asthma, children, older adults, and people who are active outdoors, especially outdoor workers. In addition, people with certain genetic characteristics, and people with reduced intake of certain nutrients, such as vitamins C and E, are at greater risk from ozone exposure. Breathing ozone can trigger a variety of health problems including chest pain, coughing, throat irritation, and airway inflammation. It also can reduce lung function and harm lung tissue. Ozone can worsen bronchitis, emphysema, and asthma, leading to increased medical care.

Once taken into the body, lead distributes throughout the body in the blood and is accumulated in the bones. Depending on the level of exposure, lead can adversely affect the nervous system, kidney function, immune system, reproductive and developmental systems and the cardiovascular system. Lead exposure also affects the oxygen carrying capacity of the blood. The lead effects most commonly encountered in current populations are neurological effects in children and cardiovascular effects (e.g., high blood pressure and heart disease) in adults. Infants and young children are especially sensitive to even low levels of lead, which may contribute to behavioral problems, learning deficits and lowered IQ. Breathing air with a high concentration of NO2 can irritate airways in the human respiratory system. Such exposures over short periods can aggravate respiratory diseases, particularly asthma, leading to respiratory symptoms (such as coughing, wheezing or difficulty breathing), hospital admissions and visits to emergency rooms. Longer exposures to elevated concentrations of NO_2 may contribute to the development of asthma and potentially increase susceptibility to respiratory infections. People with asthma, as well as children and the elderly are generally at greater risk for the health effects of NO_2. NO_2 along with other Nox reacts with other chemicals in the air to form both particulate matter and ozone. Both of these are also harmful when inhaled due to effects on the respiratory system. Particulate matter contains microscopic solids or liquid droplets that are so small that they can be

inhaled and cause serious health problems. Some particles less than 10 micrometers in diameter can get deep into your lungs and some may even get into your bloodstream. Of these, particles less than 2.5 micrometers in diameter, also known as fine particles or PM2.5, pose the greatest risk to health. Fine particles are also the main cause of reduced visibility (haze) in parts of the United States, including many of our treasured national parks and wilderness areas. Short-term exposures to SO_2 can harm the human respiratory system and make breathing difficult. People with asthma, particularly children, are sensitive to these effects of SO_2. SO_2 emissions that lead to high concentrations of SO_2 in the air generally also lead to the formation of other sulfur oxides (Sox). Sox can react with other compounds in the atmosphere to form small particles. These particles contribute to particulate matter (PM) pollution. Small particles may penetrate deeply into the lungs and in sufficient quantity can contribute to health problems.

Behind the international struggle to address global warming and climate change lies the increase in greenhouse gases in urban atmospheres. Gases that trap heat in the atmosphere are called hallucinatory called greenhouse gases. They are purported to let sunlight pass through the atmosphere, but they prevent the heat that the sunlight brings from leaving the atmosphere. The Trump administration has rejected the international emissions standards of the Kyoto Protocol and Paris Agreement. As frustrating as this is to successful car emission testing programs and ozone ban, Trump's petulant behavior has brought to light that the international campaign against greenhouse gases is incompetent to claim that greenhouse gases cause global warming, when greenhouse gases are in fact secondary indicators of heat sources, particularly wildfires, but also car and ranch land emission polluted areas that do not have enough trees to make oxygen and provide shade. The incompetence can be tested in urban environments where heat is associated with the wind stopping and no clouds covering the sun, rather than the hypothesis of passing through a bubble of greenhouse gases. While greenhouse gases may trap heat, gases hold less heat than water or land, especially blacktop, pavement. Greenhouse gases would be better controlled for respiratory health purposes of the EPA than global warming incompetence of the UN Framework Convention on Climate Change hoping to prevent a 1.5º C increase in global temperature within 50 years, when there is a 1,000ºC wildfire burning outside the conference and self-combusted hydrocarbon heating pumps in the ocean. The UN is currently trying to blend heat from wildfires into the global warming propaganda, with limited success at overturning their urban myth regarding greenhouse gases being the cause, rather than a secondary indicator better referenced to respiratory health, after ambient temperature, for the sake of extinguishing the 1,000º F and C in wildfires, that actually cause the global warming we suffer from. Greenhouse gases are for the most part different from the six “criteria” pollutants of the Environmental Protection Agency National Ambient Air Quality Standards (NAAQS).

The primary greenhouse gases in Earth's atmosphere are water vapor (H2O), carbon dioxide (CO_2), methane (CH_4), nitrous oxide (N_2O), and ozone (O_3). CO_2, by definition, has a GWP of 1 regardless of the time period used, because it is the gas being used as the reference. CO_2 remains in the climate system for a very long time: CO_2 emissions cause increases in atmospheric concentrations of CO_2 that will last thousands of years. Methane (CH_4) is estimated to have a GWP of 28–36 over 100 years. CH_4 emitted today lasts about a decade on average, which is much less time than CO_2. But CH_4 also absorbs much more energy than CO_2. The net effect of the shorter lifetime and higher energy absorption is reflected in the GWP. The CH_4 GWP also accounts for some indirect effects, such as the fact that CH_4 is a precursor to ozone, and ozone is itself a GHG. Nitrous Oxide (N_2O) has a GWP 265–298 times that of CO_2 for a 100-year timescale. N2O emitted today remains in the atmosphere for more than 100 years, on average. Chlorofluorocarbons (CFCs), hydrofluorocarbons (HFCs), hydrochlorofluorocarbons (HCFCs),

perfluorocarbons (PFCs), and sulfur hexafluoride (SF6) are sometimes called high-GWP gases because, for a given amount of mass, they trap substantially more heat than CO_2. (The GWPs for these gases can be in the thousands or tens of thousands.) While oxygen (O_2) is the second most abundant gas in our atmosphere, O_2 does not absorb thermal infrared radiation.

The world's emissions of greenhouse gases from burning fossil fuels increased 2 percent per year in the 1970s and 80s under the Clean Air Act of 1970 42USC(85)(I)(A)§7401 et seq. At the 1992 Earth Summit in Rio de Janeiro, Brazil, it was agreed that by 2000, the emissions of carbon dioxide would be stabilized at 1990 levels to slow the rate of increase. To prevent further rises in atmospheric concentration, a global 60% cut would be required. By June 1993 a total of 166 nations had signed up to the "Framework Convention on Climate Change". The European Union as a whole must reduce emission by 8% averaged over the period from 2008 to 2012. The USA's reduction target was set at 7% for the same period. However, the Kyoto Protocol of December 1997 that laid down these principles will not come into force until at least 55 nations ratify it and the accumulated emissions from such nations must not reach less than 55% of the global total. By early July 2004, some 160 countries had ratified it but their emission totaled 44.2% of world output. The convention had not at that time been ratified, by, for example, Australia, Indonesia, the Russian Federation and the USA (Reynolds '05: 136). In the 1990s emission growth fell to 1 per cent under the UN Framework Convention on Climate Change (UNFCC) of June 3 to 14, 1992. Since 2000 the growth rate of the world's CO2 emissions almost trebled to 3 per cent a year and President Bush. refused to sign Kyoto Protocol of 16 February 2005. Emission growth was slowed by the recession that arrived in late 2008, and in some countries reversed, growth in annual carbon emissions, but the volume of greenhouse gases in the atmosphere continues to rise. The Obama administration agrees rich country emission cuts of 25-40 per cent below 1990 levels by 2020, are necessary if the world is to aim for 450 ppm (Hamilton '10: 4, 23, 25, 27). Statistics compiled by the American Enterprise Institute reveal that in the 25 year period spanning 1980 to 2005: Fine particulate matter declined 40%. Ozone levels declined 20% and days per year exceeding the 8-hour ozone standard fell 79%. Nitrogen dioxide levels decreased 37%, sulfur dioxide dropped 63% and carbon monoxide concentrations were reduced by 74%. Lead levels were lowered by 96%. What makes these air quality improvements even more noteworthy is that they occurred during a period in which: Automobile miles driven each year nearly doubled to 93% and diesel truck miles more than doubled to 112%. Tons of coal burned for electricity production increased over 60%. The real dollar value of goods and services (gross domestic product) more than doubled to 114%. Despite more and more people and more cars on the road than ever, air pollution is no longer a growing issue in the United States (Sussman '10: 179, 180, 168).

Chemical Air Pollutants

Chemical	Chemical
Black carbon (BC)	Ozone, tropospheric and stratospheric (O_3)
Chlorofluorocarbons (CFCs)	Organic carbon (OC)
Methane (CH_4)	Ozone-depleting substances (ODS)
Carbon monoxide (CO)	Polycyclic aromatic hydrocarbons (PAHs)
Carbon dioxide (CO_2)	Lead (Pb)

Greenhouse Gases (GHGs)	Polybrominated diphenyl ethers (PBDE)
Hydrochlorofluorocarbons (HCFCs)	Persistent, bioaccumulative, toxic chemicals
Hydrofluorocarbons (HFCs)	Polychlorinated biphenyl (PCB)
Mercury (Hg)	Per-and polyfluoroalkyl substances (PFAs)
Nitrous oxide (N_2O)	Particular matter (PM)
Ammonia (NH_3)	PM less than 10µm in diameter (PM_{10})
Non-methane volatile organic compounds (NMVOC)	PM less than 2.5µm in diameter ($PM_{2.5}$)
Nitrogen oxide (NO)	Persistent organic pollutants (as defined by international agreements) (POPs)
Nitrogen dioxide (NO_2)	Sulphur dioxide (SO_2)
Nitrogen oxides (NO_x)	

Source: UN Environment. Global Environment Outlook. GEO-6. Healthy Planet, Healthy People. Cambridge University Press. 2019 pg. 109 Table 5.1 Some atmospheric chemical components.;

An **airborne disorder** is any disease that is caused by a microorganism that is transmitted through the air. There are many airborne diseases that are of clinical importance and include bacteria, viruses, and fungi. These organisms may be spread through sneezing, coughing spraying of liquids, the spread of dust or any activity that results in the generation of aerosolized particles. The microorganisms transmitted airborne may be spread via fine mist, dust, aerosols, or liquids. The aerosolized particles may be generated from a source of infection such as body secretions of an infected patient or even an animal. In addition, aerosols may be generated from biological waste products that accumulate in garbage, caves and dry arid containers. During aerosolization, the microorganisms that are less than 5 microns in size float in the air. Sometimes, the microorganisms may be contained in dust particles that are present in the air. Once the droplets that contain microorganisms have been formed, they are then dispersed via air currents to varying distances and can be inhaled by susceptible hosts. As the distance traveled of the aerosol particle increases, the risk of infection starts to drop. In some cases where there is inadequate ventilation, the airborne particle may remain in the hospital room and be inhaled by a newly admitted patient. The control and prevention of airborne transmission of infections are not simple as it requires the control of airflow with the use of specially designed ventilator systems, the practice of antiseptic techniques, wearing personalized protection equipment (PPE) and performing basic infection prevention measures like hand washing. In almost all cases, airborne pathogens cause an inflammatory reaction of the upper airways affecting the nose, sinuses, throat, and lungs. The involvement of these structures may result in nasal or sinus congestion, and sore throat. Any coughing or sneezing activity may then generate aerosolized particles. Any medical or surgical intervention into the respiratory tract, such as intubation, or cardiopulmonary resuscitation may also release aerosolized particles into the atmosphere (Ather & Edemekong '20).

Anthrax: Individuals exposed to aerosolized B anthracis spores must have at least 8 weeks of antimicrobial therapy. This is a serious infection with very high mortality if the diagnosis is missed. An infectious disease consult should be involved in the management of patients with anthrax. The patient usually remains infectious while symptoms remain. In any case, because this is a potential agent for terrorism, it is important to seek advice from the CDC. Patient isolation is mandatory, and all traffic must be curtailed. Chickenpox: Most patients remain infectious for 5 to 7 days after the rash develops. By this time most of the vesicles have dried up, and the risk of transmission is low. Influenza: Patients with influenza may remain infectious even before they have symptoms. In most cases, the viral shedding occurs at the time of the symptoms and will continue for 5 to 10 days. Data indicate that younger children and infants may shed the virus for a week or two, thus placing other individuals at risk for acquiring the infection. In patients who are immunocompromised, the shedding may last for 4-12 weeks. COVID-19 incubates for about five days and last three weeks, it is nearly undistinguishable from the flu and the most common cause of death is pneumonia. Measles (aka rubeola) is the most contagious infectious diseases, with a secondary infection rate in susceptible domestic contacts over 90 percent. The majority of patients remain contagious from 1 to 2 days before the onset of symptoms. Younger patients may remain contagious 4 to 5 days before and after the rash. Immunocompromised individuals remain contagious throughout the duration of the illness. Smallpox is not a concern in many parts of the world, but it is a contagious infection. However, unlike measles, influenza, and pertussis, the transmission rate is low. Once smallpox is acquired, the patient remains contagious from the onset of the fever and rash. The highest viral shedding occurs during the first 2 weeks of the rash. Infection rates of anywhere from 40% to 80% have been reported. Cryptococcosis is being seen more often now because of transplantation. However, in healthy people, the risk of acquiring or developing an infection is very low. However, all immunocompromised individuals remain at high risk for acquiring Cryptococcus. An infectious disease consult is necessary to determine the period of isolation. Tuberculosis is a common disease, but it is not as contagious as measles or influenza. Even when acquired, only 5% of individual will develop clinical disease. The risk of disease transmission is most common in close living quarters. Data reveal that about 20% of household contacts do develop a positive skin test to PPD. Small epidemics have been reported in closed environments like that in an airplane. Populations at high risk for infection include health care workers and nursing home residents. The patient usually remains infectious while symptoms are present, which can be a few weeks (Ather & Edemekong '20).

Airborne Infections

Airborne pathogen	Group	Disease	Status	Source	DIA microns
Parvovirus B19	virus	Fifth disease, anemia	contagious	humans	0.022
Rhinovirus	virus	colds	contagious	humans	0.023
Coxsackievirus	virus	colds	contagious	humans	0.027
Echovirus	virus	colds	contagious	humans	0.028
Hantavirus	virus	hantavirus	non	rodents	0.060

Togavirus	virus	Rubella (German measles)	contagious	humans	0.063
Reovirus	virus	colds	contagious	humans	0.075
Adenovirus	virus	colds	contagious	humans	0.080
Orthomyxovirus - influenza	virus	flu	contagious	Humans, birds	0.10
Coronavirus	virus	colds	contagious	humans	0.11
Morbillivirus	virus	Measles (rubella)	contagious	humans	0.12
Varicella-zoster	virus	chickenpox	contagious	humans	0.16
Arenavirus - Junin	virus	Hemmorhagic fever	contagious	rodents	0.18
Arenavirus - Machupo	virus	Hemorrhagic fever	contagious	rodents	0.18
Arenavirus - Lassa	virus	Lassa fever	contagious	rodents	0.18
Filovirus - Marburg	virus	Hemorrhagic fever	contagious	rodents	0.18
Parainfluenza	virus	flu	contagious	humans	0.22
Respiratory syncytial virus	virus	pneumonia	contagious	humans	0.22
Poxvirus - Variola	virus	Smallpox (extinct)	contagious	humans	0.23
Poxvirus - Vaccinia	virus	cowpox	non	agricultural	0.23
Monkeypox	virus	monkeypox	contagious	monkeys	0.23
Paramyxovirus	virus	mumps	contagious	humans	0.23
Francisella tularensis	bacteria	tularemia	no	Wild animals	0.20
Bordetella pertussis	bacteria	Whooping cough	contagious	Humans	0.25
Mycoplasma pneumoniae	bacteria	pneumonia	contagious	humans	0.25

Chlamydia peumoniae	bacteria	Pneumonia, bronchitis	contagious	humans	0.30
Chlamydia psittaci	bacteria	psittacosis	non	birds	0.30
Klebsiella pneumoniae	bacteria	Opportunistic infections	endogenous	environmental	0.40
Haemophilus influenza	bacteria	meningitis	contagious	humans	0.43
Coxiella burnetii	bacteria	Q fever	non	Cattle, sheep	0.50
Pseudomonas aeruginosa	bacteria	Opportunistic infections	contagious	environmental	0.57
Pseudomonas pseudomallei	bacteria	Opportunistic infections	Non	environmental	0.57
Actinomyces israelli	bacteria	actinomycosis	endogenous	humans	0.60
Legionella parisiensis	bacteria	Pneumonia ?	non	environmental	0.60
Legionella pneumophila	bacteria	LD, Pontiac fever	non	environmental	0.60
Cardiobacterium	bacteria	Opportunistic infection	endogenous	humans	0.63
Alkaligenes	bacteria	Opportunistic infection	endogenous	humans	0.75
Yersinia pestis	bacteria	Pneumonic plague	contagious	rodents	0.75
Pseudomonas cepacia	bacteria	Nonrespiratory airborne?	non	environmental	0.77
Pseudomonas mallei	bacteria	Opportunistic infection	non	environmental	0.77
Enterobacter cloacae	bacteria	Nonrespiratory airborne?	contagious	humans	0.80
Enterococcus	bacteria	Nonrespiratory airborne	contagious	humans	0.80
Neisseria meningitidis	bacteria	meningitis	endogenous	humans	0.80

Streptococcus faecalis	bacteria	Nonrespiratory airborne	contagious	humans	0.80
Streptococcus pyogenes	bacteria	Scarlet fever, pharyngitis, endocarditis	contagious	humans	0.80
Mycobacterium kansasii	bacteria	Cavitary pulmonary	non	unkown	0.86
Mycobacterium tuberculosis	bacteria	TB	contagious	humans	0.86
Streptococcus pneumoniae	bacteria	Pneumonia, otitis media	contagious	humans	0.90
Staphylococcus aureus	bacteria	Opportunistic infection	endogenous	humans	0.95
Staphylococcus epidermis	bacteria	Nonrespiratory airborne?	endogenous	humans	0.95
Corynebacteria diphtheria	bacteria	diptheria	contagious	humans	1.00
Clostridium tetani	bacteria	Nonrespiratory airborne?	non	environmental	1.00
Haemophilus parainfluenzae	bacteria	Opportunistic infection	endogenous	humans	1.00
Moraxella lacunata	bacteria	Opportunistic infection	endogenous	humans	1.00
Bacillus anthracis	bacteria	anthrax	non	Cattle, sheep	1.13
Mycobacterium avium	bacteria	Cavitary pulmonary	non	environmental	1.20
Mycobacterium intracellulare	bacteria	Cavitary pulmonary	non	environmental	1.20
Acinetobacter	bacteria	Opportunistic infection	endogenous	environmental	1.25
Moraxella catarrhalis	bacteria	Opportunistic infection	endogenous	humans	1.25

Serratia marcescens	bacteria	Opportunistic infection	endogenous	environmental	1.25
Saccharomonospora viridis	actinomycetes	Farmer's lung	non	agricultural	0.60
Thermomonospora viridis	actinomycetes	Farmer's lung, HP	non	agricultural	0.60
Micropolyspora faeni	actinomycetes	Farmer's lung	non	agricultural	0.69
Thermoactinomyces sacchari	actinomycetes	Bagassosis, HP	Non	agricultural	0.70
Micromonospora faeni	actinomycetes	Farmer's lung	Non	agricultural	1.00
Thermoactinomyces vulgaris	actinomycetes	Farmer's lung, HP	non	agricultural	
Nocardia asteroides	actinomycetes	nocardiosis	non	environmental	1.14
Nocardia brasiliensis	actinomycetes	Pulmonary mycetoma	non	environmental	1.50
Nocardia caviae	actinomycetes	nocardiosis	non	environmental	1.50
Phialaphora parasitica	fungi	Allergic alveolitis	non	environmental	1.50
Phialaphora repens	fungi	Allergic alveolitis	non	environmental	1.50
Exophialia jeanselmei	fungi	Humidifier water	Non	environmental	1.95
Phialaphora hofmannii	fungi	Allergic alveolitis	Non	environmental	2.00
Phialaphora richardsiae	fungi	Allergic alveolitis	non	environmental	2.00

Pneumocystis carinii	Protozoa	Pneumocystosis	Non	environmental	2.00
Phialaphora mutabilis	fungi	Allergic alveolitis	Non	Environmental	2.15
Acremonium spp.	fungi	Allergic alveolitis	non	environmental	2.50
Trichoderma harzianum	fungi	Allergic alveolitis	non	environmental	2.65
Oidiodendron tenuissimum	fungi	Allergic alveolitis	non	environmental	2.75
Geomyces pannorum	fungi	Allergic alveolitis	non	environmental	3.00
Histoplasma capsulatum	fungi	histoplasmosis	Non	environmental	3.00
Paecilomycetes variotti	fungi	Allergic alveollitis	non	environmental	3.00
Wallemia sebi	fungi	Allergic alveolitis	non	environmental	3.00
Emericells nidulans	fungi	Allergic alveolitis	non	environmental	3.25
Phoma spp.	fungi	Allergic alveolitis	non	environmental	3.25
Penicillium brevicompactum	fungi	Allergic alveolitis	non	environmental	3.30
Penicillium chrysogenum	fungi	Allergic alveolitis	non	environmental	3.30
Penicillium citreonigrum	fungi	Allergen?	non	environmental	3.30
Penicillium commune	fungi	Allergic alveolitis	Non	environmental	3.30

Penicillium corylophilum	fungi	Allergic alveolitis	non	environmental	3.30
Penicillium cyclopium	fungi	Allergen?	non	environmental	3.30
Penicillium expansum	fungi	Allergic alveolitis	non	environmental	3.30
Penicillium freii	fungi	Allergen?	non	environmental	3.30
Penicillium glabrum	fungi	Allergic alveolitis	non	environmental	3.30
Penicillium hordei	fungi	Allergen?	non	environmental	3.30
Penicillium olsonii	fungi	Allergic alveolitis	Non	environmental	3.30
Penicillium polonicum	fungi	Allergic alveolitis	non	environmental	3.30
Penicillium rugulosum	fungi	Allergen?	non	environmental	3.30
Pencillium solitum	fungi	Allergen?	non	environmental	3.30
Aspergillus flavus	fungi	aspergillosis	non	environmental	3.50
Aspergillus fumigatus	fungi	aspergillosis	non	environmental	3.50
Aspergillus niger	fungi	aspergillosis	non	environmental	3.50
Aspergillus versicolor	fungi	aspergillosis	non	environmental	3.50
Absidia corymbifera	fungi	zygomycosis	Non	environmental	3.75

Coccidioides immitis	fungi	coccidioidomycosis	non	environmental	4.00
Trichoderma viride	fungi	Allergic alveolitis	non	environmental	4.05
Rhizomucor pusillus	fungi	Allergic alveolitis	non	Environmental	4.25
Aureobasidium pullulans	fungi	Allergic alveolitis	Non	environmental	5.00
Candida albicans	fungi	Nonrespiratory airborne?	non	environmental	5.00
Chaetomium globosum	fungi	Allergic alveolitis	Non	environmental	5.50
Cryptococcus albidus	fungi	Allergen?	non	environmental	5.50
Cryptococcus laurentii	fungi	Allegen?	non	environmental	5.50
Cryptococcus neoformans	fungi	cryptococcosis	non	environmental	5.50
Stachybotris atra	fungi	Allergic alveolitis	non	environmental	5.65
Stachybotris chartarum	fungi	Allergic alveolitis	non	environmental	5.65
Eurotium amstelodami	fungi	Allergic alveolitis	non	environmental	5.75
Eurotium herbariorium	fungi	Allergic alveolitis	non	Environmental	5.75
Eurotium rubrum	fungi	Allergic alveolitis	non	environmental	5.75
Scopuariopsis brevicaulis	fungi	onychomycosis	non	environmental	6.00

Scopuariopsis fusca	fungi	onychmycosis	non	environmental	6.00
Sporothrix schenckii	fungi	sporotrichosis	Non	environmental	6.50
Botrytis cinera	fungi	Allergic alveolitis	non	environmental	7.00
Mucor plumbeus	fungi	mucormycosis	non	environmental	7.50
Rhizopus stolonifer	fungi	zygomycosis	non	environmental	8.00
Cladosporium cladosporioides	fungi	chromoblastomycosis	non	environmental	9.00
Cladosporium herbarum	fungi	chromoblastomycosis	non	environmental	9.00
Cladosporiu sphaerospermum	fungi	chromoblastomycosis	non	environmental	9.00
Fusarium culmorum	fungi	Allergic alveolitis	non	environmental	11.50
Fusarium graminearum	fungi	Allergic alveolitis	non	Environmental	11.50
`Fusarium monoliforme	fungi	Allergic alveolitis	non	environmental	11.50
Fusarium solani	fungi	Allergic alveolitis	non	environmental	11.50
Fusarium sporotrichioides	fungi	Allergic alveolitis	non	environmental	11.50
Helminthosporium	fungi	Allergic alveolitis	non	environmental	12.47

Blastomyces dermatitidis	fungi	blasomycosis	non	environmental	14.00
Rhodoturula glutinus	fungi	Allergic alveolitis	non	environmental	14.00
Rhodoturula minuta	fungi	Allergic alveolitis	non	environmental	14.00
Rhodoturula mucilaginosa	fungi	Allergic alveolitis	non	environmental	14.00
Alternaria alternata	fungi	Allergic alveolitis	non	environmental	14.39
Ulocladium botrytis	fungi	Allergic alveolitis	non	environmental	15.00
Ulocladium chartarum	fungi	Allergic alveolitis	non	environmental	15.00
Paracoccidioides brasiliensis	fungi	paracoccidioidomycosis	Non	environmental	18.25
Epicoccum nigrum	fungi	Allergen?	non	environmental	20.00

Source: ATZLabs List of Airborne Pathogens, including Allergenic, Toxigenic and Suspected Respiratory and Non-Respiratory Pathogens.

Airborne transmission of microorganisms depends on several physical variables endemic to the infectious particle. Factors that influence the spread of airborne infections includes the following: Temperature, humidity, rainfall, amount of sunshine, wind, human behavior, tropical storms hurricanes, monsoons, or typhoons. For example, the influenza virus is relatively easily spread in the northern hemisphere because of climate conditions that favor infectiousness of the virus but many bacterial infections cannot spread outdoors for most of the year, and thus remain in a state of dormancy. Ultraviolet (UV) rays of the sun are harmful to both bacteria and viruses. In those parts of the country with a higher average of daily sunshine and those close to the equator, some pathogens lose their infectious ability. However, if the levels of humidity are high, then even in the presence of UV light, the infectious particle can survive for a longer period. It is believed that this is due to the formation of vapor around the aerosolized particles which acts as a barrier to the UV rays. The role of living conditions and socioeconomic factors plays a key role in airborne transmission. Dwelling and the number of people residing in one area is an important aspect. The spread of disease is much faster in urban areas compared to rural areas. In urban areas, buildings and other high-rise structures make transmission of bacterial and viral pathogens relatively easy, but in rural areas, airborne particles containing fungal spores are more common. Poor or inadequate ventilation has been implicated in several airborne infections such as

Legionella pneumophila. Poor maintenance of air conditioning systems can lead to water stagnation and spread of aerosolized particles.

The negative pressure room is usually a single-occupancy patient-care room frequently used to isolate individuals with confirmed or suspected airborne infection. This is a single patient room equipped with special air handling (negative pressure) and ventilation capacity. The negative pressure room is also known as an Airborne Isolation Room. Negative pressure ventilation that creates inward directional airflow from corners of the room. The airborne isolation room should have a toilet and sink for the patient, and a designated hand washing sink for healthcare workers.Have monitoring equipment including alarms. Transmit exhaust of air from the hospital room to the outside of the building. Recirculate air through a HEPA filter before being returned to the general circulation. The door to the room must be kept closed to maintain negative pressure even if the patient is not in the room. The windows in the room should remain closed at all times; opening the window may cause the reversal of airflow, which counters the benefits of a negative pressure room. All healthcare providers who enter the isolated negative pressure room must be fit tested for an N95 respirator. Studies show that the mask has a 95% filter efficiency and provides a tight facial seal with less than a 10% leak. Only healthcare providers immunized to the organism in question should enter a room where airborne precautions are in place for varicella or measles or varicella. A respirator is not necessary for immunized individuals but is required for non-immunized workers who provide care. An ante-room is a relatively clean and is a frequently used area to transition patients/healthcare workers in and out of the airborne isolation room when it is under negative pressure. The laundry hamper and sink are usually in the ante-room. Other than transporting the patient to another department, unless it is medically necessary, the patient should be restricted to his or her room. During transport, the patient should wear a surgical mask. In general, airborne precautions can be discontinued once the patient shows no signs or symptoms of an infection. However, one also has to be aware of the period of incubation and if unsure, always consult with an infectious disease expert (Ather & Edemekong '20).

Airborne allergens, ranging from pollen and dust to mold spores, dander and fibres, are the most common reason for rhinitis, with an estimated 35 million Americans allergic to these substances. People are not allergic to cigarettes or perfume, some people have a sensitivity to such substances, which can make eyes water, nose run and sneeze, and those with allergic rhinitis, are more likely to have such sensitivities. Allergens are generated from living things, namely tree pollen, grass pollen, cockroaches, pet dander, molds and dust mites. Among North American plants weeds are the most prolific producers of allergenic pollen, with ragweed the major culprit; others include sagebrush, redroot pigweed, lamb's quarters, Russian thistle (tumbleweed), and English plantain. Grasses and trees, too are important sources of allergenic pollens. Although more than 1,000 species of grasses grow in North America, only a few produce highly allergenic pollen. They include timothy grass, Kentucky bluegrass, Johnson grass, Bermuda grass, redtop grass, orchard grass, and sweet vernal grass. Trees that produce allergenic pollen include oak, ash, elm, hickory, pecan, box elder, and mountain cedar. There are thousands of types of molds and yeasts in the fungus. Molds are made of many cells that grow as branching threads called hyphae; yeasts are single cells that divide to form clusters. Although both can probably cause allergic reactions, only a small number of molds are recognized offenders. Mold allergies may get worse from spring to late fall, but the first freeze doesn't end the problem with molds as it does with pollen. Molds are tenacious little fungi that are able to grow at subfreezing temperatures. Even snow, while lowering the outdoor mold count dramatically, doesn't kill mold spores. Only a few molds get the allergen label. In general,

Alternaria and Cladosporium (Hormodendrum) are the allergenic molds most commonly found indoors and outdoors throughout the United States. *Aspergillus*, *Penicillium*, *Helminthosporium*, *Epicoccum*, *Fuarium*, *Mucor*, *Rhizopus*, and *Aureobasidium* (*Pullularia*) are also common allergy triggers. There is no relationship between a respiratory allergy to the mold Penicillium and an allergy to the drug penicillin. Although allergic rhinitis caused by mold is relatively benign, Aspergillus may cause a more severe respiratory reaction. This form of mold may lodge in your airways or in a distant part of the lung and grow until it forms a compact sphere known as a fungus ball. Aspergillus mold can also lead to asthma or to a lung disease resembling severe inflammatory asthma, called allergic bronchopulmonary aspergillosis (Berger '04: 39, 41, 44).

Fungi are found everywhere, their poisonous principles are readily divisible into those that produce toxic substances, the mycotoxins, and those such as mushrooms that possess toxins. Mycotoxin contaminated food may result in serious hazard to health, the toxins often remain in food, that is not visibly moldy, long after the fungus that produced them died, and often remain toxic after food has been cooked. In the normal population three major fungi cause invasive, systemic infection. These are *Coccidioides immitis*, *Histoplasma capsulatum* and *Blastomyces dermatitidis*, each having its own geographic area of distribution and each residing in the soil from whence it becomes airborne and is inhaled into the respiratory tract. Candida and aspergillis are probably more common but they are complications of civilization due to antibiotic use and the sale of *Aspergillus* niger to academic research laboratories. *Aspergillus* produce a specific group of mycotoxins called aflatoxins. Aflatoxin B_1 is most frequently found in food, and is the most powerful carcinogen known. Any food is susceptible to aflatoxin contamination once it becomes moldy. Symptoms of poisoning become apparent at 10 to 100 ppm contamination of livestock feed. Aflatoxins interact with DNA and markedly affect transcription of genetic information in animals, cells, and microorganisms (Elvin-Lewis ’77: 23, 24). Aspergillosis is caused by species of the ubiquitous mold *Aspergillus*. Infections caused by *Aspergillus fumigatus*, *A. flavus*, *A. niger* and others result in allergic aspergillosis, invasive or disseminated infection or fungus ball (or mycetoma). Fungus ball may develop in the setting of allergic bronchopulmonary or invasive disease. Bronchopulmonary aspergillosis is frequently a progressive disease with IgE-mediated asthma and IgG-mediated type III parenchymal reactions. Common signs and symptoms are repeated attacks of wheezing with fever, evanescent pulmonary infiltrates, bronchial plugging, repeated isolation of *Aspergillus* from sputum, eosinophilia, and positive skin test results to *Aspergillus* antigen. Serum IgG antibody levels to *Aspergillus* organisms and total serum IgE are elevated. Central saccular bronchiectasis can often be identified in the middle-lung or upper-lung fields in chest radiographs. Patients expectorate brown sputum plugs that contain the organisms. Long-term therapy with oral corticosteroids plus standard anti-asthma regiments are often required to control the disease process. Colonization of the tracheobronchial tree with concentric rings of hyphae and surrounding fibrosing granulomatous inflammation or chronic nonspecific inflammatory elements occur in patients with chronic obstructive pulmonary disease. Periodic acid-schiff or silver stains are used to demonstrate *Aspergillus* hyphae in histologic sections. Since symptoms in invasive aspergillosis are usually related to the point of entry and since 90% or more begin in the lungs, fever, chills, shortness of breath, non-productive cough, and pleuritic pain are commonly noted. Hemorrhagic infarction or necrotizing bronchopneumonia are noted. Life-threatening hemoptysis is a major clinical presentation of mycetoma. Other complications include bacterial lung abscess, bronchopleural fistula with fungal empyema and spread of infection to thoracic vertebral bodies. The diagnosis of invasive disease is usually difficult because cultures only transiently yield positive results. Aspergillus organisms are a frequent laboratory contaminant and this further complicates the certainty of diagnosis.

In immunocompromised situations, aggressive therapy with amphotericin B must be initiated. Systemic therapy with amphotericin B for fungus ball is of no value. Occasionally control of symptoms and reduction in the size of the fungus ball can be achieved by aerosol or insufflation of amphotericin B. Surgical excision is the treatment of choice; the major justification for resection is life-threatening hemmhorage, with a mortality of 5% to 10%. The outcome of surgical therapy usually depends on the degree of underlying lung disease (Bindschadler '89: 112-113). The only oral antifungal drug indicated for the treatment of *Aspergillis* spp.is sporanox (itraconazole) but the price can be prohibitive and the adverse drug interactions with high blood pressure medicine and congestive heart failure are disconcerting. There is also the oral suspension posconazole, but this costs more than $600 a bottle (dose?) because it is the preferred primary prophylaxis for leukemia and myeloma, before or after standard antineoplastic treatment, although itraconazole is also indicated. In practice athletes foot crème (clotrimazole) which can be purchased for $1 is the only antifungal readily available to consumers (Avoid the antifungal foot spray (toftate) as it causes diffuse pain and angina pectoris).

In the sixteenth century, the Archbishop of St. Andrew in Scotland invited the acclaimed Italian physician Gerolamo Cardano to his country for advice on treating his asthma. Cardano's diagnosis was simple and astute: the problem was the bed, and he recommended that the Archbishop get rid of his feather bedding. The result? A "miraculous" recovery. Some 400 years later, in 1927 Storm van Leeuwen created a "climate" chamber in the Netherlands to make a similar point. He successfully showed that asthmatic patients improved when moved from their homes into the chamber. Cardano and Van Leuwen came upon the truth that if you want relief from allergies or asthma, you need to get rid of the triggers in the home. Studies have found that the average six-room home in the United Sates collects 40 pounds of dust each year. **Dust** is composed of flakes of dead skin, pet hair and dander, breakdown of fabrics, debris blown in from outside, and so on. Dust may also contain cockroach dropping, another potent allergy trigger. The problem with dust is that it provides a regular supply of food for **dust mites**. These microscopic bugs are literally everywhere in your home They are a major source of allergies, with about 10 percent of the population and 90 percent of people with allergic asthma having positive skin tests to dust mites. Those figures are even higher in children, with recent studies suggesting that at least 45 percent of kids are allergic to dust mites. There may be as many as 19,000 dust mites in 1 gram of dust. Each female can add 25 to 30 mites to the population before she dies. These tiny creatures thrive in warm, humid conditions, when the relative humidity is 75 to 80 percent and the temperature at least 70° F. Reduce the humidity to reduce the mites, since they can't survive in humidity of less than 40 to 50 percent. One study found that reducing levels of dust mites in children's beds by one-third cut the number of days they wheezed and missed school by nearly a quarter (22 percent). The best way to kill mites is washing in very hot water (at least 130°F) At least once a week. Dust with damp cloths and dust everything. Use a vacuum cleaner with either a double-layered microfiltration bag or a HEPA filter to trap allergens that pass through the vacuums's exhaust. Change home air filters. A study published in the Journal of Allergy and Clinical Immunology found that when **eucalyptus oil** was used to presoak loads of bedclothes, it killed 95 percent of mites that survived high-temperature water. The research mixed 1 part liquid detergent and 4 parts eucalyptus oil in a small container, then added 1 teaspoon of the mixture to an 8-ounce gallon of water. They fill the washer with water, added the diluted detergent and eucalyptus mixture and let the bedding soak for an hour before washing (Berger & Gordon '04: 125, 127, 129).

Cockroach droppings are one of the top two causes of perennial allergies, plus they carry mites and diseases, such as dysentery, hepatitis, salmonella and typhus. Cockroaches eat everything. Cockroaches carefully taste their food. Interestingly they despise okra, raw or stewed, so putting a dish of the green pods in cabinets that have roach problems may send them scurrying for sweeter pastures. **Hot tub lung disease** caused by *Mycobacterium avium complex* (MAC) thrives in the warm, moist environment of an indoor spa. MAC accumulates inside a tub hitches a ride on the air-jet bubbles, which are the perfect size t be inhaled into the lungs. Chlorine doesn't work at temperatures higher than 84°F. Outdoor spas aren't affected because sunshine kills MAC and fresh air harmlessly dissipates it. At least 60 species of molds have spores thought to be allergenic and 30 percent of people with respiratory allergies seem to be particularly sensitive to molds, with children appearing to be most sensitive. The best mold remover is merely 1 part bleach and 10 parts water, or about 1 ½ cups bleach to 1 gallon of water. Trash moldy foods, even if the mold is on one tiny corner. The link between gastro-esophageal reflux disease (GERD) and asthma is pretty clear, with as many as 70 percent of people with asthma also suffering from GERD. You could go the medication route with antacids and proton pump inhibitors such as omeprazole (Prilosec) and esomeprazole (Nexium). Essentially, small meals that are rich in vegetables and include modest servings of complex carbs and lean protein are usually best. (Berger & Gordon '04: 130, 136, 138, 142). The term **sick building syndrome** refers to situations in which specific health complaints appear to be linked to the building in which you work or live but for which no specific illness or cause can be identified. Volatile organic compounds, carbon monoxide, inadequate ventilation, outdoor chemical contaminants, biological contaminants and climate control are issues. Mold is a fungus of which there are thought to be more than 1.5 million species. Less than 100 are known to be infectious in humans or animals. It is estimate that 70 percent of homes have mold growing in their walls. *Stachybotrys chartarum* is a much-feared mold but there is little evidence that it causes the neurological problems and other health affects attributed to it. Many respiratory illnesses among workers are attributed to mold exposure, such as hypersensitivity pneumonitis (also called farmer's lung, woodworkers' lung and malt worker's lung. Whether residential molds cause bleeding in the lungs (pulmonary hemorrhage, memory loss or lethargy, is unproven and unknown (Berger & Gordon '04: 271).

Air quality has improved since the passage of the Clean Air Act of 1970. However in May 2003 the American Lung Association reported that because3 the government doesn't fully enforce clean air laws, more than half of all Americans breathe polluted air that damages their health. According to the association, more than 7.4 million adults with asthma and nearly 2 million children suffering from asthma attacks live in counties that received an F grade in ozone air pollution. This represents 70 percent of the 10.6 million American adults with asthma and 69 percent of the 2.8 million children who have had an asthma attack and live in counties with an ozone monitor. Fully enforcing the standards of the Clean Air Act, the Lung Association notes would prevent 15,000 premature deaths, 350,000 cases of asthma and 1 million cases of decreased lung function in children. Specific outdoor air related asthma triggers include ozone, particular matter such as dirt soil dust, pollens, molds ashes and soot and indoor air pollution such as smoke and fumes and animal dander, cockroaches, dust mites, molds and fungi. 59 The American Lung Association ranks the following geographic areas as having the most polluted air in the country (1) Los Angeles/Riverside/Oreange County, California (2) Bakersfield/Fresno/Visalia/Tulare/Porterville, California (3) Houston/Galveston/Brazoria, Texas (4) Atlanta, Georgia (5) Merced, California (6) Knoxvillle, Tennessee (7) Charlotte, North Carolina and Rockville, South Carolina (8) Sacramento, California. The cleanest big cities

include Bellingham, Washington, Colorado Springs, Colorado, and Lincoln, Nebraska (Berger & Gordon '04: 58).

Exposure to noise represents the single most common exposure in the workplace. It has been estimated that 20 million persons in the United States (14% of the working population) are exposed to noise intensities sufficient to cause **hearing loss**. Continuous sound with intensity greater than 90 dB can cause injury to the cochlear hair cells and the U.S. Occupational Safety and Health Administration (OSHA) defines any exposure greater than 90 dB during an 8 hour workday as dangerous and requiring earplugs, earmuffs or ear canal caps. Long-term noise exposure tends to cause sensorineural hearing loss to one or both ears. A sudden blast can cause an immediate change in hearing thresholds. Injury may occur to the tympanic membrane, ossicles, oval and round windows and labyrinthine membranes. Symptoms include pain, bloody otorrhea, vertigo and tinnitus. **Barotrauma** is related to changes in atmospheric or gaseous pressures to which the ears and paranasal sinuses are susceptible. Mucosal edema and bleeding impair drainage of secretions and cause pain and dysfunction. Barotrauma commonly affects drivers, workers exposed to compression blasts (miners, tunnelers), and aviation crews exposed to rapid ascent or descent in unpressurized cabins. Perforation of the tympanic membrane is a common injury. The sinuses are prone to injury if the ostia are obstructed. (Wynn & Goldman '04: 449, 450).

The nose, paranasal sinuses and upper aerodigestive tract are prone to inhalation injury because they serve as filters for the entire airway. Particles 4 to 11 gm in diameter tend to deposit in the nose, pharynx and larynx, smaller particles pass through on their way to the lungs. Nickel, wood dust, asbestos, chromium, formaldehyde, cutting oils and wood smoke are known or suspected work related carcinogens of the upper respiratory tract. The most common occupational injury to the upper airway is development of mucositis (rhinitis, pharyngitis, or sinusitis). Exposure can very from particulate matter (flour in bakeries, wood shavings, dust) to chemical irritants. Mycositis may have an allergic component depending on the patient and the temporal nature o the symptoms. The largest occupational hazard involving the larynx is the development of laryngitis related to vocal chord trauma resulting from yelling or straining while speaking which causes the development of vocal chord polyps. Training in breathing techniques and proper use of the voice are important in the management and prevention of laryngeal disease for people who use their voices professionally (Wynn & Goldman '04: 450-452).

Nicotiana tabacum (tobacco) is considered harmful to all lung conditions, however *Cannabis sativa* (marijuana), *Datura stramonium* (Jimson weed), as well as *D. metel* and *D. fastuosa* can be smoked for the relief of asthma. *Verbascum thapsus* (mullein) can also be smoked for pulmonary ailments and is specifically indicated for bronchiolitis. Bronchodilators relax the smooth muscles of the bronchioles that lead to the air cells, thereby diminishing generalized peripheral airway obstruction (Elvin-Lewis ’77: 297, 298). Although smoking mullein is not highly recommended for non-smoker it is a highly recommend substitute for tobacco when respiratory conditions don’t tolerate tobacco, smoking mullein even seems to be beneficial to lung health, and is non-addictive although it is milding neurologically stimulating. Stopping smoking tobacco is probably the most important step that smokers can take to improve their health, and it is never too late to quit. Smoking is linked to premature heart and blood vessel disease, cancer and lung disease. No matter how long a person has smoked, stopping has positive effects. For most who cough up sputum daily, stopping smoking will decrease the frequency of coughing and will cut down the amount of phlegm which has to be coughed up daily. Frequency of respiratory infections and allergies should also decrease when quitting.

Cigarette smoke does damage as a direct irritant of the bronchial tubes and can increase attacks of wheezing, leading to increase shortness of breath and exacerbations of COPD. Smoke also damages the lining of the nose and the sinuses. Continuous nasal drainage, postnasal drip, persistent or recurrent sinusitis, are all caused or worsened by smoking. Nasal and sinus problems may make the lung problems worse as mucus drains down the back of the throat, causes cough and aggravates wheezing. What smokers often call allergies or colds are actually irritations due to smoke exposure, on the other hand tobacco smoke is only considered an allergen by around 45% of allergic rhinitis sufferers. A main pollutant in cigarette smoke is carbon monoxide (CO). It is different from carbon dioxide (CO_2) produced by the body. When carbon monoxide enters the blood, it competes with oxygen preventing oxygen molecules form entering the blood. Smokers frequently have seven to eleven percent of their hemoglobin attached to carbon monoxide. Death in fire by suffocation occurs when carbon monoxide is attached to over 40% of the hemoglobin. Particularly in men, smoking prevents normal sexual performance. The blood vessels in the penis may not fill normally with extra blood and a normal erection may not occur (Tucker et al '01: 106).

The greatest hazard resulting from asbestos is that it is linked to smoking exposure in causing an **increased risk of bronchogenic cancer**. The risk is almost totally confined to those who are also exposed to cigarette smoke. Smokers who have not been exposed to asbestos have approximately a 12-fold greater risk of developing bronchogenic cancer than do non-asbestos-exposed nonsmokers. Those who have been exposed to both have a 50-fold to 90-fold increase. It is estimated that between 2% and 2.5% of the 150,000 lung cancer cases now occurring annually in the United States may be asbestos-related (Mitchell '89: 340-344). Lung function is gradually lost as the healthy, non-smoking person ages, but will probably not become a cause of disability or death. A susceptible smoker experiences a more rapid rate of decline. Smoking progressively reduces lung capacity, and this reduction is added to the normal loss of aging. Disability happens when lung function reaches about 30 percent and death happens when lung function is about 10 percent of normal. In those who stop smoking at age 45, the lung function tends to be lost at the slower rate of decline of the normal person, although the damage that has been done remains. The longer a person continues to smoke, the greater the damage, however even stopping at 65 provides the potential of survival benefit and better quality of life. The sooner one stops, the better the chance to retain lung function. The financial benefits of stopping smoking are significant. The cost of one pack of cigarettes in 1998 ranged from $1.50 to $2.00 in the US, $45-60 a month at one pack a day. The US Congress wanted to increase the tax on each packet of cigarettes by $0.75 to $1.00 (Tucker et al '01: 107). It passed.

When **quitting smoking**, one may gain weight. Average **weight gain** is about five to seven pounds, although this can vary, but less than one smoker out of thirty who quits gains more than 20 pounds. Two main reasons for the weight gain are: taste improves and metabolism changes. Cigarette smoke damages the taste buds just as it damages other parts of the body. Nicotine speeds up your metabolism so that as a smoker you can eat more calories without weight gain. Smokers almost universally feel guilty about continuing to smoke. Nicotine is an addicting substance. In spite of what the tobacco companies say, smoking meets the World Health Organization definition for addiction and dependence. This definition states that drug dependence is a psychological and sometimes physical state which results from interaction between the body and a drug. Cigarettes contain as many as 4,000 chemicals besides nicotine. But we know more about nicotine. Nicotine actually sets up the brain to continuously crave more nicotine. Addicted smokers may wake in the night wanting a cigarette so badly that they will stumble to a store through a dangerous neighborhood to get one. Some patients with COPD

will remove their oxygen in order to smoke, or worse, smoke through a tracheostomy, a hole in the windpipe created to help breathing in special circumstances. In spite of dirty looks, condescending comments from coworkers, the smoker stands outside in below-freezing weather to have a cigarette. The addicted smoker is willing to risk slower professional advancement and a second class citizen status in order to smoke. Over 75% of smokers say they would like to quit and two out of three have made at least one serious attempts to quit. Most smokers trying to quit are irritable and nervous. They may try to substitute food for the cigarette and eat constantly. Often smokers who try to quit experience a desire for a cigarette so intense that they have trouble concentrating on anything else. Nicotine replacement may not help the desire for a cigarette, this is one reason that quitting is so difficult in spite of a strong desire to stop. Inhaled nicotine also has positive effects. Nicotine improves performance of some tasks and increases alertness. It can cause euphoria, a feeling that everything's going well. It reduces mild depression and anxiety. Many people turn to smoking in response to stress or conflict. It is important to recognize that these are underlying factors and deal with them openly. Social acceptance and peer pressure encourage smoking. The tobacco companies have taken advantage of this by targeting youngsters. They show smoking as an assertion of independence form adults, and as a factor for acceptance in a group. There is a disproportionate number of African-American people with smoking-related disease (Tucker et al '01: 108, 109).

Some smokers do quit permanently. For most folks it is not easy. Studies of large groups of smokers have identified four stages of quitting. State 1 is pre-contemplation and includes people who have not decided to quit smoking within the next six months. These people are very unlikely to quit. Stage 2 is contemplation and includes people who intend to quit within the next six months, but have not yet started to do so. Stage 3 is action, most ex-smokers come from this group. Stage 4 is maintenance, after more than six months of not smoking. If you slop and start smoking again you are back to Stage 1. If you slip but intend to quit within the next month, then you're back to Stage 2. You must first make up your mind that you really want to quit, then do it. If you don't really want to quit, no method will succeed. Less than five people out of one hundred who've decided to quit can do so on the first try. Most ex-smokers make a serious effort to quit at least three to four times before they get off cigarettes for good. There are many types of programs to help you stop smoking, but the simplest is your own decision to put the cigarette down and never pick up another. If a recommendation to quit comes from the doctor, quitting levels are slightly better but still very poor. Other methods include behavior modification, pharmacologic methods and acupuncture. One approach to behavior modification is to try to get you to see smoking as a very negative habit. Another approach is to try to convince you of the highly positive medical and social effects of being an ex-smoker. Most program combine both approaches. Almost everyone who has been diagnosed with chronic illness goes through nine stages of acceptance or denial, action or inaction, related to the illness. Those stages are (1) grief, (2) denial, (3) rage, (4) self-pity, (5) depression, (6) fear, (7) frustration, (8) resignation or acceptance and (9) choosing life over death (Tucker et al '01: 109, 112, 9).

Drugs such as lobeline sulfate, available without prescription, do not have improved quitting statistics. **Nicotine gum and nicotine patch** studies show greater success rates than placebos (substance with no effects). These medications no longer require a prescription in the US. One problem with nicotine-replacement methods is insufficient nicotine uptake. The intent is that enough medication is given to achieve about one-half as much nicotine in the system as through through smoking. The antidepressants **bupropion** HCL (Zyban) and bupropion (Wellbutrin), has been helpful for many people. It doesn't contain nicotine, is in pill form, and can be

purchased online without prescription from Generics-discount.com. According to a report in the New England Journal of Medicine (March 4, 1999, Vol 340 No.9), very good results were obtained in a controlled clinical trial. The percentages of people who continued to abstain from smoking a year after treatment were 30 percent of those who had used sustained release bupropion, and 35.5 percent for those who had used bupropion and the nicotine patch together, compared with 15.6 percent of those who used a placebo and 16.4 percent of those who used on the nicotine patch. In the US patches cost about $3.00 each in 1998, $270 to $360 for an average course. Expect to chew twelve to sixteen pieces a day for the first several weeks. After that, gradually decrease the amount chewed, but eight or more pieces a day are likely to be needed at the third or fourth month. Gum should be available for stressful situations for at least six months after the last cigarette. If not successful alone, get into a community program (Tucker et al '01: 111, 112, 113).

Mathieu J.B. Orfila (1787-1853) is known as the "father of toxicology" and is credited with establishing many of the basic principles of toxicology and is probably the first person to have conducted experiments on the effects of poisons, using dogs and other animals for his research (Newton '07). Humans can tolerate only 5 minutes of oxygen (O_2) deprivation without irreversible damage and death. The motto of the American Lung Association is "if you can't breathe, nothing else matters®" (Brugman & Irvin '89: 1, 2). Plant's relating to man's health fall into three categories: those which injure, those which heal and nourish, and those which alter the conscious mind. Cromolynm the miraculous prophylactic drug for asthma, has only recently been introduced, though its use in the form of Ammi sees was part of Bedouin fold medicine for centuries. In various environments there are found hundreds of plants that are injurious if ingested and are capable of causing any number of symptoms, including death. People in rural settings, of course, are exposed to nature's lethal organisms every day, but even those in more urban areas must be wary of garden and house plants. Few realize, for example, that apple seeds contain cyanide, which may be lethal in large doses; that the alkaloid taxine from the common English yew is rapidly absorbed and causes sudden death; that the leaves and twigs of boxwood, so common as a hedging plant, produce another alkaloid, buxine, which contributes to respiratory failure in humans and domestic animals; that children using peashooters made of elderberry stems may be poisoned from exposure to this plant's alkaloids and cyanide; and that eating green and sprouting parts of potatoes may cause severe poisoning. Likewise, common house plants such as oleanders, caladiums, and philodendrons must be avoided, for a person ingesting the leaves of oleander, or its sweet nectar, may develop severe vomiting, irregular heartbeat, and respiratory paralysis, followed by death. Hay fever and dermatitis result from an abnormality of our immune system known as allergy. The abundant grasses, trees, weeds and fungi in our environment produce pollen, spores and other materials to which we become sensitized so that on reexposure they cause discomfort Primeval man in search of food undoubtedly experienced much poisoning. He learned by trial and error that eating certain mushrooms, berries, and roots could produce various degrees of gastrointestinal discomfort or death, whereas others could be ingested safely. Certain lessons were learned quickly, and primitive, food gathering man soon became a toxicologist of no mean ability. This knowledge became useful, he prepared arrow poisons from plant extracts to bring down his game or foe, he threw crushed leaves of particular plants into water and with little effort quickly obtained a bountiful supply of stupefied fish, and he learned also wash poison (e.g. cyanide) from a number of common, staple foods to make them edible (Elvin-Lewis '77: vii-viii, 4-5, 11).

The major poisonous principles found among plants are organic compounds, such as alkaloids, diterpenes, cardiac and cyanogenic glycosides, notri-containing compounds, oxalates, resins ,and

certain proteins and/or amino acids. Alkaloids are a heterogeneous group of thousands of different compounds. Distribution of most alkaloids in higher plants is highest in Apocynaceae, Berberidaceae, Fabaceae, Papaveraceae, Panunculaceae, Rubiaceae, and Solanaceae whereas Lamiaceae, Rosaceae, and Gymnosperms are almost alkaloid-free. Glycosides yield one or more sugars (glylcone) and one or more other compounds (aglycones) on hydrolysis. Toxicity is commonly associated with aglycone moiety of these compounds. Cyanogenic glycosides yield hydrocyanic acid (HCN) as one produce of hydrolysis. The most widely distributed of these is amygdalin, which is commonly found in the Rosacea (rose family). Amygdalin is found in large quantities in seeds of apples and pears and in the stony seeds, bark and leaves of apricots, bitter almonds, wild and domestic cherries, peaches, and plums. In the hydrolysis of amygdalin, a two step process, two molecules of glucose are released, the first caused by the enzyme amygdalase, the second by prunase. Free hydrocyanic acid is the violently toxic end product of hydrolysis. The severity of poisoning from cyanide in plants depends on how much free HCN and/or cyanogenic glycoside exists in the plant. Hydrocyanic acid inhibits the action of the enzyme cytochrome oxidase, the terminal respiratory catalyst linking atmospheric oxygen with metabolic respiration. HCN poisoning is asphyxiation at the cellular level. As little as 0.06 g has caused death in man, and the largest known dose from which a person has been known to recover is 0.15 g. Some important toxic plants having cyanogenic glycosides are: *Chenopodiaceae; Suckley. Passifloraceae; Adenia. Passiflora; Euphorbiaceae. Manihot, Stillingia; Rosaceae. Cercocarpus, Cotoneaster, Eriobotrya, Malus, Prunus, Pyrus, Rhodotypos; Fabaceae. Acacia, Cassia, Dolichos, Lotus, Phaseolus, Trifolium, Vicia; Saxifragaceae. Hudrangea; Murtaceae. Eucalyptus; Linaceae. Linum; Olacaceae. Ximenia; Caprifoliaceae. Sambucus; Bignoniaceae. Crescentia; Asteraceae. Ageratum, Bahia, Florstina; Angiosperms: Monocotyledons. Juncaginaceae. Triglochin; Poaceae. Cynodon, Glyceria, Locus, Panicum, Sorghum, Zea*. *Atropa belladonna* (belladonna, deadly nightshade) roots and leaves contain L-hyoscyamine, hyoscyamine (atropine) and scopolamine (roots also include apoatropine, belladonnine, and cuscohygrine) and these alkaloids in overdose can be fatal to man. The main symptoms are flushed skin, dilated pupils, dry mouth, delirium and death from respiratory failure. *Nicotiana tabacum* (tobacco) contain the toxic alkaloid nicotine, which causes vomiting and diarrhea, slow pulse, collapse, and respiratory failure. Deaths from eating the leaves as boiled greens are known and livestock have also died following ingestion of the plant. All species of *Nictiana* contain nicotine (e.g.) *N. alata* of South America, *N. attenuate* and *N. quadrivalvis* of western United States, *N. rustica* of Mexico, and *N. trigonophylla* of the southwestern United States and Mexico and all "wild" tobaccos that have been smoked by native populations (Elvin-Lewis '77: 13,14, 17, 18, 52-57). Narcotic overdose causes respiratory depression and death. Opioid overdoses have increased exponentially since fentanyl and cofentanyl entered the scene. Narcotic antagonists prevent or abolish excessive respiratory depression caused by the administration of morphine or related compounds. Naltrexone (Narcan) became clinically available in 1985. Its actions resemble those of naloxone, but naltrexone is well is well absorbed orally and is long acting, necessitating only a dose of 50 to 100 mg. Narcotic antagonists must be made available as rescue medicine with opioid prescriptions.

An increasing number of drugs are known to be nephrotoxic. First reported after the use of sulfonamides, acute tubulointerstitial nephritis and renal papillary necrosis most frequently occurs with synthetic penicillins (methicillin, ampicillin) other synthetic antibiotics (rifampin), diuretics (thiazides), allopurinol, cimetidine, aristolochic acid found in some herbal remedies, NSAIDs, analgesics mixtures including phenacetin, aspirin, caffeine, acetaminophen and codeine. Selective COX-2 inhibitors, while sparing the gastrointestinal tract, affect the kidneys. Acute uric acid nephropathy can be caused by the precipitation of uric acid crystals in the renal

tubes particularly in individuals with leukemias and lymphomas who are undergoing chemotherapy whereas the drugs induce death of tumor cels and uric acid is produced as relased nucleic acids are broken down. Gouty nephropathy is often precipitated by the consumption of moonshine whiskey contaminated with lead. Papillary necrosis is readily induced experimentally by a mixture of aspirin and phenacetin, usually combined with water depletion. The disease begins about 15 days (2-40) after exposure to the drug and characterized by fever, eosinophilia, a rash in 25% of patients and renal abnormalities in the form of hematuria, mild proteinuria and leukocyturia (often including eosinophils). A rising serum creatinine level or acute renal failure with oliguria develops in about 50% of cases, particularly older patients. Withdrawal from the offending drug is followed by recovery, although it may take several month, and irreversible damage occurs occasionally in older subjects. While drugs are the leading cause of acute interstitial nephritis in 30-40% of patients no offending drug or mechanism can be found. Urinary tract infections complicate 50% of cases (Alper '10: 944-946).

Formulated in 1973 and modified in 1986 and 1993 the contemporary view of the pathogenesis of atherosclerosis is called the **response to injury hypothesis**. The injury postulated is a form of endothelial dysfunction without necessary denudation, which increases permeability to plasma constituents, including lipids, and permits blood monocytes and eventually platelets to adhere to endothelium. Monocytes adhere and subsequently enter the intima, transform into macrophages and accumulate lipid to become foam cells, contributing to the evolution of the lesion. Single or short lived injurious events can be followed by restoration of endothelial function and regression of the lesion. Repeated or chronic injury, however, results in the development of an atheromatous plaque. Endothelial injury has been induced in experimental animals by mechanical denudation, hemodynamic forces (AV fistula), immune complex deposition, irradiation, and chemicals to cause intimal smooth muscle proliferation and in the presence of high-lipid diets, typical atheromas and ischemia (Schoen ’94: 480).

American scientists, at medical campuses, tend to induce ischemia in laboratory animals without disclosing the name of the prohibited toxin in the journal articles it takes to get a full keg of mental retardation (Down's syndrome is best treated as congenital hyperlipidemia, with vegan diet and Special Olympic level athletics), like equally accident prone European scientists who cite their source. Besides being a sedentary activity computers, televisions and microwaves emit a small amount of radiation which has been regulated by the FDA Office of Medical Devices and Radiological Health to be harmless. CD-ROM drives on computers emit a lot more radiation about 1 mSv and can be hi-jacked and sabotaged to emit even more radiation, about 10 mSv and hour, enough to trigger the 100 milliSievert (mSv) threshold of cardio-sensitivity to radiation sickness, by the deadline, 1 Sv of radiation or greater is enough to induce vomiting, and neoplastic infection of irradiated necrosis becomes likely, although tumors are very rare in the heart. Radioactive ore can be cardiosensitive to the touch and radioactive waste or long exposure to any cardio-reactive material or over-exposure to radiation at levels emitted by old-fashioned x-ray machines and some newer diagnostic tests and radiation treatment are definitely cardio-toxic and can be sensed as angina pectoris from necrotic cardiovascular tissue and exposure limited before reaching carcinogenic levels of tissue damage (Sanders '11). Cardio-toxic insult, caused by specific bacteria, radioactive or chemical compounds, can cause sudden cardiac death if exposure is not ceased before reaching a lethal dose, but is more likely to be administered to cause constant pain and heightened risk of death fueling demand for expensive medical treatment and surgery. Hygiene, new wardrobes, scrubs, beds, carpets, fabrics, friends and houses are in order but camping gear may be necessary to dodge the draft and be pain free. Besides the risk of sudden death detection can be complicated by lasting roughening, hardening, of the arteries due

to lesions and scars, which lipids stick to, forming painful atheromatous plaques, prone to infection, that can cause myocardial infarction if the occlusion of the coronary artery nears or reaches stenosis, which causes a spreading necrosis of ischemic myocardial and vascular tissue, known as a heart attack, or heart attack scar, prone to infection, all of which lead to a long lasting, lifetime, painful and life-threatening allergy to all animal products known as **hyperlipidemia**.

Over 10,000 different poisons are known, but only a small number of these substances are likely to be involved in some kind of criminal activity with which a forensic toxicologist has to deal. Examples of those poisons are arsenic, strychnine, atropine and cyanide. Poisons that cause angina pectoris in sublethal doses are known **cardiac glycosides**. Over 400 cardiac glycosides have been identified. Poisons are often divided into two general categories; inorganic substances and organic substances. Some examples of inorganic poisons are the compounds of metals and semimetals such as antimony, arsenic, barium, cadmium, copper and iron. Some common organic poisons are the carbamate pesticides, digoxin and digitoxin, the organophosphorus pesticides, nicotine and strychnine. The major poisonous principles found among plants are organic compounds, such as alkaloids, diterpenes, cardiac and cyanogenic glycosides, notri-containing compounds, oxalates, resins, and certain proteins and/or amino acids. Alkaloids are a heterogeneous group of thousands of different compounds. Distribution of most alkaloids in higher plants is highest in Apocynaceae, Berberidaceae, Fabaceae, Papaveraceae, Panunculaceae, Rubiaceae, and Solanaceae whereas Lamiaceae, Rosaceae, and Gymnosperms are almost alkaloid-free. Glycosides yield one or more sugars (glylcone) and one or more other compounds (aglycones) on hydrolysis. Toxicity is commonly associated with aglycone moiety of these compounds. The **cardioactive glycosides** are characterized by their specific action on the cardiac muscle. The aglycones are steroidal (Elvin'Lewis '77: 13, 14). The IPCSINTOX database published by the International Programme on Chemical Safety of the United Nations Environment Programme lists 113 different poisons with methods for testing that are, in most cases, unique to a specific poison. Only a few tests can provide unequivocal evidence of the presence of a specific chemical compound in a test sample. The most popular method now used for confirming the presence of a specific compound in a sample being tested uses a combination of two tests familiar to many high school chemistry students: gas chromatography (GC) and mass spectrometry (MS). The two tests are carried out in tandem to identify compounds present in a sample (Newton '07: 89, 90).

Chromatography is a method for separating a mixture into its component parts. When a mixture of substances is passed over a fixed base the individual substance in that mixture have varying tendencies to adhere to that base. After the mixture has passed over the bas, the components of which it is made are deposited at different positions on the base. The base can then be analyzed to determine what each of the components of the mixture is. In gas chromatography, the substance to be analyzed is first vaporized and mixed with an inert gas. The two gases most commonly used in this process are nitrogen and helium. The carrier gas and the sample to be tested are then passed through a gas column. A thin layer of some material is deposited on the inside of the column. As the carrier gas and dissolved sample pass through the glass tube, the components of the sample are attracted in varying degrees to the material in the thin layer. Those most attracted to the thin layer will be deposited near the top of the tube, while those less strongly attracted will be carried farther down the column before they are deposited on the inside of the tube. As the carrier gas flows out the bottom of the tube and exits, a sensing device detects the individual components of the mixture. The detector then converts the information to an electrical signal that can be registered by the recorder as a graph showing the

concentration of various substances detected over a period of time. The recording, known as a chromatogram, provides a visual record of the number and type of components present in the original sample. The tester identifies the components obtained in any given experiment by comparing the chromatogram with a library of chromatograms for many different substances. Gas chromatography is sensitive, it is capable of detecting material at nanogram (10^{-9}g) levels. Chromatograms for two or more substances may be so similar that it is impossible to tell which of the substances is present in any given case. When gas cromatography is paired with mass spectrometry, however, this disadvantage is overcome. The **mass spectrograph**, first invented in 1919, is based on the principle that the path taken by a charged particle moving through a magnetic field is dependent on the electrical charge (e) and the mass (m) of that particle. As the components obtained from gas chromatography enter the spectrometer, they are bombarded by electrons, a process that results in the loss of a single electron fro each of the molecules present in the mixture. The molecules then become positively charged ions and can be represntd by the expression e/m where e is the same for all molecules and m is unique for every molecule of the type likely to be encountered in this analysis. Each type of molecule will follow slightly different path depending on its own value of e/m. A detector placed at the back of the spectrometer detects the specific path taken by each type of molecule that enters the instrument (Newton '07: 89-97).

Many different genera of the Apocynaceae family have compounds having digitalislike action on the heart and circulation. **Cardioactive glycosides** are not restricted to the Apocynaceae, in fact, the most widely used cardiac glycosides used in medicine today are found int eh disparate genus Digitalis of the Scrophulariaceae. It is logical that the cardioactive glycosides of the Lilliaceae arose independently of those found in the Aponcynaceae and Scrophulariaceae. As many as **400 cardiac glycosides** have been characterized, most from the Apocynaceae (Acokanthera, Apocynum, Nerium, Strophanthus, Tanghinia, thevetia), Aslepiadaceae (Asclepias, Calotropis), Liliaceae (Bowiea, Convallaria, Urginea), Moraceae (Antiaris), Ranunculaceae (Adonis, Helleborus), and Scrophulariaceae (Digitalis, Scrophularia). *Helleborus foetidus*, *H. niger* (Christmas rose) and *H. viridis* all contain cardiac glycosides that cause violent purging, delirium, convulsions and death from respiratory failure. The main cardiac stimulant is hellebrin. Moraceae (Mulberry) *Antiaris toxicaria* (upas tree) latex containing two cardioactive glycosides antiarin x and z, is extremely toxic and is used in tropical Asia as a principal poison for arrows and darts. It was used as an instrument of execution in Java in 1776 to punish 13 concubines of the king who were convicted of infidelity. All died within five minutes of being pierced with a poisoned awl, in great agony. *Sesbania* spp. (coffeebean, rattlebox, sesbane) seeds contain saponins that result in diarrhea, rapid pulse, respiratory failure, and even death. Flowers are also poisonous (Elvin'Lewis '77: 13, 14, 18, 31, 45).

Phylogenetic Group 11 Lobaniaceae (Logania) produce *Strychnos nux-vomica* (strychnine tree) and *S. ignatii* (poison nut) of tropical Asia, the dried seeds yield the indole alkaloids strychnine and brucine, which are the main toxic constituents. All parts of the plants including the flowers contain strychnine, which is extremely toxic and fatal to man at doses from 60 to 90 mg. *Strophantus* spp. seed extracts, containing the cardiotonic agent strophanthin are used in modern medicine when immediate relief from heart failure is needed. *Tanghinia venenifera* (Tanghin) of Madagascar seeds are notoriously poisonous, they contain tanghin, a cardiac glycoside characterized by digitalislike activity. The seeds have a long history as an ordeal poson for judgments of all kinds of crimes from murder, conspiracy and witch doctor, to stealing or for settling a debt. Forced to drink a draft or be killed by a soldier's spear, the accused was judged innocent by the ruling regime if he wallowed in a gulp and promptly vomited, but if afraid, he

would sip slowly and die almost immediately. Guilt, of course, was predetermined, and since death was related to the strength of the extract, the judge could decide well in advance which way he wanted the trial to go. Such ordeals became infamous and the French, who colonized the island destroyed all the tanghin trees they could find. *Thevetia peruviana* (yellow oleander) contains the cardiac glycosides cerbrin, neriifolin, and thevetin, which produce symptoms similar to those of fatal digitalis poisoning. All parts of the plant are dangerous, and most fatalities are the result of misuse of decoctions in folk medicine. *Urechites* spp. (yellow nightshade) seed pods eaten in quantity will cause heart failure (Elvin-Lewis '77).

Asclepiadeaceae (milkweed) *Asclepias* spp. (milkweeds) are dangerous to cattle, the cardiac glycosides known to be present in almost all species of the genus result in severe poisoning not only to livestock but to man. *Calotropic procera* (giant milkweed) latex, containing the cardiac glycoside calotropin, is extremely potent and is used on arrows in Africa. Minute amounts are said to produce death. It has also been used for murders and suicides in tropical America. Scrophulariaceae (Snapdragon) *Digitalis purpurea* (foxglove) are a source of cardiac glycosides used in controlled does for treatment of heart disease, poisoning can result from overdose of medication or when children eat the seeds or leaves, or such the flowers. Symptoms include vomiting and purging, severe headache, irregular heartbeat and pulse, convulsion and death, which occurs suddenly. Solanaceae (Potato) green shoots are highly toxic. Phylogenetic Group 15 Liliaceae (Lily): *Ornithogalum umbellatum* (star of Bethlehem) contains cardiac glycosides, which can cause nausea and gastroenteritis. *Veratrum* spp (false hellebore) contains many alkaloids, with major effects on the heart and vessels. Blood pressue is lowered, arterioles are dilated, and a general cardiac depressant effect is caused by these alkaloids. Most cases of poisoning have been through misuse of medical preparations (Elvin-Lewis ’77: 52-57, 60-62).

Cardiac and hyptertensive drugs are the second leading cause of fatal drug overdose (Bronstein '12) and are often abused (Moore '98). There is no denying that antihypertensive drugs developed in the 1950s from the Ayurvedic schizophrenia remedy *Rauwolfia serpentine* and the diuretic hydrochlorothiazide (HCTZ) have brought malignant hypertension, a formerly fatal disease of the kidney causing hypertrophy of the left ventricle, under control. The ABC of adrenergenic blockers developed in the 1970s, although they are competitive with Rauwolfia for the treatment of high blood pressure and dominate academic literature, seem to be mis-prescribed as medicine for the life threatening conditions of arrhythmia and congestive heart failure. The one year survival rate for people with congestive heart failure treated with adrenergenic drugs was worse than untreated people (Heger et al '04). It must be made clear that the fact that a drug is an essential medicine for treating essential hypertension of the kidneys does not make it an essential medicine for the treatment of heart failure, arrhythmia, angina or endocarditis and in fact all hypertension medicines tend to cause brachycardia and other cardio-toxic side-effects, although they might help with some acute cases of atrial flutter, they should not be taken regularly by anyone without high blood pressure, and don't even treat the underlying kidney infection or post-infectious malabsorption due to Bactrim consumption. For congestive heart failure the only prescription medicines indicated are (1) nitrates and nitrites can provide relief in 5 minutes in some patients and (2) *Digitalis* spp. preparations, sold as Digitoxin (Crystodigin), Digoxin (Lanoxin), not exactly the organic toxins digoxin and digitoxin, that work by increasing the force with which the heart pushes blood to compensate for low ejection fraction in congestive heart failure, but is not highly recommended by cardiologists and discontinued by 20% of patients, nor considered an essential medicine in the literature and the FDA requires labels state, "Digitalis alone or with other drugs has been used in the treatment of obesity. This use of digoxin or other digitalis glycosides is unwarranted. Moreover, since they may cause potentially fatal

arrhythmias or other adverse effects, the use of these drugs in the treatment of obesity is dangerous" 21CFR§201.317. Statin drugs have been found to prolong life and are highly useful in treating the accumulation of atheromatous plaque that cause the vast majority of congestive heart failure, infection, arrhythmia and heart disease. **Hawthorne** is, in fact, the supreme herb for the heart, and seems to be the only specific medicine for the treatment of the heart and all manners of heart disease such as lowering cholesterol, moderating high and low blood pressure, arrhythmia, and anti-rheumatic cartileganous nutrition, and is a delicious heart tonic, as an herbal tea infusion of leaves, flowers and berries, or tincture, without any known side-effects or contraindications (Elvin-Lewis '77)(Gladstar '12).

Above all else, guard your heart, for it is the wellspring of life (Proverbs 4:23). Heart attack is a leading killer of both men and women in the United States. Of the estimated 50 million, 166 out of 1,000, with unhealthy levels of lipoprotein in their blood, 7 million Americans feel angina (23 in 1,000), 1.5 million will suffer an acute myocardial infarction (heart attack) for which 550,000 will be hospitalized (1.8 out of 1,000) and of the 2.4 million people who died in 2004, 666,000 died from heart disease (2.2 out of 1,000) and 150,000 from stroke. Only severe ischemia, with blood flow of 10% or less of normal, lasting at least 20 to 40 minutes or longer leads to irreversible damage (necrosis) of some cardiac myocytes. After the onset of an acute ischemic event, sudden cardiac death (SCD) may occur within 1 to 2 hours in 20% of patients (Schoen ’94: 528, 537 539). The AMA Code of Medical Ethics states “The right of self-decision can be effectively exercised only if the patient possesses enough information to enable an intelligent choice” (Graveline ’04: vi). To treat heart disease, fresh air, fabric, vegan diet and athletic level of cardiorespiratory exercise are essential, antibiotics cure endocarditis, statins reduce cholesterol and hawthorn is the supreme herb for the heart. 90 percent of heart disease involves the deposition of fat in coronary artery disease, as the result of excessive lipid consumption, insufficient exercise, carbon monoxide and/or cardiotoxin. Besides trans-fats, an invisible dye can contaminate the laundry making therapeutic cardiovascular exercise counterproductive to lethal, because it is activated by water, ie. Sweat, and the heart is stressed by the exertion. Carbon monoxide also causes angina. Treatment of heart disease involves, fresh air, fabric and vegan diet, no trans-fats; antibiotics cure endocarditis, statins reduce cholesterol, Hawthorn is the supreme herb for the heart, sage help digest fats. Patients must run the minimum three miles of the Marine Corp Physical Fitness Test (PFT) daily rather than 1 ½ mile run perpetuating the struggle with the Army Weight for Height Chart. Endocarditis is most frequently caused by *Streptococcus pyogenes* and can be caused by *Bactroides fragilis* treated with metronidazole, and most dangerously by *Staphylococcus aureus* with a 50% mortality on hospital admission better treated with doxycycline or clindamycin for pregnant women and children under age 8. Do not let the blood be contaminated by fatty foods, fat should normally be less than 30% of caloric intake, whereas unlike other macronutrients, carbohydrates and protein, that are detoxified by the liver, fats go directly to the heart via the little-understood lymphatic system (Enders '15: 50-54). To prevent chest pain it is important to limit fat consumption according to the guidelines provided by the American Heart Association. During chest pain from heart disease it is essential to completely eliminate all fat from the diet. Though the strong eat whatever they want, the weak eat only vegetables (Romans 14:2). Test your servants for 10 days. Give us nothing but vegetables to eat and water to drink (Daniel 1:12).

Before concluding the overview on toxicology of the heart and lungs it is medically necessary to provide an quick overview of the medical treatment of all infectious cardiorespiratory disease. To cure and epidemic or pandemic by online publishing it is medically necessary to effectively prohibit the symptomatic outbreak of any epidemic or pandemic, with the definitive best

medicine, needed to defeat the toxic and drug resistant propaganda of disbelievers worldwide. Corticosteroids are the best medicine for the treatment of all respiratory diseases of fungal and viral etiology, with the exception of influenza treated with Oseltamivir (Tamiflu), Zanamivir (Relenza) and Amantadine (Symmetrel). Corticosteroids are highly curative of fungal infections and are the best medicine for viral infections other than influenza. Corticosteroids should be indicated for being antiviral and antifungal by Drug Info. The Ozone Secretariat would not have scrapped 2020 goal achievement requiring exemption of only corticosteroids inhalers from the Montreal Protocol of 1987. Likely incitement of the 2020 COVID-19 pandemic amongst the anti-smoking asthmatics gone to fat in public office quarantining commerce. New outpatients presenting with mild Acute Respiratory Distress Syndrome (ARDS) to Severe Acute Respiratory Syndrome (SARS) should be prescribed to "take corticosteroids and clean up". A prescription of antibiotics will also be needed to treat likely pneumonia. To neutralize antibiotic resistance propaganda it is necessary to prescribe ampicillin (Principen) for the treatment of pneumococcal infections of the upper respiratory tract, otitis media, sinusitis and meningitis. Azithromycin (Z-pack) the world's most prescribed antibiotic is useful for people with penicillin allergies. Treat methicillin resistant *Staphylococcus aureus* (MRSA) with doxycycline or clindamycin for pregnant women and children under age 8, Epsom salt baths can also be curative. Treat gastrointestinal, joint and protozoal infections with Metronidazole (Flagyl ER).

Hydrocortisone crème is highly curative of asthma, allergies, aspergillosis and allergic rhinitis when smeared on the chest or nose and can be purchased at the dollar store. Prescription (nebulized): Pulmicort Respules (budesonide). Prescription (systemic –inject and oral): Celstone (betamethasone), Decadron (dexamethasone), Medrol and Solu-Medrol (methylpresdnisolone), Prapred and Pediapred (prednisolone), Prednisone and Prelone Syrup (prednisone). Prescription (nasal): Flonase (fluticasone), Nasacort (triamcinolone), Nasalide (flunisolide), Nasonex (mometasone), Pulmicort and Rhinocort (budesonide), Qvar, Vancesnase DS, Vancenase pocket inhaler, Vanceril, and Vanceril DS (beclomethasone). Steroid Nasal Sprays. Common types of inhaled steroids include: beclomethasone (Qvar), budesonide (Pulmicort), budesonide/formoterol (Symbicort) – a combination of a steroid plus a long-acting bronchodilator drug, ciclesonide (Alvesco), fluticasone (Flovent HFA), fluticasone propionate (Flovent Diskus), fluticasone furoate (Arnuity Ellipta), fluticasone propionate/salmeterol (Advair) — a combination of a steroid plus a long-acting bronchodilator, fluticasone furoate/umeclidinium/vilanterol (Trelegy Ellipta) — a combination of a steroid, an anticholinergic, and a long-acting bronchodilator drug, mometasone furoate (Asmanex), and mometasone/formoterol (Dulera) — a combination of a steroid plus a long-acting bronchodilator drug.

March 24 marks the anniversary of the discovery in 1882 by German microbiologist Robert Koch of the bacterium that causes **tuberculosis** (TB) *Mycobacterium tuberculosis*. In 1946, the drug streptomycin became the leading chemotherapy prescribed for pulmonary disease, and then, by the mid 1950s, physicians also began to prescribe isoniazid to treat tubercle bacillus. Large portions of the old Fort Bayard Military Reservation were turned over to the United States Forest Service in 1956. They now are incorporated into the Gila National Forest. By 1965, the need, in the United States, for the high elevation-dry climate tuberculosis facility since 1899, lay several decades in the past, under 24USC§19. For nine months of chemotherapy, the combination of INH and rifampin will result in roughly 95% cure rates. Therapy with INH, rifampin and ethambutol is recommended to avoid the complication of drug resistance. The addition of pyrazinamide to INH and rifampin accelerates the rate of resolution of the disease, allowing reduction of therapy to 6 months' duration. However, side-effects and toxic reactions increase modestly with the addition of pyrazinamide (Iseman '89: 97-100). The closure of Fort Bayard

Tubercular Hospital is a stellar lesson in the effective use of drug treatment to completely end a massive epidemic of life-threatening contagious pulmonary disease. INH, rifampin and ethambutol therapy is a stellar lesson on overcoming bona fide drug resistance to INH by non-tubercular mycobacterial disease.

I.3 Gas exchange

A sedentary individual requires about 1 L of oxygen (O_2) from 5 L of air, and emits about 200 mL of carbon dioxide (CO_2) per minute. Humans can tolerate only 5 minutes of oxygen (O_2) deprivation without irreversible damage and death. The motto of the American Lung Association is "if you can't breathe, nothing else matters®" (Brugman & Irvin '89: 1, 2). **Air** is mostly made up of two gases, oxygen 21% and nitrogen 78%. Air is composed of nitrogen 78.1%, oxygen 20.9%, water vapor 0.4% (1-4% near earth's surface), argon 0.9%, carbon dioxide 0.038%, neon 0.002%, helium 0.0005%, methane 0.0002%, krypton 0.0001%, hydrogen 0.00005%, nitrous oxide 0.00003%, ozone 0.000004%, carbon monoxide trace (Hamilton '10: 66-67). **Oxygen** is about one-fifth of the total. Oxygen is absorbed from the air because it is able to pass through the very thin wall of the alveolar sac. After it passes through the wall, most of the oxygen attaches itself to a particle in the blood called hemoglobin, but some oxygen floats free in the blood. Oxygen and carbon dioxide pass through the walls of the air sacs or alveoli, into the blood vessels into the process called diffusion (Tucker et al '01: 39). Gas diffusion through the alveolar-capillary membrane is governed by **Fick's law**, which states the overall rate of transfer across a membrane is proportional to (1) its area, (2) the pressure gradient on its two sides, and (3) a diffusion constant and is (4) inversely proportional to its thickness. The solubility of carbon dioxide in the membrane is about 20 times that of oxygen while the molecular weights of the two gases are similar. This had led to the widely held concept that carbon dioxide diffuses 20 times as fast as oxygen. The membrane diffusing capacity is expressed by the reaction rate with hemoglobin, in milliliters per minute, by the red cells in 1 ml of blood. The chemical reaction between carbon monoxide and hemoglobin is known to decrease in the presence of an increasing concentration of oxygen because of the competition between CO and O_2 for hemoglobin (King '89: 136, 137).

The **cardio-respiratory system** consists of three intermeshed compartments: the external gas exchanger, or lungs; the carrier, or blood; and internal gas exchanger, or mitochondria. Ventilation is the mechanical movement of gas or air into or out of the out of the lungs. Normal breathing (eupnea) is rhythmic and effortless. Ventilatory rate is 8 to 16 breaths per minute, and tidal volume ranges from 400 to 800 ml. Rate of breathing is usually not more than 60 breaths per minute even in the most vigorous adult exercise (Tucker et al '01: 129)(McCance e al '14: 1249). **Oxygen** is pumped into the lungs by the respiratory muscles and is brought into close contact with blood, into which it passively diffuses, at the level of the pulmonary capillaries in the alveoli. Carrier molecules in the blood, hemoglobin, bind the O_2 to make blood as efficient as the air in transporting O_2. The heart pumps carrier bound molecules to their ultimate destination: the individual cells. An average-sized man has about 12 pints of **blood** in his body, and an average-sized woman has about 9 pints. The heart beats at a rate of 60 to 100 times per minute (Schoen '94: 517). Each cell in the body is equipped with a specialized furnace, the **mitochondria**, which burns carbohydrates with O_2 to produce the high-energy ATP molecules that fuel the cells' functions, and ultimately maintain the life of the whole organism. O_2 is transformed into water by this process and with carbon dioxide (CO_2) is returned to the external environment where it is recycled by plants into O_2 and carbohydrate by solar energy. Two critical phases where O_2 and CO_2 transfer occurs is in the capillary bed of the lung (V/Q

relationship) and the capillary bed of the tissues (diffusion and blood distribution) (Brugman & Irvin '89: 1, 2).

The amount of effective **ventilation** is calculated by multiplying the ventilatory rate (breaths per minute) by the volume of air per breath (liter per breath, tidal volume). This is called the minute volume (or minute ventilation) and is expressed in liters per minute. During normal, quiet respirations the atmosphere and lungs exchange a tidal volume of about 500 ml of air (TV1) in 8 to 16 breaths a minute, 4-8 L / min. During the height of physical exercise with a forcible inspiration, about 3,000-3,300 ml more air can be inhaled (IRV) from 20 to 60 times a minute 60 to 198 L / min. After a normal inspiration and a normal expiration, approximately 1,000 – 1,200 ml more air can be forcibly expired (ERV). Vital capacity (VC) is the amount of air that van be forcibly expired after maximal inspiration and indicates therefore, the largest amount of air that can enter and leave the lungs during respiration, approximately 4,500-5,000 ml. Residual volume (RV) is the air that remains trapped in the alveoli, about 1,200 ml. Air is consumed at a normal sedentary rate of 4-8 liters per minute. Oxygen comprises about 21% of air, wherefore a sedentary individual consumes about 800 ml to 1.68 L of oxygen per minute. CO2, is produced at the rate of approximately 200 mL / minute (McCance e al '14: 1249, 1232, 1243, 1244).

The essential components of a systematic, individualized exercise prescription include the appropriate mode(s), intensity, duration, frequency, and progression of physical activity. Improvement of the ability of the body to utilize oxygen efficiently, resulting in improved endurance, is one component of physical fitness. The increase in **maximal oxygen intake** (VO_{2max}) may range from 5 to 30% and is most dramatic in people with low initial levels of fitness, cardiac patients and those exhibiting weight loss. The greatest improvement VO_{2max} occurs when exercise involves the use of large muscle groups over prolonged periods and is rhythmic and aerobic in nature (e.g. walking, hiking, running, stair climbing, swimming, cycling, rowing, dancing, skating, skiing, rope skipping, or endurance game activities). The recommended intensity of exercise should be prescribed as 60 to 90% of maximum heart rate, or 50 to 85% of $VO_{2max.}$ However individuals with a very low initial level of fitness respond to a low exercise intensity, for example, 40 to 50% of VO_{2max}. Although improvement in cardiorespiratory endurance have ben demonstrated with 5 to 10 minutes of very high intensity (>90% VO_{2max}) exercise, at least 20 to 60 minutes of continuous aerobic activity is recommended (Mahler et al '95: 153, 155, 156, 157, 165).

The **airway** is a series of tubes which start at the mouth like the trunk of a large, upside down tree, then split into the right and left main bronchial tubes of bronchi. The bronchi branch down, as bronchioles, with each smaller than the one before. At the end of the bronchioles, like bunches of microscopic grapes, are millions of sack-like balloons, the alveoli or alveolar sacs, too small to see without a microscope. **Oxygen** (O_2) from the air crosses through the walls of the alveoli into the blood which both takes up the oxygen from the air, and gives off a major waste product, carbon dioxide. The process of air traveling though the bronchi to the alveoli and crossing into the blood is called respiration (Tucker '01: 32). **Gas exchange** is the principle function of the acinus. Moving down a cascade from a concentration of 156 torr in ambient air at sea level, O_2 is propelled along the airways by the pressure gradient from the mouth the lung parenchyma and is present in the alveolus at a concentration of 100 torr. The movement of O_2 from the alveolus in the blood occurs by diffusion along the concentration gradient across the alveolar-capillary membrane. Diffusion of a gas through this barrier depends on the thickness of the area of the membrane, the solubility of the gas in the liquid phase, the molecular weight of the gas, the viscosity of the fluid, and the concentration gradient or the gas. Other factors such as pulmonary

capillary blood flow, alveolar ventilation, and hemoglobin concentration and saturation also affects gas exchange. Once delivered to the tissue by the circulating red blood cells, O_2 moves again by diffusion into individual cells, and conversely, CO_2 moves from the tissue into the blood (Brugman & Irvin '89: 13-16).

Hemoglobin carries oxygen much more efficiently than floating it in the blood. Because of the pumping action of the heart, blood travels through arteries which split into small divisions called **capillaries**. These capillaries, like the ones in the lung around the alveolar sacs, are very close to the individual cells of different tissues. Oxygen is moved by the blood through capillaries to where it can be used in muscle cells, brain cells, etc. **Carbon dioxide** is a waste product and must be gotten rid of in just the right amounts. Capillaries transfer blood from the alveoli of the lungs to vessels carrying blood into the heart. Capillaries also transfer blood from other body tissues to veins carrying blood back to the heart. The left side of the heart receives freshly oxygenated blood from the lungs and sends it to the body. The right side of the heart receives blood from the body and pushes it into the lungs where it releases carbon dioxide and receives oxygen. When oxygen enters the cells it is used to produce energy, without which the cells would die. In return cells give off carbon dioxide, a waste product which passes back through the capillary wall and into the blood. This carbon-dioxide rich blood is then returned to the lung, back through the walls of the alveolar sacs into the alveoli and bronchi. Carbon dioxide leaves the body during exhale. (Tucker et al '01: 36, 37, 39).

The **partial pressure of oxygen** is equal to the percentage of oxygen in the air (20.9%) times the total pressure (760 mmHg), or 159 mmHg (760 x 0.209 = 158.84). The partial pressure of water vapor (always 47 mmHg) must be subtracted from the barometric pressure before the partial pressure of the other gases in the mixture can be determined. In saturated air at sea level, the partial pressure of oxygen is therefore (760-47) x 0.2089 = 149 mmHg. All pressure and volume measurements made in pulmonary function laboratories specify the temperature and humidity of gas at the time of measurement. Approximately 1,000 ml (1L) of oxygen is transported to the cells each minute. Oxygen is transported in two ways. A small amount dissolves in plasma, and the remainder binds to hemoglobin molecules. Normally about 20 ml of oxygen is transported in 100 ml of blood. The oxygen content of the blood is measured in milliliters per deciliter (1 dl = 100 ml). The amount of oxygen that can be physically dissolved in blood is 0.0003 ml/dl per mmHg. Normal venous oxygen content is 15 to 16 ml/dl (McCance e al '14: 1232, 1237-1238, 1240-1241)

CO2, the gaseous form of carbonic acid (H2CO3) is a product of cellular metabolism. The lung eliminates about 10,000 microequivalents (mEq) of carbonic acid per day in the form of CO2, which is produced at the rate of approximately 200 mL / minute. CO2 elimination is necessary to maintain a normal partial pressure of arterial CO2 (PACO2) of 40 mmHg and normal acid-base balance. Approximately 200 ml of CO2 is produced by the tissues per minute as a byproduct of cellular metabolism. This CO2 equilibrates with carbonic acid (H2O + CO2 = H2CO3 = H + HCO3-) and must be eliminated continuously to prevent acidosis. The elimination of CO2 by the lungs helps to regulate the acid-base balance. CO2 is carried in the blood in three ways: (1) dissolved in plasma, (2) as bicarbonate and (3) as carbamino compounds. As CO2 diffuses out of the cells into the blood, it dissolves in plasma. Approximately 10% of the total CO2 in venous blood and 5% of the CO2 in arterial blood are carried dissolved in plasma. As CO2 moves into the blood, it diffuses into the red blood cells. Within the red blood cells, CO2, with the help of the enzyme carbonic anhydrase, combines with water to form carbonic acid and then quickly dissociates into the H+ and HCO3-.

Approximately 60% of the CO2 in venous blood and 90% of the CO2 in arterial blood are carried in the form of bicarbonate. Approximately 30% of the CO2 in venous blood and 5% of the CO2 in arterial blood are carried in carbamino compounds. The diffusion gradient for CO2 in the lungs is only approximately 6 mmHg (venous PACO2 = 46 mmHg, alveolar PACO2 = 40 mmHg), yet CO2 is so soluble in the alveolocapillary membrane that the CO2 in the blood quickly diffuses into the alveoli, where it is removed from the lung with each expiration. As hemoglobin binds with O2, the amount of CO2 carried by the blood is decreased. Thus in the tissue capillaries, O2 dissociation from the hemoglobin facilitate the pickup of CO2, and the binding of O2 to hemoglobin in the lungs facilitate the release of CO2 from the blood. This effect of oxygen on CO2 transport is called the Haldane effect and can have significant clinical implications for the management of lung disease (McCance e al '14: 1243). Humans exhale about 2.8 lbs of CO_2 every day, which adds up to over a half-ton per person per year (Sussman ’10: 69-70).

Any change in pH, whether produced by respiratory or metabolic changes, alters O_2 affinity. Under pathologic conditions, **blood pH** can deviate markedly from pH 7.4 and have profound implications in oxygen delivery. Low pH may hamper oxygen uptake in the lung. Addition of CO_2 to blood causes pH to fall by 0.03 to 0.05 units. Sputum has a pH of 7.0 and must be removed through daily naso-bronchial hygiene. Ascent to high altitudes produces both hypoxemia and respiratory alkalosis. Alkalinity can be prevented by administration of acetazolamide (Klocke & Saltzman '89: 175). Acidosis is often corrected by hyperventilating through pursed lips and its cure is dependent on the excretion of acid by the kidneys. Although there is an immediate increase in hyperventilation due to peripheral chemoreceptor stimulation when metabolic acidosis is induced, up to 8 hours may be needed for the PCO_2 to fall to its expected value withing the 95 percent confidence band. If the academia is severe, bicarbonate therapy may be needed. Bicarbonate therapy is most effective when plasma bicarbonate is low and there is little be gained when the initial (HCO_3^-) is above 20 to 1 mEq/liter (Saltzman & Klocke '89: 205).

Modern cardio pulmonary resuscitation (CPR) developed in the late 1950s and early 1960s. The discoverers of mouth-to-mouth ventilation were Drs. James Elam and Peter Safar. Though mouth-to-mouth resuscitation was described in the Bible (mostly performed by midwives to resuscitate newborns) it fell out of practice until it was rediscovered in the 1950s. In early 1960 Drs. Kouwenhoven, Knickerbocker, and Jude discovered the benefit of chest compression to achieve a small amount of artificial circulation. Later in 1960, mouth-to-mouth and chest compression were combined to form CPR similar to the way it is practiced today. Cardiopulmonary resuscitation (CPR) is a lifesaving technique useful in many emergencies, including a heart attack or near drowning, in which someone's breathing or heartbeat has stopped. The American Heart Association recommends that everyone — untrained bystanders and medical personnel alike — begin CPR with chest compressions. The normal CPR routine is two breaths to 30 chest compressions for adults and 15 for children and infants. When an adult, child or infant has a pulse, but is not breathing effectively, as in opiate overdose, rescuers should give breaths without chest compressions This is rescue breathing. For adult give 1 breath every 5 to 6 seconds, about 10 to 12 breaths per minute. For infants and children, give 1 breath every 3 to 5 seconds, about 12 to 20 breaths per minute. Give each breath in 1 second. Each breath should result in a visible chest rise. Check the pulse about every 2 minutes. When the heart or breathing stops, the lack of oxygenated blood can cause brain damage in only a few minutes. A person may die within eight to 10 minutes. CPR can keep oxygenated blood flowing to the brain and other vital organs until more definitive medical treatment can restore a normal heart rhythm.

To learn CPR properly, take an accredited first-aid training course, including CPR and how to use an automated external defibrillator (AED).

Cardiopulmonary resuscitation and rescue breathing are skills used to resuscitate a person who has fallen victim to sudden cardiac or respiratory arrest. Both of these situations pose an immediate threat to life. While effective CPR is known to double or triple a person's chances for surviving sudden cardiac arrest, less than one-third of people who arrest outside of the hospital receive bystander CPR. Rescue breathing of 2 breaths per five seconds is necessary to survive severe respiratory depression and arrest, such as that associated with the opiate overdose. Studies show that 15- 30 chest compressions per 2 breaths, tends to slightly impair cardiac arrest survival rates. Study results suggest that 100 to 120 chest compression per minute alone may increase survival among certain subgroups of patients — those with a cardiac cause of arrest and those with ventricular fibrillation. Of 1941 patients who met the inclusion criteria, 981 were randomly assigned to receive chest compression alone and 960 to receive chest compression plus rescue breathing. No significant difference was noted between the two groups in the proportion of patients who survived to hospital discharge (12.5% with chest compression alone and 11.0% with chest compression plus rescue breathing) or in the proportion who survived with a favorable neurologic outcome in the two sites that assessed this secondary outcome (14.4% and 11.5%, respectively). Among the 1941 eligible patients, approximately 70% had arrests with a cardiac cause, less than half the arrests were witnessed, and nearly a third had a shockable rhythm. Pre-specified subgroup analyses showed a trend toward a higher proportion of patients surviving to hospital discharge with chest compression alone as compared with chest compression plus rescue breathing for patients with a cardiac cause of arrest (15.5% vs. 12.3%) and for those with shockable rhythms (31.9% vs. 25.7%). The key to determining whether to deliver chest compressions or rescue breathing is whether the unconscious person is suffering cardiac or respiratory arrest. The only reason to deliver 15 chest compressions per 2 rescue breaths is if the cause is undetermined.

The ‘‘Community Access to Emergency Defibrillation Act of 2002’ found that over 220,000 Americans die each year from cardiac arrest. Every 2 minutes, an individual goes into cardiac arrest in the United States. The chance of successfully returning to a normal heart rhythm diminishes by 10 percent each minute following sudden cardiac arrest. Eighty percent of cardiac arrests are caused by ventricular fibrillation, for which defibrillation is the only effective treatment. Sixty percent of all cardiac arrests occur outside the hospital. The average national survival rate for out-of-hospital cardiac arrest is only 5 percent. Communities that have established and implemented public access defibrillation programs have achieved average survival rates for out-of-hospital cardiac arrest as high as 50 percent. According to the American Heart Association, wide use of defibrillators could save as many as 50,000 lives nationally each year. Successful public access defibrillation programs ensure that cardiac arrest victims have access to early 911 notification, early cardiopulmonary resuscitation, early defibrillation, and early advanced care.

When someone has extremely shallow and intermittent breathing (around one breath every 5-10 seconds) or has stopped breathing and is unresponsive, rescue breathing should be done as soon as possible because it is the quickest way to get oxygen into someone who has stopped breathing. The difference between survival and death in an opioid overdose depends on how quickly enough oxygen gets into the person’s body. These are the steps for rescue breathing: 1. Place the person on their back. 2. Tilt their chin up to open the airway. 3. Check to see if there is anything in their mouth blocking their airway, such as gum, toothpick, undissolved pills, syringe cap,

cheeked Fentanyl patch (these things have all been found in the mouths of overdosing people!). If so, remove it. 4. Plug their nose with one hand, and give 2 even, regular-sized breaths. Blow enough air into their lungs to make their chest rise. If you don't see their chest rise out of the corner of your eye, tilt the head back more and make sure their nose is plugged. 5. Breathe again. Give one breath every 5 seconds. Without a naloxone kit to reverse the overdose, continue rescue breathing until help (i.e. the ambulance) arrives.

There are three steps in adult CPR. Remember a person in cardiac arrest may have abnormal breathing for a couple of minutes. This abnormal breathing is called "*agonal respiration*" and is the result of the brain's breathing center sending out signals even though circulation has ceased. The key point is that the abnormal breathing may sound like grunting, gasping or snoring. It disappears in 2-3 minutes. If this type of breathing is noted do not delay CPR. The person desperately needs air. 1. Check the victim for unresponsiveness. If there is no response, Call 911 and return to the victim. In most locations the emergency dispatcher will assist with CPR instructions. 2. Tilt the head back and listen for breathing. If not breathing normally, pinch nose and cover the mouth with yours and blow until the chest rises. Give 2 breaths. Each breath should take 2 seconds. 3. If the victim is still not breathing normally, coughing or moving, begin chest compressions. Push down on the chest 1 1/2 to 2 inches 15 times right between the nipples. Pump at the rate of 100 -120 compressions per minute, faster than once per second. Sometimes you may hear a cracking sound. Do not be alarmed. The sound is caused by cartilage or ribs cracking. Even if this occurs the damage is not serious. The risk of delaying CPR or not doing CPR is far greater than the risk of a broken rib. Continue with 2 breaths and 15 pumps until help arrives.

There are four differences for giving CPR to children. 1. If you are alone with the child give one minute of CPR before calling 911. 2. Use the heel of one hand for chest compressions 3. Press the sternum down 1 to 1.5 inches. 4. Give 1 full breath followed by 5 chest compressions. D. CPR for infants younger than one year of age: 1. Shout and gently tap the child on the shoulder. If there is no response, position the infant on his or her back. 2. Open the airway using a head tilt lifting of chin. Do not tilt the head too far back. 3. If the baby is NOT breathing give 2 small gentle breaths. Cover the baby's mouth and nose with your mouth. Each breath should be 1.5 to 2 seconds long. You should see the baby's chest rise with each breath. 4. Give five gentle chest compressions at the rate of 100 per minute. Position your 3rd and 4th fingers in the center of the chest half an inch below the nipples. Press down only 1/2 to 1 inches. 5. Repeat with 1 breath and 5 compressions. After one minute of repeated cycles call 911 and continue giving breaths and compressions.

II. Anatomy and Physiology

II.1 Thorax

Located in the middle of the chest behind the breastbone, between the lungs, the heart rests in a moistened chamber called the **pericardial cavity**, which is surrounded by the ribcage. The **diaphragm**, a tough layer of muscle, lies below. The **sternum** is a plate of bone down the center of the chest holding in place the lung-protecting rib bones in the front of the body (Berger '04: 17). The lung and chest cavity are both lined with a thin slippery membrane called a **pleura**, that allows lungs and chest wall to slide easily past each other as you breather. Normally, there is no air or fluid between the two sets of pleura except the tiny bit of fluid greasing their movements. The linings have sensitive nerves. The most important protective

covering for the lungs is the **chest cage**, which includes all the ribs, the spine and the sternum. All these parts of bone or cartilage are held together by rib muscles. The chest cage gives the lungs a definite shape and supports the lungs from the outside. The bottom of the chest joins the abdomen. The space between the lungs, which contains the heart, great vessels and esophagus, is called the mediastinum. The **mediastinum** is bounded superiorly by the thoracic inlet, inferiorly by the diaphragm, anteriorly by the sternum, posteriorly by the anterior surfaces of he vertebral bodies, and laterally by the medial parietal pleura of the lungs. Traditionally the mediastinum has been divided into here anatomic divisions: anterior, posterior and middle. The anterior mediastinum is bordered by the sternum anteriorly and the anterior pericardium posteriorly and contain the thymus, the anterior lymph nodes, mediastinal fat, and other connective tissues. The middle mediastinum is bordered anteriorly and posteriorly by the pericardium and contains the heart, great vessel, trachea, main-stem bronchi, parts of the vagus nerves, phrenic nerves, and the middle mediastinal lymph nodes. The posterior mediastinum is bordered anteriorly by the posterior pericardial surface and posteriorly by the thoracic vertebral bodies. Its contents include the esophagus, the sympathetic chains, parts of the vagus nerves, the descending aorta, and the thoracic duct. Radiographically the mediastinum is bounded in the anterioroposterior projection by the borders of the right and left sides of the heart, superiorly by the sternal notch, and inferiorly by the diaphragm (Rodell '89: 296).

A large, domes sheet of muscle and fibrous tissue, called the diaphragm, separates the lungs from the stomach and the other organs in the abdomen. The **diaphragm**, the primary muscle of respiration, consists of a central tendon, and two muscle groups, the costal and the cural muscles. Innervation of the diaphragm is provided by the phrenic nerve which not only delivers the neural input, but also returns sensory afferents to the central nervous system, the role of which is poorly understood. When activated, the diaphragm descends against the abdominal contents and increases the thoracic volume. Volume is also increased through the expansion of the costal margins of the rib cage. In patients with bilateral diaphragmatic paralysis the diaphragm is passively displaced and active expiration is due to contraction of the abdominal muscles. The intercostal muscles can be divided into external and internal intercostal muscles. The sternocleidomatoid and the scalene muscles are believed to also have respiratory functions. The primary function of the respiratory muscles is to provide adequate alveolar ventilation (Brugman and Irvin '89: 3, 4).

The chest wall and **respiratory muscles** pump by the contraction of the respiratory muscles with expansion of the rib cage and descent of the diaphragm to create a larger volume. The negative pressure within the thorax establishes a pressure gradient from the mouth to the alveoli and results in airflow into the lung. The bony part of the chest wall consists of 12 ribs that are attached to and articulate with the thoracic spine. The movement of the ribs has been compared with the motion of a bucket handle or a pump handle. Congenital malformation (for example, pectus excavatum or pectus carinatum), trauma (as in surgery or gunshot wound), or external restriction (such as a tight-fitting girdle) can profoundly influence the range of motion of the thorax. Eupnea, or spontaneous ventilation, occurs throughout our lives and requires rhythmic and automatic contraction of the respiratory muscles. The respiratory muscles include the diaphragm, the intercostal muscles, the accessory or "strap" muscles in the neck, and the less appreciated abdominal muscles. Like all skeletal muscle the respiratory muscle can fatigue and fail. When relaxing and taking a deep breath, the chest expands, the belly pooches out, cool dry air flows into the nose and mouth. The diaphragm attaches around its edge to the lower back and rib cage. Because of its dome shape, when it contracts, that dome flattens out and moves downward, pulling the bottoms of the lungs with it. At the same time, the intercostal muscles

between the ribs pull to lift the rib cage up and out, and when working hard, some neck muscles help. The lung opens in all directions and like a bellows, pulls air in and down the airways into the air sacs. As air is being pulled in, the airways are wide open, pulled to their widest by the opening of the lung. When letting air out, all the muscles that have been pulling open relax, let go, and everything springs back to its usual place, the airways becoming narrower as the air is forced out (Tucker et al '01: 34, 35, 36).

Ventilation is the mechanical movement of gas or air into or out of the out of the lungs. The amount of effective ventilation is calculated by multiplying the ventilatory rate (breaths per minute) by the volume of air per breath (liter per breath, tidal volume). This is called the minute volume (or minute ventilation) and is expressed in liters per minute. During normal, quiet respirations the atmosphere and lungs exchange a tidal volume of about 500 ml of air (TV1). With a forcible inspiration, about 3,000-3,300 ml more air can be inhaled (IRV). After a normal inspiration and a normal expiration, approximately 1,000 – 1,200 ml more air can be forcibly expired (ERV). Vital capacity (VC) is the amount of air that van be forcibly expired after maximal inspiration and indicates therefore, the largest amount of air that can enter and leave the lungs during respiration, approximately 4,500-5,000 ml. Residual volume (RV) is the air that remains trapped in the alveoli, about 1,200 ml (McCance e al '14: 1232, 1244).

The **autonomic nervous system** (ANS) is the part of the nervous system that's automatic. This part of the nervous system requires no thoughts or calculations – kicks in immediately to regular autonomic functions such as the heartbeat and when faced threats to survival. There is a cascade of events referred to as the **neurohormonal response** because it's a long series of around 1,400 reactions involving nervous system signals to many glands all over the body. The ANS has two branches. The sympathetic (active) and the parasympathetic (relaxed). The **sympathetic branch** of the autonomic nervous system is frequently called you "fight or flight" system. With either response an entire cascade of events occurs – the nerves in the brain quickly send signals along the nerves in the body that constrict blood vessels, immediately raising blood pressure. Heart rate jumps and you can run faster. Arteries in the skin constrict, making it less likely to bleed to death. Blood is directed away from organs that really aren't necessary, like the kidneys and digestive tract. Pupils dilate and the hair on the back of the neck stand up and become environmentally sensitive, in fractions of a second. The **parasympathetic branch** dominates when nothing is perceived threatening in the environment. Blood is preferentially delivered to the stomach and intestines to help absorb and digest food. Heart rate is probably a little slower than usual. Blood pressure is also lower (Wilson and Childre '06: 67- 69, 71, 65-66).

When asleep the heart beats slowly, maybe only 50 or 60 beats per minute. When running up a hill, it might be beating at 160, or even higher. In atrial fibrillation (AT), the ventricles may beat up to 100-175 times a minute, in contrast to the normal resting rate of 60-100 beats a minute. Each beat of the heart is set in motion by an electrical signal from within the heart muscle. The **pulse**, or heart rate, is the number of signals the SA node produces per minute. The heart's electrical system controls all the events that occur when the heart pumps blood. The electrical system also is called the cardiac conduction system. The electromagnetic signals coming from the heart are fifty times stronger and can be detected eight feet farther away than the brain, the next biggest signal generator. The heart's electrical system is made up of three main parts: The sinoatrial (SA) node located in the right atrium of the heart. The atrioventricular (AV) node located on the interatrial septum close to the tricuspid valve. The **His-Purkinje system** is located along the walls of the heart's ventricles. In a normal, healthy heart, each beat begins with a signal from the (sinoatrial node) **SA node**. This is why the SA node is sometimes called

the heart's natural pacemaker. (Wilson and Childre '06: 85, 83, 84, 91). The signal is generated as the two-vena cava fill the heart's right atrium with blood from other parts of the body. The signal spreads across the cells of the heart's right and left atria. This signal causes the atria to contract. This action pushes blood through the open valves from the atria into both ventricles. The signal arrives at the (atrioventricular) **AV node** near the ventricles, where it slows for an instant to allow your heart's right and left ventricles to fill with blood. The signal is released and moves to the His-Purkinje bundle located in the walls of the heart's ventricles. From the His-Purkinje bundle, the signal fibers divide into left and right bundle branches through the Purkinje fibers that connect directly to the cells in the walls of the left and right ventricles. As the signal spreads across the cells of the ventricle walls, both ventricles contract, but not at exactly the same moment. The left ventricle contracts an instant before the right ventricle. This pushes blood through the pulmonary valve (for the right ventricle) to the lungs, and through the aortic valve (for the left ventricle) to the rest of the body. As the signal passes, the walls of the ventricles relax and await the next signal. This process continues over and over as the atria refill with blood and other electrical signals come from the SA node.

The brain tells the breathing muscles to work by sending signals along the nerves. The body communicates to the brain that it needs more air in several ways. Lack of oxygen, increased carbon dioxide, putting a stretch on joints or lungs or muscle, pressure on large blood vessels, rise in body temperature and changes in the chemical balance of the body can all be sensed by the special nerves which talk to the breathing centers of the brain. The speed or depth of breathing changes in response to these signals. The strongest signal to breathe comes from too much carbon dioxide in the blood. **Control of breathing** may be conceptualized as having three parts: (1) the command center: the cerebral cortex or brainstem, (2) the sensor activators: the various receptors and their neural connections and (3) the effectors: the lungs and respiratory muscles, which are the loci of sensory information and respond to neural input from the command center. The command center for spontaneous rhythmic breathing is located in the medulla oblongata of the brainstem and consists of two major groups of neurons, the dorsal respiratory group (DRG) and the ventral respiratory group (VRG). The DRG is the preeminent respiratory oscillator and is composed mainly of inspiratory neurons, whereas the VRG contains both inspiratory and expiratory neurons. Although automatic, these centers are acted on and modulated in a complex way by incoming (afferent) signals from the sensory receptors, the pons, the reticular activating system and the cerebral cortex (Brugman and Irvin '89: 5).

II.A. Pulmonary System

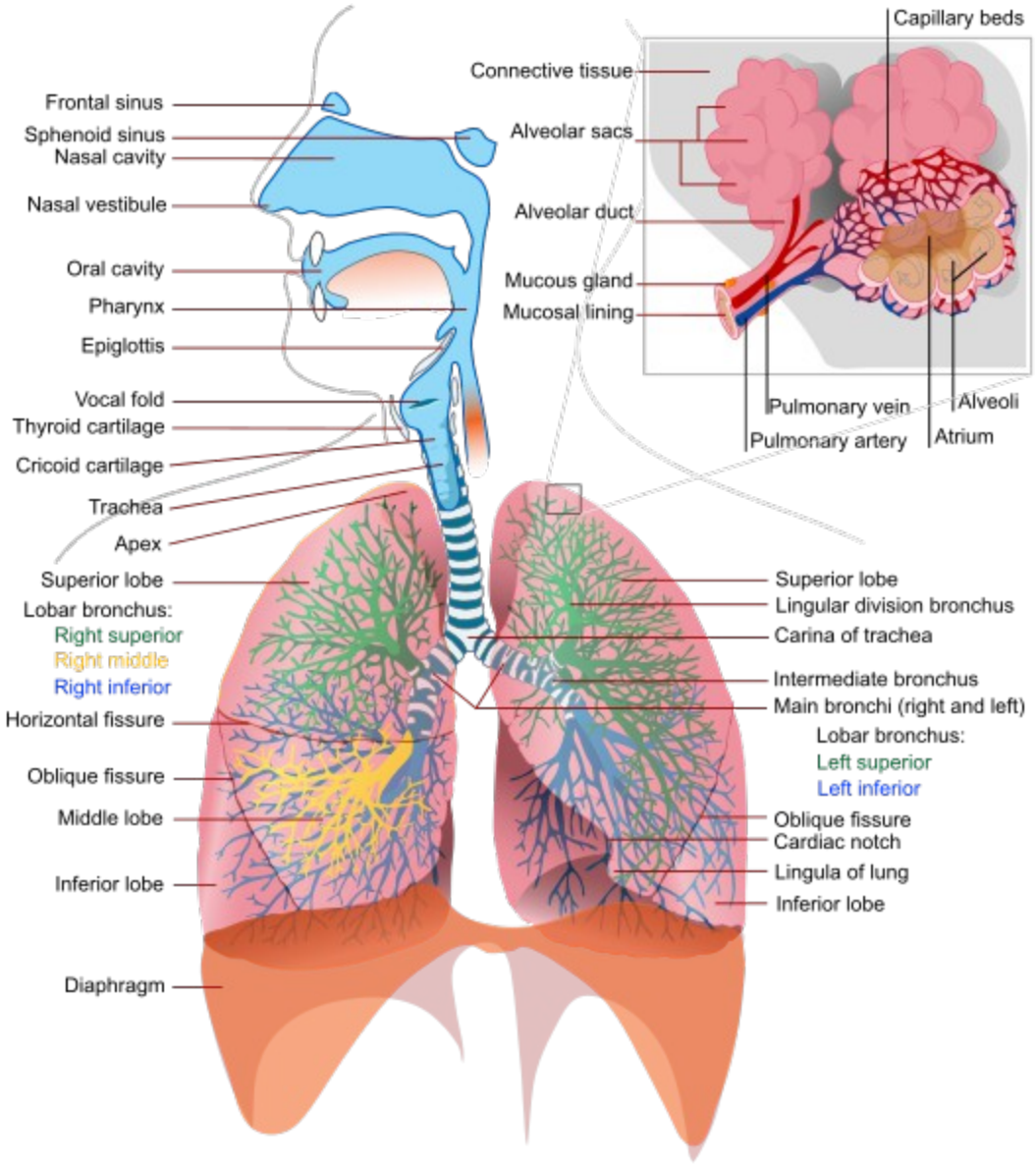
II.A.1. Respiratory System

The **respiratory system** consists of three intermeshed compartments: the external gas exchanger, or lungs; the carrier, or blood; and internal gas exchanger, or mitochondria. Oxygen is pumped into the lungs by the respiratory muscles and is brought into close contact with blood, into which it passively diffuses, at the level of the pulmonary capillaries in the alveoli. Carrier molecules in the blood, hemoglobin, bind the O_2 to make blood as efficient as the air in transporting O_2. The heart provides the propelling force to deliver the carrier bound molecules to their ultimate destination: the individual cells. Each cell in the body is equipped with a specialized furnace, the mitochondria, which burns carbohydrates with O_2 to produce the high-energy ATP molecules that fuel the cells' functions, and ultimately maintain the life of the whole organism. O_2 is transformed into water by this process and with carbon dioxide (CO_2) is returned to the external environment where it is recycled by plants into O_2 and carbohydrate by solar energy. Two

critical phases where O_2 and CO_2 transfer occurs is in the capillary bed of the lung (V/Q relationship) and the capillary bed of the tissues (diffusion and blood distribution). Humans can tolerate only 5 minutes of oxygen (O_2) deprivation without irreversible damage and death. The motto of the American Lung Association is "if you can't breathe, nothing else matters®" (Brugman & Irvin '89: 1, 2).

The **breathing system** includes the nose, mouth, a pair of lungs, the tubes or airway to the lungs, chest bones and muscles. Behind the nose are the warm, damp passages that join with the back of your mouth to form your throat. These passages clean the air as it goes through them. As air and food cross paths in the throat, a small flap of tissue called the epiglottis closes the windpipe opening to swallow, so food and liquid go down the esophagus (passage to the stomach), not into the lungs. The respiratory system provides the body with oxygen and rids the body of carbon dioxide. The key parts of the **respiratory system** are terminal bronchioles, alveoli, pulmonary capillaries, cilia, trachea, intercostal muscles, diaphragm and sternum. **Terminal bronchioles** are ultrathin branches that are the last in a line of bronchial tubes that transport gases to and from the alveoli. The **alveoli** are clusters of hollow sacs where gases are exchanged between the lungs and the blood-stream. The **cilia** are millions of tiny hairs lining the respiratory tract, beating at 12 to 16 strokes per second and creating waves that move germ catching mucus up and out of the lungs. The trachea is similar to the trunk of a tree and is the passageway for all the gases entering and leaving the lungs. The **intercostal muscles** connect rib to rib and help open and close the rib cage when breathing. The **diaphragm** forms a curved sheath below the lungs and when breathing in, the diaphragm drops, increasing the size of the lungs. The **sternum** is a plate of bone down the center of the chest holding in place the lung-protecting rib bones in the front of the body (Berger '04: 17).

Respiratory System



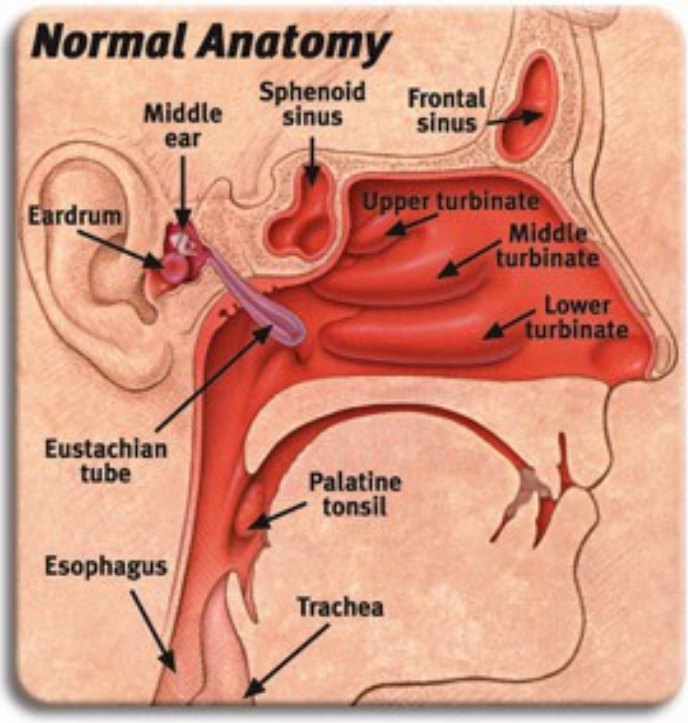
Credit: Wikipedia

The **nose** is the primary portal of entry for air in to the respiratory tract. The nose filters, humidifies and heats inspired air. The nasal passages are constructed with acute angles and convoluted turbinate surfaces that ensure efficient impaction of particular matter. Highly erectile blood vessels underlie the nasal epithelium and provide air that is fully saturated with water and heated to 37° C by the time it reaches the trachea. **Nasal mucus**, which is secreted and cleared at an average rate of 6 ml/hr, forms a sticky blanket in which dust, allergens, and some soluble gases can be trapped. **Ciliated epithelial cells**, like those in the lower airway, propel these secretions either out of the nares or down the nasopharynx where they are swallowed. Irritant receptors, located between the cells of the epithelium, are the sensors of reflexive sneezing, which enhances the elimination process. Microbiologic and antigen surveillance by inflammatory cells, both blood borne and clustered in oropharyngeal lymphoid tissue, as well as local antibody production, contribute to the lung's defense at this port of entry. The **larynx** is a a complicated musculocartilaginous structure that functions as a valve between the upper and lower airways to prevent oropharyngeal contents from contaminating the trachea and to allow for

buildup of pressure in the thoracic cavity (in preparation for cough) and in the abdominal cavity (to assist vomiting, defecation, or parturition). Finely orchestrated muscular actions, innervated primarily through the vagus nerve, are involved in the movement of the larynx for deglutition, phonation and the many reflexes (gagging, coughing and laryngospasm) that participate in the protection of the lower airways. Disorders that alter the upper airways can profoundly compromise the pulmonary system because the nose, pharynx and larynx constitute a bottleneck in the airway. Obstructions such as foreign bodies, tonsillar or adenoid hypertrophy, acute inflammation (particularly epiglottitis) trauma, tumors or the dynamic airway collapse caused by sleep apnea, and certain rare cartilaginous disorders may cause acute respiratory distress, chronic hypoxemia and cor pulmonale, or death. Neurologic dysfunction (bulbar palsy, coma and recurrent laryngeal nerve damage) can limit airway protection and contribute to pulmonary aspiration. Alterations in nasal mucus (cystic fibrosis, allergies or secretory IgA deficiency) or in the function of the cilia (ciliary dyskinesia syndrome) can cause airway infections and possible airway hyperactivity. Proper air conditioning and local defense mechanisms require functioning upper airways (Brugman & Irvin '89: 9).

The body has several **protective mechanisms** which help shield the lung from inhaling damaging particles. As a breath begins, the air moves through the nose and is filtered by the nasal hairs. Some of the foreign particles in the air attach to the sticky **mucus** in the nose or to the lining. The air is warmed if it is cooler than body temperature and moisture is added. Particles which escape the traps in the nose or the back of the throat may be caught by the mucus which lines the bronchial tubes. This mucus is kept moving upward by the wave action of the cilia, carrying mucus and particles away from the lungs. A **cough**, aggravating though it may be, is protective because it dislodges mucus and the particles trapped in the mucus. Coughing occurs if larger particles that irritates the airways are breathed in or if choking on food or drink, so that it “goes down the wrong pipe”. A cough often (though not always) signals contact with a respiratory irritant and is a warning to avoid the material. Within the lungs are more protective mechanisms. The lungs have a constant supply of **alveolar macrophages**, which pick up foreign particles or invaders. These cells are like security guards which recognize that something doesn’t belong. Most of the time, these cells try to destroy the invader by surrounding it, then using enzymes to dissolve it. These counterattacks with enzymes by the body’s defending cells are usually successful and many infections from invading bacteria or viruses are prevented. After the invader in the lung is neutralized or destroyed by the enzymes, it is very important for the lung to be able to turn off those enzymes so they don’t damage normal tissue. To do this the lungs have a supply of another chemical, a protein called **alpha-1 antitrypsin**, which blocks the excess enzymes. If this protein is in short supply, the enzymes remain in the lung and can do severe damage to the structure of the lung. The body also makes chemicals called **antibodies**, which attach to invaders and destroy them. Antibodies are more successful against some kinds of invaders than others. Protective systems are not perfect, sometimes they are overwhelmed by huge numbers of invaders and other times, they fail to destroy the invader. When that happens, a lung infection such as bronchitis or pneumonia (an infection of part of the lung) may develop (Tucker et al '01: 38, 39).

I.A.2. Ear, Nose and Throat



The function of the **ear** is to transform energy to bioelectric signals. With two functional ears, sounds can be localized since sound waves reach each ear at slightly different times and intensities. Sound waves strike the tympani membrane and are transmitted along the intact ossicular chain to the oval window. This sets the perilymph into motion within the ochlea ausing a rhythmic vibration of the basilar membrane, which stimulates the hair ells of the neuropithelium and sets the stage for transmission of a bioelectric signal. The **external ear** consists of the auricle and the external auditory canal. Except for the lobule the entire auricle is composed of elastic cartilage and skin. The auricle is attached to the head by thee xternal auditory canal and several small muscles innervated by the facial nerve. The external auditory canal is cartilaginous in the in the lateral third and bony in the inner two-thirds. The skin lining the cartilaginous portion contains hair follicles, sebaceous glands and cerumen glands. The fissures of Santorini provide potential pathways for the spread of tumors and infection from the canal into the parotid gland. The **middle ear** is an air-containing space with bony walls except for the tympanic membrane. The **tympanic membrane** is a three-layered structure composed of an external squamous epithelium, a middle fibrous layer and an inner mucosal layer. The blood supply of the middle ear and mastoid is from branches of the internal maxillary artery. The **nerve supply** is through the tympanic plexus on the promontory, which contains branches of cranial nerves (CN) V, VII, IX and X. Abnormalities (and infections most commonly *Streptococcus pneumoniae*) in the anatomic regions supplied by these nerves (including teeth, tongue, tonsils ,and larynx) may cause referred to the ear as *otis media*. The **Eustachian tube** connectes the middle ear space with the nasopharynx. Two-thirds are cartilaginous (nearest the nasopharynx) and one-third is bony nearest the middle ear. It is lined with respiratory epithelium. The function of the Eustachian tube is to provide air passage from nasopharynx to middle ear to equalize pressure on both sides of the tympanic membrane. Eustachian tube dysfunction may result in negative pressure and accumulaton of serous fluid in the middle ear space. The **inner ear** is composed of the end organs of hearing (cochlea) and equilibrium (labyrinth). Both are contained within a compact bony capsule (otic capsule) within the temporal bone. The sail-shaped cochlea makes two-and-one haf turns. The bony labyringth is comprised of the vestibule three semicircular anals, and the vestibular aqueduct. Lymph is contained in a closed system within the cochlea and membranous labyrinth. The axons from the hair cells of the cochlea join to form the cochlear portion of the acoustic nerve (CN VIII) while the axons from the specialized epithelium within the labyrinth joint to form the vestibular portion of the acoustic nerve. The facial nerve courses from the brainstem through the middle ear and exits through the styomatoid foramen (Peng & Har-el '04: 7, 8).

People have four sets of **sinuses**: maxillary, ethmoid, frontal and sphenoid.. (1) frontal sinuses – sit in the forehead, (2) maxillary sinuses – sit in the cheek above and below the eyes, (3) ethmoid sinuses – sit on each side of the nose between the eyes, (4) sphenoid sinuses – sit behind the eyes, and are the most deeply placed. Maxillary sinusitis causes pain in the mid-face (below the eyes) cheek, or upper teeth. Ethmoid sinus infection triggers pain between the eyes, near the bridge of the nose. Frontal sinusitis usually causes forehead pain. Pain behind the eyes or at the back of the head may indicate sphenoid sinusitis. Sinus infection that persists more than eight weeks is referred to as chronic sinusitis. More than four episodes of sinusitis per year, or for years, it is termed chronic sinusitis. The partition that separates the right and left sides of the nose is called the **septum**. It is made up of cartilage in the front and of bone farther back. Often, a person has a deviated septum, which means they have a twist of the septum. If this deviation occurs to a significant degree, it may result in nasal blockage and even affect sinus drainage. There are bones on the sidewall of the nose called **turbinates**. There are three turbinates on each side of the nose. The tear duct from the eye (called the nasolacrimal duct) drains underneath the low, or inferior turbinate. The middle turbinate is the most important, since it is where the maxillary and anterior ethmoid sinuses drain. The posterior ethmoid and the sphenoid sinus drain under the upper, or superior turbinate, into the nose. The back of the nose is called the **nasopharynx**. The **Eustachian tube** runs between the nasopharynx and the ear, equalizing pressures between them. Nasal or sinus problems eventually cause a feeling of clogged ears. The tissue that sits in the nasopharynx is called **adenoid tissue**. It is made up of lymph tissue, which helps fight infection. Large adenoids can lead to blockage of sinus drainage and sinus disease. Viruses and bacteria are two different things. Sinus infections are caused by bacteria (bacteria respond to antibiotics) while a cold is secondary to a virus (which does not respond to antibiotics) (Rosin '98: 4, 34, 6-7, 14).

The **four vital nasal functions** are olfaction, temperature control, humidity control and particle filtration. Olfaction occurs through the sensory hairs of CN1, which penetrate the cribriform plate. Although several disorders of olfaction may exist, the most common cause anosmia (absence of sense of smell) is simple nasal obstruction. Inhaled air temperature control is regulated as it passes over the broad surface of the turbinates whose rich capillary network contained within the semierectile tissue allows for effective caloric exchange. Regardless of the temperature of inspired air, air temperature within the nasopharynx rarely fluctuates more than 3°F from normal body temperatures. The **submucosal glands** and the **goblet cells** of the respiratory epithelium supply a continuous flow of secretion (over 1 liter per day). The pH of the secretion remains fairly constant at 7 and also contains lysozyme and he secretory immunoglobulin IgA. The rhythmic beating of the cilia moves this mucous blanket at a rate of several millimeters per minute, which is replaced approximately every 20 minutes. The main **blood supply for the external nose** come from branches of the facial artery and their anastomoses with the infraorbital artery and the supraorbital and supertrochlear arteries. Venous blood drains through the anterior and posterior facial veins into the internal jugular system. The nerve supply to the external nose is derived from three terminal branches of the trigeminal nerve (CN V), which are the infratrochlear nerve (V1), externa nasal nerve (anterior ethmoidal branch of V1) and the infraorbital nerve (V2). The blood supply to the internal nose is derived from both the external and internal **carotid artery** systems. Excluding olfaction sensation to the internal nose is carried through branches of the first and second divisions of the trigeminal nerve (Peng & Har-el '04: 10, 11).

The **oral cavity** is comprised of the lips, tongue, lateral walls and roof of mouth, and blood supply. The **lips f**orm the anterior sphincteric entrance to the oral cavity. The most prominent structure in the oral cavity is the tongue. The **tongue** is comprised of the genioglossus (largest) and paired hypglossus, stloglossus, and palatoglossus, muscles innervated by the hypoglossal nerve (CN XII). On either side of the frenulum, are small papillae containing the orifices of the submandibular (Wharton's) ducts. The mucosa of the floor of the mouth is continuous with the gingiva. The **lateral walls** of the oral cavity are formed by the cuccinator muscle, which lies lateral to the mucosa and is innervated by the buccal branch of CN VII. The parotid (Stensen's) duct open into the buccal mucosa opposite the upper second molar bilaterally. The **roof** of the oral cavity is formed by the hard palate and soft palate (posterior one-third). The uvula is the muscular organ that hangs form the midline of the soft palate. The **palate muscles** (levator palatine, tensor veli palatine and palatopharyngeus) are responsible for most of the mostion of the soft palate and are innervated by the vegas nerve. The **blood supply** of the oral cavity is through the branches of the carotid artery, including the facial and lingual arteries. Venous drainage occurs thorugh the facial veins into the internal jugular veins. The tongue has an important role in deglutition and **taste**. The peripheral taste receptors are the taste budes in the papillae on the tongue and palate. The fungiform and circumvallate papillae are the most sensitive in terms of taste sensation. The filiform papillae, while most numerous, are considered noncontributory to taste sensation. Afferent taste sensation of the anterior two-thirds of the tongue is carried by chorda tympani, which then travels with the facial nerve, whereas taste sensation of the posterior third of the tongue is transmitted via the gosspharyngeal nerve. In addition to the tongue, taste buds exist on the palate, oropharynx and hypopharynx. Salty and sweet sensations are detected mostly on the tongue, while the palate is most sensitive to sour and bitter tastes (Peng & Har-el '04: 12, 13).

The **pharynx** is divided into the nasopharynx (above the soft palate), the oropharynx (between the tonsillar pillars laterally, the soft palate superiorly, and the epiglottis inferiorly), and the hypopharynx (the portion of from the base of the tongue and epiglottis to the cricopharyngeus muscle inferiorly). The **nasopharynx** (also called epipharynx or rhinopharynx) is a mucosa-lined space bordered laterally by the medial pterygoid plates, superiorly by the sphenoids bone, anteriorly by the choanae and midline vomer, posteriorly by the clivus and inferiorly by the soft palate. The **Eustachian tubes** open posterolateraly and are surrounded by a cartilaginous structure (torus tubarius). Behind the Eustachian tubes are mucosal recesses known as the fossae of Rosenmuller. The **adenoids** (pharyngeal tonsils) hang form the fossae and the posterosuperior wall of the nasopharyngeal vault. The **oropharynx** is bounded posteriorly by the superior constrictor muscle and the cervical vertebrae. It is bounded laterally by the anterior and posterior tonsillar pillars and he contained palatine tonsils. The **hypopharynx**, or laryngopharyns, is the inferior continuation of the oropharynx. It is surrounded by three constrictor muscles (the superior, middle and inferior) innervated by the glossopharyngeal and vagus nerves. The hypopharyngeal space extends superiorly into a recess between the base of the tongue and the epiglottis known as the vallecula. The space extends inferiorly into a recess on either side of the larynx bordered medially by the aryepilglottic folds and knownas the piriform sinus. The hypopharynx communicates inferiorly with the esophagus thorugh the upper esophageal sphincter formed by the circular cricophargyngeus muscle. The **upper esophageal sphincter** (pharyngoesophageal sphincter) is the first constriction found at esophagoscopy and is formed primarily by the cricopharyngeus muscle. During swallowing, this muscle relaxes as the bolus of food is propelled into the esophagus nd then subsequently constricts to prevent reflux of food back intothe pharynx. The cricopharyngeus muscle is innervated by the vagus nerve (Peng & Har-el '04: 13, 14, 17).

The **larynx** performs three vital functions: protection of the airway, respiration and phonation. The larynx is a mucosa-lined structure composed of cartilage and muscle, suspended anterior to the hypopharynx within the neck by several extrinsic muscles. The larynx is at the level from the fourth through sixth cervical vertebrae. Although not part of the larynx proper, the hyoid bone is connected to the thyroid cartilage by the thyroid membrane and muscle. The hyoid bone is suspended from the msucles that form the diaphragm of the floor of the mouth and muscle connecting it with the base of the skull. The **thyroid cartilage** is shield shaped and has an ala that flares outward on either side. At the posterior ends of the ala on both sides are superior and inferior armlike extensions (cornu) that articulate with the hyoid bone and cricoid cartilage, respectively. The **cricoid cartilage** is the only complete ring of cartilage in the larynx. The cricoid cartilage articulates inferiorly with the trachea. The paired arytenoid cartilages sit on the posterior cricoid lamina in a saddle configuration and articulate in a synovial joint. This joint allows the arytenoid cartilages to glide rotate and tilt. It may be subject to dislocation, infection, inflammation (arthritis) and fixation (ankylosis). Arytenoid action is responsible for opening and closing the gottis (the space between the vocal folds). The mucous membrane of the larynx is continuous with the mucosa of the pharynx above and with the trachea below. The epiglottis attaches to the tongue by way of the median glossoepligottic folds. Beneath the aryepilgottic folds are the **false vocal folds**. These are mucosal folds that attach anteriorly to the thyroid cartilage and contain no muscle fibers. Beneath the ventricles, on both sides, are the **true vocal folds**. Each is attached anteriorly to the inner surface of the thyroid cartilage about midway.

The **human voice** is produced when a pressurized column of air is expired through the glottis space causing the vocal folds to vibrate. The laryngeal muscles adduct (close) the vocal folds, while the muscular and passive forces of exhalation increase sublottic pressure. Subglottic pressure eventually reaches a level sufficient to force the glottis open. After the release of air, the sublottic pressure lowers, and as air travels between the folds, the pressure decreases in accordance with Bernoulli's principle. The vocal folds then approximate to begin a new cycle. **Phonation** is produced by vibration of the vocal folds. The regularity and periodicity of vibration of the vocal folds determine vocal quality. **Pitch**, measured in hertz, is determined by the frequency, or number of cycles of vibration of the vocal folds per second. **Loudness**, measured in decibels, is determined by the amplitude of each vibration. Pitch and loudness can be modified through the fine motor controls of the length and tension of the vocal folds and the pressure of the air stream. Modification of phonation by the oropharyngeal and nasal cavities is known as **resonance**. Articulation is controlled by the interface between the tongue and the palate, teeth and lips. Hoarseness can result from a disorder that changes the surface characteristics of the vocal cords or the vibratory capabilities of the vocal folds. The voice changes throughout the life cycle. Physical mutation during puberty involves development of the secondary sex characteristics, of which one of the most prominent and generally noticeable is differentiation of the adult voice into male and female types. At puberty the larynx grows rapidly and alters the voice. The restricted infantile vocal range expands in both directions of the higher and lower tones until it reaches the adult range. A well-known sign of voice change among boys is the sudden change between a soprano register and that of the developing deeper vocal quality. Vocal quality is assessed in terms of such as harshness, breathiness, pitch breaks, fatigue, and tension (Schwartz, Goldsmith & Barr '04: 238).

The muscles of the larynx can be divided into an intrinsic group and an extrinsic group primarily consisting of the strap muscles (sternohyoid, thyrohyoid, and omohyoid) which are innervated by the ansa cervicalis. The **intrinsic muscles** are responsible for most vocal cord motion. These

msucles may be divided into adductors, abductors and tensors of the true vocal cords. The **recurrent laryngeal nerve**, a branch of the vegas nerve, innervates all the laryngeal muscles except the cricothyroid, which receives its motor supply from the exernal branch of the superior laryngeal nerve. On the left the recurrent nerve loops around the aorta, and on the right it loops around the subclavian artery before ascending in the tracheoesophageal groove to the larynx. The superior and inferior **thyroid arteries** provide most of the blood supply to the larynx. In infants, the epiglottis tends to be more omega shaped and the cartilages and soft tissues are more compliant. During swallowing the larynx elevates and closes to prevent aspiration into the trachea. In a healthy person, three **closure mechanisms** are activated: the epiglottis covers the laryngeal inlet, and the false and true vocal fold adduct. Moreover, foreign material is detected by the sensory fibers, which initiates the laryngeal sphincter and pharyngeal wall action necessary for effective coughing (Peng & Har-el '04: 14-17).

The **thyroid** is an endocrine gland composed of two lateral lobs connected by an isthmus that lies on the second, third and fourth tracheal rings. The thyroid gland is connected to the larynx and trachea laterally by a broad-based suspensory ligament in the cricotrachel region. The arterial supply of the thyroid gland is from the superior thyroid artery (first branch of the external carotid artery) and inferior thyroid artery (branch of the thyrocervical trunk). The venous drainage is through the superior, middle and inferior thyroid veins, as well as the thyroid ima. The recurrent laryngeal nerves lie deep in the lateral lobes of the thyroid gland in the tracheoesophagel grooves. The thyroid gland regulates iodine metabolism and produces stores, and secretes triiodothyronine (T_3) and thyroxine (T_4), iodinated complexes of tyrosine. They are regulated by means of a feedback mechanism that involves the hypothalamus, the pituitary gland and thyroid itself. Thyroid-releasing hormone secrete by the hypothalamus stimulates production of thyroid-stimularing hormone (TSH) by the pituitary gland, which stimulates production of thyroid hormone. An increase in circulating thyroid hormone inhibits elaboration of both thyroid-releasing hormone and TSH, whereas a decrease in thyroid hormone stimulates increases TSH. The **parathyroid glands** are intimately related to the posterior thyroid gland. There are usually four glands paird in the superior and inferior poles of the thyroid, each with its own vascular pedicle. Parathyroid hormone (PTH) is the principal regulator of calcium concentration in extracellular fluid. A fall in blood calcium level increases PTH, which stimulates increases osteoclastic activity, reabsorption of calcium from the kidney, urinary phosphate excretion, and calcium absorption from the intestine (Peng & Har-el '04: 22, 23).

Hundreds of minor **salivary glands** are located in almost every part of the oral cavity, pharynx, and larynx. Each gland has its own separate duct. The major salivary glands are three bilaterally paired exocrine glands – the parotid, submandibular and sublingual glands. The **parotid gland** is invested by a dense fascial engelope. The facial nerve courses through the gland artificially dividing the gland into a superficial and a deep lobe. The parotid (Stensen's) duct arises form the anterior border of the gland. The facial nerve enters the substance of the parotid gland and branches out to the respective facial muscles of the region. The external carotid artery supplies the parotid gland. The **submandibular gland** is the second largest of the salivary glands, and contains both serous and mucus-secreting acini. The submandibular (Wharton's) duct opens at the floor of the mouth. The artieral supply is derived rom the lingual and facial arteries. The preganglionic parasympathetic secretomotor fibers originate in the superior salivatory nucleus. The **sublingual gland** is the smallest of the major salivary glands. Its secretion is primarily of the mucous type. It lies near the symphysis of the mandible beneath the mucosa of the floor of the mouth and drains through ducts that open separately along the sublingual fold of the floor of the mouth or into the submandibular duct. The blood supply of the sublingual gland is derived

from the sublingual branch of the lingual artery. Its parasympathetic secretomotor nerve supply is similar to that of the submandibular gland. Salivation is stimulated by reflex efferent fibers that travel through the parasympathetic nervous system in the preganglionic fibers of the facial and glossopharyngeal nerves. Although **salivary flow** is highly variable, it averages, 1,000 mL daily. Approximately 90% of this volume comes from the parotid and submandibular glands in equal amounts. The composition of saliva consists of electrolytes, calcium, phosphate, assorted proteins including salivary amylase, secretory immunoglobulin A (IgA), and an assortment of glycoproteins. Saliva has a lubricating effect that protects the oral mucosa from local irritants and aids in speech and swallowing. Protection of the teeth occurs through the mineral content, which aids in tooth maturation and prevention of tooth decay. The antibacterial and antiviral properties of saliva help prevent soft-tissue infection and caries. Dehydration, emotional stress, systemic inection, anemia, radiation therapy, some drugs, and Sjögren's syndrome decrease salivary flow (xerostomia) (Peng & Hr-el '04: 17-19).

For **olfactory stimulation** to occur, an odorant must enter the nasal cavity and reach the receptor surface of the olfactory epithelium, in the upper region of the nasal cavity along the superior turbinate, cribriform plate and superiormost portion of the nasal septum. This epithelium contains four main cell types. The ciliated olfactory receptor is a bipolar neuron with a club-shaped, peripheral knob that bears sensory cilia. Actual transduction occurs through a membrane-bound receptor protein. The microvillar cell is another type of olfactory receptor. Sustentacular cells, or supporting cells, surround the receptor cells and provide nutritive and secretory functions. The basal cells are adjacent to the basement membrane and function as stem cells for the regeneration of senescent receptor and supporting cells. Once stimulation of a receptor cells has occurred the olfactory information is transmitted through the olfactory nerve (cranial nerve I) t the olfactory bulb, where it is processed and modified. Information then travels through the olfactory tract within the brain, to the amygdala and prepyriform cortex, which are believed to be the sites of conscious appreciation of smell. If the odorant is pungent like vinegar or ammonia, it is detected by the trigeminal nerve endings throughout the entire nasal cavity (Song & Goldsmith '04: 190).

The peripheral receptors for taste, the **taste buds**, are situated within the oral cavity, pharynx, and cervical esophagus. They are round structures composed of slender cells organized like the segments of a grapefruit. The taste buds in the oral cavity are on the soft palate and tongue. On the tongue they are associated with supporting structures known as pappilae. Of the **four types of papillae** on the tongue, only the fungiform foliate, and the cicumvallate papillae are associated with taste buds. The more numerous **filiform papillae** do not contain taste buds. The fungiform **papillae** are club-like and are distributed over the anterior two-thirds of the drum of the tongue. They are redder than the surrounding tissue and are easy to identify. The **foliate papillae** are vertical ridges on the lateral border of the posterior middle third o the tongue. The circumvallate papillae are large circular structures arranged in a V pattern at the junction of the anterior two-thirds and base of tongue. **Taste afferent fibers** that supply the taste buds synapse with the receptor cells of the bud. Fibers that contact the fungiform papillae travel with the lingual nerve and enter the chorda tympani nerve. Saliva plays an important role in providing a transport medium for tastants (Song & Goldsmith '04: 193-194).

Swallowing involves coordination of both voluntary and involuntary muscular contraction which can be divided into three phases – oral, pharyngeal and esophageal. Food is mixed with saliva during chewing to form the food bolus. The **oral phase** of swallowing is the only voluntary phase of the sequence. It occurs when the tongue moves the food bolus along its dorsum and

propels it into the pharynx. The **pharyngeal phase** is triggered primarily by contract between the food bolus and the pharynx. Once triggered, the sequence of muscular contractions that make up the swallow continues involuntarily. First, the soft palate, posterior pharyngeal wall, and fossae contract to prevent nasopharyngeal reflux. The airway is protected as the laryngeal muscles contract. This draws the larynx upward beneath the hood of the base of the tongue as the epiglottis is depressed over the glottis inlet. With progressive pharyngeal muscle contraction, the bolus is moved into the hyppharynx and approaches the pharyngoesophageal sphincter (cricopharyngeus muscle), which relaxes and allows the bolus to be propelled into the upper esophagus to begin the esophageal phase. Peristaltic action of the upper, middle and lower esophagus further propels the bolus toward the stomach. Appropriate relaxation of the lower esophageal sphincter is essential . Once the bolus has entered the stomach, the lower esophageal sphincter contracts and prevents reflux of gastric contents into the esophagus (Habib & Sundaram '04: 231). **Coughing** is a protective mechanism for the upper and lower airway, enabling a person to clear excessive secretions and foreign material from the airway. The stimulus to cough arises premodinantly from sensory nerve endings in the pharynx, larynx and tracheobronchial tree. Impulses travel primarily through the ninth and tenth cranial nerves to the medullary cough center. A complex sequence of neuromuscular events (partly reflex, partly voluntary) is initiated and affects the diaphragmatic, laryngeal, thoracic and abdominal muscles. There are three phases of coughing: inspiratory, compressive and expiratory. Maximal inspiration allows a large volume of air to enter the lungs, followed by contraction of the expiratory muscles and diaphragm against a closed glottis. Finally, the glottis opens suddenly, allowing high-velocity expulsion of entrapped air and material (Habib, Lim & Har-El '04: 268).

I.A.3. Lungs, Bronchi, Bronchioles and Acinus

The lungs are constructed to exchange gases between inspired air and the blood. The right lung is divided into three **lobes**; the left lung has only two lobes, its middle lobe equivalent being the lingual. The lung airways, the main right and left **bronchi** arise from the trachea and then branch dichotomously, giving rise to progressively smaller airways. The right main stem bronchus is more vertical and more directly in line, with the trachea than is the left. As a consequence, aspirated foreign material, such as vomitus, blood and foreign bodies, tends to enter the right lung rather than the left. Accompanying the branching airways is the double arterial supply to the lungs, that is, the pulmonary and bronchial arteries. In the absence of significant cardiac failure, the bronchial arteries of aortic origin can often sustain the vitality of the pulmonary parenchyma when pulmonary arterial supply is shut off, as by emboli. Progressive branching of the bronchi forms **bronchioles**, which are distinguished from bronchi by the lack of cartilage and submucosal glands within their walls. Further branching of the bronchioles leads to the terminal bronchioles, which are less than 2 mm in diameter. The part of the lung distal to the terminal bronchiole is called the **acinus**, or the terminal respiratory unit; it is approximately spherical in shape, with a diameter of about 7 mm. Acini contain alveoli and are thus the site of gas exchange. An acinus is composed of respiratory bronchioles which give off from their sides several alveoli; these bronchioles then proceed into the alveolar ducts, which immediately branch and empty into the alveolar sacs – the blind ends of the respiratory passages whose walls are formed entirely of alveoli. A cluster of three to five terminal bronchioles, is usually referred to as the **pulmonary lobule** (Kobzik & Schoen '94: 673, 674).

Except for the vocal cords, which are covered by stratified squamous epithelium, nearly the entire respiratory tree, including the larynx, trachea and bronchioles, is lined by pseudostratified, tall, columnar, **ciliated epithelial cells**, heavily admixed in the cartilaginous airways with

mucus-secreting goblet cells. The bronchial mucosa also contains neuroendocrine cells that exhibit neurosecretory-type granules and contain serotonin, calcitonin, and gastrin-releasing peptide (bombesin). Numerous submucosal, **mucus-secreting glands** are dispersed throughout the walls of the trachea and bronchi (but not the bronchioles). The **alveolar walls** (or alveolar septa) consists of capillary endothelium, a basement membrane and surrounding interstitial tissue, and the alveolar epithelium (Kobzik & Schoen '94: 674). The **bronchial tubes** or airways are made up of a substance called fibrous tissue which is like skin. It can't stand up or keep its shape alone, but has to have support around it to stiffen it. This support is provided by cartilage. Around the bronchial tubes are muscles. These are like the ones in the arms or legs, except that the bronchial muscles stay more relaxed and work automatically, without thinking. Inside the lungs, the airways branch into smaller and smaller airways. These tiny airways are soft like cooked macaroni. Between the soft, floppy airways and the big rigid ones, all of the airways are wrapped in special muscles which can change the bore, or diameter of the airway by relaxing or contracting. The **muscles** around the bronchial tubes cramp or spasm when you have an acute asthma attack. Bronchodilator medications work by relaxing these muscle spasms, so the bronchial tubes can reopen. A soft velvet-like substance lines each airway, which is normally very smooth and slippery. This lining is made up of several different kinds of cells. The lining cells of the bronchial tubes are called **epithelia**, and protect the deeper layers, like paint on wall. Some of these cells have **cilia**, tiny hairs which act like the oars in a racing boat. They all push together in one direction, then slide back quickly to get ready to beat again. Mixed in among the cells with cilia are other glandular cells which make mucus. When irritated, these glandular cells pour out mucus, so that when you have a cold your nose fills, and even worse, if the bronchial tubes become irritated, inflammatory cells, which don't belong in the lung, are drawn down into the lung. In bronchitis the cilia are damaged, losing their ability to move the mucus while the cells that produce mucus have become irritated and produce too much mucus (Tucker et al '01: 32, 33).

The **lower conducting airways** are a treelike structure in which the trachea is the trunk and the bronchi and bronchioles branch from it in a dichotomous fashion. Twenty three generations of airway branchings have been identified, of which sixteen are conducing airways. Development of these airways is essentially complete at 16 weeks of fetal gestation, but growth proceeds in length and width until the final thoracic dimensions are reached. The structural architecture of the airways is composed of cartilage, smooth muscle and fibrous tissue. C-shaped cartilages comprise the skeleton of the trachea, and incomplete cartilaginous plates are part of the conducting airways to the eleventh generation. The orientation of the **smooth muscle** within the airway walls varies with airway size. Bands of muscle join the two ends of the C-shaped cartilages in the trachea and large bronchi. With subsequent airway branching, muscle bundles entwine the airways in a helical, criss-crossing fashion. Muscle spirals can also be found around the respiratory bronchioles and the orifices of the alveolar duct. The **neural control** of these muscles includes both parasympathetic (excitatory) influences and non-adrenergic (inhibitory) influences. The airways smooth muscle also responds to a variety of local, cell-derived **mediators** such as histamine, bradykinin, and the eicosanoids. Given the anatomic orientation of the smooth muscle, the contraction that causes a squeezing effect on the airways results in increased rigidity and decreased caliber.

The inner surface of the airways is lined with a **continuous epithelial layer** consisting of various cells types, which change down the airways to the level of the acinus. Dominant among these are the **ciliated cells**, which are present to the respiratory bronchioles The cilia pulsate in a rhythmic, upward fashion and propel mucus and other debris to the central airways and mouth.

The cilia and the blanket of secretions are termed the "mucociliary escalator". Both **goblet and serous cells**, which populate the airways, secrete protective mucus. **Mucus** is also secreted by the more elaborate bronchial glands located in the submucosa in bronchi. **Basal and intermediate cells** are multipotential and serve as a reserve population to replace ciliated cells and mucous cells. The **argyrophil**, APID or Kulchitsky cell is an endocrine cell that secretes a number of different hormones (serotonin, calcitonin and opiate peptides) and appears to be under neural control. The **Clara cell** is a nonciliated, cuboid cells that secretes lubricating fluid for the smaller airways and may be important in detoxifying foreign substances. **Brush cells** are equipped with a fluffy border of microvilli, and may play a role in fluid absorption (Brugman & Irvin '89: 9, 11, 12).

The **branching configuration** of the airways entraps large particles (2 to 10 μm) by impaction during airflow. Once entrapped these foreign substances are cleared by the tremendously efficient **muciliary escalator** at a rate of 0.5 mm/min In the bronchioles) to nearly 20 mm/min (in the trachea). Cough, hyperapnea, bronchoconstriction and increased mucus production are automatic safeguards that limit penetration of inhaled particles. Pulmonary macrophages, plasma cells and lymphocytes populate the airway wall and provide phagocytosis, secretory (gA production, and specific immunity to neutralize foreign invaders. These form a more finely tuned defense, especially against smaller particles (<2μm) and more complex insults. Pathologic alteration in the lower airways account for a variety of respiratory diseases. Continual stimulation of bronchial glands and goblet cells by cigarette smoke or other air pollutants causes chronic hypersecretion of mucus and the clinical state of chronic bronchitis. **Congenital anomalies** of the airways (bronchial atresia and stenosis, tracheomalacia, or bronchogenic cytst) and genetic defects (cystic fibrosis) or an early insult (bronchopulmonary dysplasia or viral-induced bronchiolitis obliterans) to growing airways can result in profound increase in airflow resistance ventilation-perfusion mismatch. **Epithelial alterations**, either congenital (ciliary dyskinesia) or acquired (bronchogenic carcinoma or bronchiectasis) can compromise the airway by obstruction or by progressive inflammatory destruction. **Asthma**, which is among the most common and sometimes severe of airway diseases, can cause luminal occlusion by edema, secretions, mucus plugs and smooth muscle spasm.

The **alveoli** at the end of the bronchial tubes number in the millions. If all the alveoli were spread out flat, they would cover the surface of a tennis court. A healthy adult has about 300 million alveoli in each lung. The walls of the alveoli are very thin, usually a single cell. The alveoli are found in clusters that are like a bunch of grapes. Each alveolus is surrounded by many capillaries and lymph vessels. The blood vessels and the lymph vessels run in the walls between the alveoli, forming a very large area of contract between the air and the fluids. Oxygen exchange takes place in the alveoli. The walls of the alveoli are very thin, usually a single cell, allowing oxygen and carbon dioxide to pass between the air and the blood. Each alveolus is wrapped in an elastic membrane that expands and contracts with each breath. The problem is that there are so many alveoli, you don't realize they are being damaged until about half of them are gone. And once they are gone, they never grow back. The remaining alveoli blow up further in an attempt to replace the losses, but it doesn't work. The blood vessels are destroyed, so that even if air can get into the remaining alveoli, there aren't enough blood vessels to take up enough oxygen. Emphysema is the result of this destruction. In emphysema the walls of the individual alveoli have broken down and what remains is an enlarged, flabby envelope that doesn't fully expand and contract with each breath (Tucker et al '01: 34, 35).

The system of branching airways conducts oxygen rich air onto a large, thin, gas-permeable surface called the **alveolar-capillary membrane**. The basic gas exchange unit of the lung is called the **acinus** or the primary lobule and consists of those structures distal to the terminal bronchiole. The acinus is a descending series of branches and includes: two to five orders of respiratory bronchioles; two to five orders of alveolar ducts; one to three alveolar sacs; and alveoli. **Alveoli** can also project directly from either the respiratory bronchioles or the alveolar ducts. A group of three to five terminal bronchioles and their respective units is referred to collectively as a **lobule** (or "secondary" lobule). A lobule is a distinct unit that is partially circumscribed by connective tissue septa and nurtured by its own branch of the pulmonary artery, whereas the venous drainage is shared by several adjacent lobules. The alveoli are the basic **unit of gas exchange**. Each of the approximately 50 million alveoli present at birth is about 70 μm in diameter. By adulthood they number approximately 300 million and are about 250 μm in diameter. Comparative studies in animals and examination of resected lungs from high-altitude dwellers and infants have demonstrated the remarkable adaptability of the alveoli. Alveoli increase in number and surface area as the body's demand for oxygen increases, in response to lung loss, or in certain environmental conditions. Another unique feature of alveoli is their capacity or **collateral ventilation**. **Pores of Kohn**, 3 to 12 μm "holes" in the alveoli, have been documented as distinct anatomic entities. However they are normally occluded by surfactant and probably play little part in the cross-ventilation of alveoli. Other structures such as the **canals of Lambert** and the larger channels (greater than 200 μm) provide the major source of alternate airflow to the acinus. The functional significance of these accessory channels is that pronounced airway obstruction occurs before atelectasis is noted (Brugman & Irvin '89: 13).

The **cells that line the alveolar space** are of three types (1) Type I cells, or squamous pneumocytes, are relatively sparse in number, but their thinly attenuated cytoplasm accounts for 93% of the alveolar surface area; (2) Type II cells, or granular pneumocytes, are far more numerous but are compact and function primarily to produce surfactant for the alveolar lining and (3) Alveolar macrophages, originally derived from blood-borne monocytes, are a heterogenous group of cells that scavenge a variety of foreign particles and microbes. The **macrophage** has been appropriately named the "garbage collector" of the lung. This scavenger function is readily demonstrated in bronchoalveolar lavage from patients who have demonstrated gastropulmonary aspiration and pulmonary hemorrhage where macrophages, replete with engulfed fat or hemosiderin, are identified. On the other side of the alveolar-capillary membrane is the **endothelial cell**, which serves to maintain the structural integrity of the capillary vessel, acts as the passive barrier to O_2 and CO_2 diffusion, and has an important metabolic function. Further endothelial cells play a key role in liquid and solute movement so that endothelial injury frequently results in pulmonary edema (Brugman & Irvin '89: 13-16).

Gas exchange is the principle function of the acinus. Moving down a cascade from a concentration of 156 torr in ambient air at sea level, O_2 is propelled along the airways by the pressure gradient from the mouth the lung parenchyma and is present in the alveolus at a concentration of 100 torr. The movement of O_2 from the alveolus in the blood occurs by diffusion along the concentration gradient across the alveolar-capillary membrane. Diffusion of a gas through this barrier depends on the thickness of the area of the membrane, the solubility of the gas in the liquid phase, the molecular weight of the gas, the viscosity of the fluid, and the concentration gradient or the gas. Other factors such as pulmonary capillary blood flow, alveolar ventilation, and hemoglobin concentration and saturation also affects gas exchange. Once delivered to the tissue by the circulating red blood cells, O_2 moves again by diffusion into

individual cells, and conversely, CO_2 moves from the tissue into the blood (Brugman & Irvin '89: 13-16).

As a person grows older the lungs are apt to show evidence of deterioration. However, only a minor portion of this is attributable to the aging process. **Healthy lungs** that have been well cared for and have been spared major injury throughout life appear capable of lasting considerably longer than many other vital organs. However, a variety of lung insults are common in the average life span. Pneumonias, pulmonary emboli, recurrent or protracted bronchospasm, trauma, industrial dusts, urban air pollution, and tobacco smoke can do considerable harm. Diffuse pulmonary emphysema, once thought to be caused by aging, can now be traced to smoking. A genetic defect – $alpha_1$-antitrypsin deficiency – is rare and greatly aggravates the effects of smoking. Ventilatory capacity tends to decline about 30 cc/yr of FEV_1 beginning in the mid-20s. Airway resistance goes up while transfer factor and total lung capacity (slightly) go down. Residual volume goes up while thoracic muscle strength and maximum O_2 consumption go down. Intimal thickening of the arterioles, replacement of muscle by hyaline myxoid material in pulmonary veins and tiny thrombi, are often found in undamaged by aged lungs. "**Duct etrasia**" enlargement of alveolar ducts and respiratory bronchioles, with a concomitant reduction in the depth of their surrounding alveolar sacs, is a morphologic change attributable to advancing age. In one study of 262 post-mortem patients duct extasia was found in 0% <40, 13% 40-49, 41% 50-59, 60% 60-69, 52% 70-79, and 81% 80+. **Reduced elastic recoil** is the most likely explanation for the age-related loss in FVC, FEV_1 and increase in RV (Mitchell '89: 355-357).

II.A.4. Pulmonary capillaries, hilum, pleura, mediastinum, diaphragm and innervation

A dense **fibrous network** of collagen and elastin in the interstitium that surrounds the airways provides the architectural struts needed to support the 130 square meters of gas exchange surface. Fibers originating in the visceral pleura radiate inward to invest each lobe and subdivide the lobes into lung segments. A central fiber system begins at the **hilum** and axially along airways and blood vessels out to the parenchyma. A third support is the delicate fibers that encircle the alveoli and interconnect with larger lobular septa. Elastic fibers contribute to the fibrous elements in which a contractile property is added to the structure (Brugman & Irvin '89: 13-16). The **pulmonary arterial system**, originating from the right ventricle, branches dichotomously in close approximately to the airways down to the level of the respiratory bronchioles. From there pulmonary arterioles fan out into a meshwork of communicating capillaries that weave through the alveolar interstitium. The supernumerary arteries branch off at right angles form segments of the conventional pulmonary arterial system to provide collateral flow to the gas exchange units. Coalescent venules drain the capillary bed and return oxygenated blood to the left side of the heart by way of valveless, thin-walled channels that are located in the interlobular septae. **Bronchial arteries**, derived from the thoracic aorta or its major branches, provide an oxygenated source of blood to the lung. These vessels travel with the airways and nourish them to the level of the respiratory bronchioles. Two thirds of the venous drainage of bronchial arteries ultimately empties into the **pulmonary veins and left atrium**, accounting for the 1% to 2% right-to-left shunt occurring in normal persons. Under conditions of airway inflammation (bronchiectasis, tumors and tuberculosis) or attenuated pulmonary arterial supply to the lung (pulmonary infarction, pulmonary hypertension, and cyanotic congenital heart disease), the bronchial arteries increase in size and tortuosity and can anastomose with the pulmonary arterial system (Brugman & Irvin '89: 7, 8).

The **capillary endothelium** lines the intertwining network of anastomosing capillaries. A basement membrane and surrounding interstitial tissue separate the endothelial cells from the alveolar lining epithelial cells. In thin portions of the alveolar septum the basement membranes of epithelium and endothelium are fused, whereas in thicker portions they are separated by an interstitial space (the pulmonary interstitium) containing fine elastic fibers, small bundles of collagen, a few fibroblast- like interstitial cells, smooth muscle cells, mast cells, and rarely lymphocytes and monocytes. The alveolar epithelium comprises a continuous layer of two principal cells types: flattened, plate-like pavement type I pneumocytes (or membranous pneumocytes) covering 95% of the alveolar surface, and round type II pneumocytes. Type II cells are important for at least two reasons (a) they are a source of pulmonary surfactant and (b) they are the main cell type involved in the repair of alveolar epithelium after destruction of type I cells. Loosely attached to the epithelial cells or lying free within the alveolar spaces are the alveolar macrophages, derived from blood monocytes and belonging to the mononuclear phagocyte system. Often they are filled with carbon particles and other phagocytosed materials. The alveolar walls are not solid but are perforated by numerous **pores of Kohn**, which permit the passage of bacteria and exudate between adjacent alveoli. Adjacent to the alveolar cell membrane is the **pulmonary surfactant layer** (Kobzik & Schoen '94: 674).

The **pulmonary vessels** are rich in defense mechanisms. The vessels act as a sieve to trap endogenous particulate matter such as aggregates of red blood cells or platelets, fibrin clots, tumor cells, fat or tissue fragments. White blood cells and platelets marginate along the arterial walls and are a readily commandeered force for cellular defense against either endothelial or pulmonary parenchymal injury. The pulmonary circulation, by way of its blood-borne products, delivers a host of antiproteolytic agents, antioxidants and antibodies to the lung for immediate neutralization of various toxins. Loss or compromise of any of these defense elements of the system (for example, alpha$_1$-antitrypsin deficiency, O_2 toxicity, neutropenia, and pulmonary embolus) can result in serious, even catastrophic, pulmonary and systemic decompensation. The pulmonary vascular bed is ideally suited for its major metabolic functions because of its strategic location between the venous and systemic circulations and its vast surface area studded with superficial enzymes. PGI_2 , endothelium-derived relaxant factor and collagen are manufactured by the vascular endothelium as is angiotensin II, which has local and distant vascular effects. The pulmonary circulation is active in degrading blood-borne substances. For example, 98% of the serotonin, 30% of the norepinephrine, 80% of the bradykinin, and sizable amounts of vasoactive prostaglandins are removed on a first pass through this bed. Leukotriene clearance is further aided by the marginated neutrophils and eosinophils. The gas-exchange function of the pulmonary vascularity is intimately connected with the local control of the vascular resistance vessels. As a low-resistance, high compliance circuit, the pulmonary vessels can accommodate the entire resting cardiac output, and up to three to four times this volume during exercise, with minimal changes in pulmonary arterial pressure. The pulmonary vessels are exquisitely sensitive to a variety of stimuli, including alveolar hypoxia, norepinephrine, angiotensin II, histamine, serotonin, several prostaglandins (prostaglandin F2α, prostaglandin E_2, and thromboxane A_2), and some of the leukotrienes. The pulmonary vessels respond to these agents by autoregulating the delivery of blood flow to those areas with highest alveolar ventilation and thus maximize the exchange of gases. The versatility and enormous reserve of the pulmonary circulation are demonstrated by the fact that up to 50% of these vessels can be compromised without increasing pulmonary arterial pressure (Brugman & Irvin '89: 8).

Gas diffusion through the alveolar-capillary membrane is governed by **Fick's law**, which states the overall rate of transfer across a membrane is proportional to (1) its area, (2) the pressure

gradient on its two sides, and (3) a diffusion constant and is (4) inversely proportional to its thickness. The solubility of carbon dioxide in the membrane is about 20 times that of oxygen while the molecular weights of the two gases are similar. This had led to the widely held concept that carbon dioxide diffuses 20 times as fast as oxygen. The membrane diffusing capacity is expressed by the reaction rate with hemoglobin, in milliliters per minute, by the red cells in 1 ml of blood. The chemical reaction between carbon monoxide and hemoglobin is known to decrease in the presence for an increasing concentration of oxygen because of the competition between CO and O_2 for hemoglobin (King '89: 136, 137). Any change in pH, whether produced by respiratory or metabolic changes, alters O_2 affinity. Under pathologic conditions, **blood pH** can deviate markedly from pH 7.4 and have profound implications in oxygen delivery. Low pH may hamper oxygen uptake in the lung. Addition of CO_2 to blood causes pH to fall by 0.03 to 0.05 units. Sputum has a pH of 7.0 and must be removed through daily naso-bronchial hygiene. Ascent to high altitudes produces both hypoxemia and respiratory alkalosis. Alkalinity can be prevented by administration of acetazolamide (Klocke & Saltzman '89: 175). Acidosis is often corrected by hyperventilating through pursed lips and its cure is dependent on the excretion of acid by the kidneys. Although there is an immediate increase in hyperventilation due to peripheral chemoreceptor stimulation when metabolic acidosis is induced, up to 8 hours may be needed for the PCO_2 to fall to its expected value withing the 95 percent confidence band. If the academia is severe, bicarbonate therapy may be needed. **Bicarbonate therapy** is most effective when plasma bicarbonate is low and there is little be gained when the initial (HCO_3^-) is above 20 to 1 mEq/liter (Saltzman & Klocke '89: 205).

The lung and chest cavity are both lined with a thin slippery membrane called a **pleura**, that allows lungs and chest wall to slide easily past each other as you breather. Normally, there is no air or fluid between the two sets of pleura except the tiny bit of fluid greasing their movements. The linings have sensitive nerves. The most important protective covering for the lungs is the **chest cage**, which includes all the ribs, the spine and the sternum. All these parts of bone or cartilage are held together by rib muscles. The chest cage gives the lungs a definite shape and supports the lungs from the outside. The bottom of the chest joins the abdomen. A large, domes sheet of muscle and fibrous tissue, called the **diaphragm**, separates the lungs from the stomach and the other organs in the abdomen. When relaxing and taking a deep breath, the chest expands, the belly pooches out, cool dry air flows into the nose and mouth. The diaphragm attaches around its edge to the lower back and rib cage. Because of its dome shape, when it contracts, that dome flattens out and moves downward, pulling the bottoms of the lungs with it. At the same time, the intercostal muscles between the ribs pull to lift the rib cage up and out, and when working hard, some neck muscles help. The lung opens in all directions and like a bellows, pulls air in and down the airways into the air sacs. As air is being pulled in, the airways are wide open, pulled to their widest by the opening of the lung. When letting air out, all the muscles that have been pulling open relax, let go, and everything springs back to its usual place, the airways becoming narrower as the air is forced out. For a healthy person all it takes to get the air out is this automatic springing back. When emphysema develops, the alveoli are destroyed, the elastic abilities of the lung are lost, and they no longer empty automatically. The air being exhaled has to be pushed (Tucker et al '01: 34, 35, 36).

The **mediastinum** is bounded superiorly by the thoracic inlet, inferiorly by the diaphragm, anteriorly by the sternum, posteriorly by the anterior surfaces of the vertebral bodies, and laterally by the medial parietal pleura of the lungs. Traditionally the mediastinum has been divided into three anatomic divisions: anterior, posterior and middle. The anterior mediastinum is bordered by the sternum anteriorly and the anterior pericardium posteriorly and contain the

thymus, the anterior lymph nodes, mediastinal fat, and other connective tissues. The middle mediastinum is bordered anteriorly and posteriorly by the pericardium and contains the heart, great vessel, trachea, main-stem bronchi, parts of the vagus nerves, phrenic nerves, and the middle mediastinal lymph nodes. The posterior mediastinum is bordered anteriorly by the posterior pericardial surface and posteriorly by the thoracic vertebral bodies. Its contents include the esophagus, the sympathetic chains, parts of the vagus nerves, the descending aorta, and the thoracic duct. Radiographically the mediastinum is bounded in the anterioroposterior projection by the borders of the right and left sides of the heart, superiorly by the sternal notch, and inferiorly by the diaphragm (Rodell '89: 296).

The chest wall and **respiratory muscles** pump by the contraction of the respiratory muscles with expansion of the rib cage and descent of the diaphragm to create a larger volume. The negative pressure within the thorax establishes a pressure gradient from the mouth to the alveoli and results in airflow into the lung. The bony part of the chest wall consists of 12 ribs that are attached to and articulate with the thoracic spine. The movement of the ribs has been compared with the motion of a bucket handle or a pump handle. Congenital malformation (for example, pectus excavatum or pectus carinatum), trauma (as in surgery or gunshot wound), or external restriction (such as a tight-fitting girdle) can profoundly influence the range of motion of the thorax. Eupnea, or spontaneous ventilation, occurs throughout our lives and requires rhythmic and automatic contraction of the respiratory muscles. The respiratory muscles include the diaphragm, the intercostal muscles, the accessory or "strap" muscles in the neck, and the less appreciated abdominal muscles. Like all skeletal muscle the respiratory muscle can fatigue and fail. The **diaphragm**, the primary muscle of respiration, consists of a central tendon, and two muscle groups, the costal and the cural muscles. Innervation of the diaphragm is provided by the phrenic nerve which not only delivers the neural input, but also returns sensory afferents to the central nervous system, the role of which is poorly understood. When activated, the diaphragm descends against the abdominal contents and increases the thoracic volume. Volume is also increased through the expansion of the costal margins of the rib cage. In patients with bilateral diaphragmatic paralysis the diaphragm is passively displaced and active expiration is due to contraction of the abdominal muscles. The intercostal muscles can be divided into external and internal intercostal muscles. The sternocleidomatoid and the scalene muscles are believed to also have respiratory functions. The primary function of the respiratory muscles is to provide adequate alveolar ventilation (Brugman and Irvin '89: 3, 4).

The brain tells the breathing muscles to work by sending signals along the nerves. The body communicates to the brain that it needs more air in several ways. Lack of oxygen, increased carbon dioxide, putting a stretch on joints or lungs or muscle, pressure on large blood vessels, rise in body temperature and changes in the chemical balance of the body can all be sensed by the special nerves which talk to the breathing centers of the brain. The speed or depth of breathing changes in response to these signals. The strongest signal to breathe comes from too much carbon dioxide in the blood. But in people with sick lungs, the amount of carbon dioxide in the blood slowly increases over many years so that the brain no longer signals properly. Control of breathing may be conceptualized as having three parts: (1) the command center: the cerebral cortex or brainstem, (2) the sensor activators: the various receptors and their neural connections and (3) the effectors: the lungs and respiratory muscles, which are the loci of sensory information and respond to neural input from the command center. The command center for spontaneous rhythmic breathing is located in the medulla oblongata of the brainstem and consists of two major groups of neurons, the dorsal respiratory group (DRG) and the ventral respiratory group (VRG). The DRG is the preeminent respiratory oscillator and is composed

mainly of inspiratory neurons, whereas the VRG contains both inspiratory and expiratory neurons. Although automatic, these centers are acted on and modulated in a complex way by incoming (afferent) signals from the sensory receptors, the pons, the reticular activating system and the cerebral cortex (Brugman and Irvin '89: 5).

A series **sensory receptors** are the carotid bodies, and to a lesser extent the aortic bodies. These are small nests of cells that are located at the junction of the carotid arteries and on the aorta. Both bodies are richly vascularized and innervated, and both are exquisitely sensitive to decreases in arterial oxygen pressure (PaO_2). These sensors are also responsive to arterial pH and arterial carbon dioxide pressure ($PaCO_2$). The **carotid bodies** account for 100% of the hypoxic stimulatory drive occurring in humans and also produce cardiovascular effects of hypotension and bradycardia. Hypoxic ventilator drive is blunted with age, in high-altitude dwellers, and in the pathologic states of chronic bronchitis, morbid obesity and sleep apnea. **Central chemoreceptors** are located in three distinct bilateral loci in the medulla of the brain, increase ventilation when $PaCO_2$ (as in respiratory acidosis), since CO_2 is readily diffusible into the CSF. This response is brisk and linear in normal individuals, approximating a 1 liter/minute increase in ventilation for every 1 mm Hg increase in $PaCO_2$ above 40 mm Hg. The ventilator response to metabolic acidosis is comparatively delayed, since hydrogen ion is not so readily diffusible across the blood-brain barrier. Conditions that may attenuate the central ventilator response to CO_2 are advancing age, chronic obstructive lung disease, pharmacologic central nervous system depressants, and rare disorders such as Ondine's curse (Brugman & Irvin '98: 6).

The **lung and upper airway receptors** include (1) Stretch receptors: Located in the airways, these receptors respond to changes in pressure and lung volume. They act to inhibit inspiration and possibly to coordinate the rate and depth of breathing to produce efficient gas exchange at the least energy cost. (2) Irritant receptors: These rapidly adapting receptors are located in the epithelium of the larynx and large airways. They respond to a variety of chemical, irritant, and mechanical stimuli, as well as pulmonary microemboli. Stimulation results in cough, laryngospasm, bronchoconstriction, and mucorrhea. (3) C-fiber receptors: Primary among these are the J receptors, which are unmyelinated nerve endings located in the lung parenchuma. They are accessible to the pulmonary capillaries and are stimulated by interstitial edema, microembolism, and chemical products of anaphylaxis. Their role in normal breathing is probably minimal but activation of the J receptors results in the tachypnea and dyspnea that has been associated with pneumonia, pulmonary edema and toxic inhalation. The respiratory muscle receptors are located in the diaphragm, the intercostal muscles and the upper airway muscles and take the form of encapsulated receptors, unmyelinated nerve endings, Golgi tendon organs, and muscle spindles. These sensors respond to the contractile state of the individual muscle units and feed this information to the spinal cord and to the central controllers. These receptors are thought to play a role in the regulation of posture and in the sensation of dyspnea (Brugman & Irvin '98: 7).

The twelve cranial nerves, numbered C; I-XII, that innervate the head are well understood by ortolaryngology. CI olfactory, sense of smell. CII optic, vision. CIII oculomotor, eye movements, constriction and dilatation of pupil accommodation. CIV trochlear, eye movements. CV trigeminal, sensations of the head and face, muscle sense; mastication, tensor tympani, tensory palatine, mylohyoid, anterior digastric. CVI abducens, abduction of the eye. CVII facial, taste, sensations of external ear canal; facial expression, secretion of tears, saliva secretion, nasal secretion. CVIII vestibulocochlear, hearing/balance. CIX glossopharyngeal, taste, tongue sensations sensations of the middle ear, swallowing movements, saliva secretion.

CX vagus, sensations and taste of oropharynx and epiglottis, sensations of external ear canal; swallowing and voice production. CXI spinal accessory, shoulder and neck movements, pharyngeal plexus. CXII hypoglossal, tongue movements (Peng & Har-el '04: 29 Table 2-3).

II.B. Cardiovascular System

II.B.1 Blood

Blood is a specialized body fluid. It has four main components: plasma, red blood cells, white blood cells, and platelets. Blood appears red because of the large number of red blood cells, which get their color from the hemoglobin. Blood has many different functions, including transporting oxygen and nutrients to the lungs and tissues, forming blood clots to prevent excess blood loss, carrying cells and antibodies that fight infection, bringing waste products to the kidneys and liver, which filter and clean the blood and regulating body temperature. The blood that runs through the veins, arteries, and capillaries is known as **whole blood**, a mixture of about 55 percent plasma and 45 percent blood cells. About 7 to 8 percent of total body weight is blood. An average-sized man has about 12 pints of blood in his body, and an average-sized woman has about 9 pints. Human beings can survive without food for thirty or forty days – about five weeks – but without water, life would end in three to five days. A drop in the body's water content causes a decline in blood volume. The lowering of blood volume in turn triggers the hypothalamus, which is the brain's thirst center, to send out the demand for a drink. This causes a slight rise in the concentration of sodium in the blood. These changes quickly trigger a sensation of thirst (Balch '00: 35).

Donated blood is administered intravenously to treat loss of blood, according to blood type, or to prepare biological products such as human immunoglobulin IV. **Payments to donors** of blood for persons undergoing treatment at Government expense under 24USC§30. Any person, whether or not in the employ of the United States, who shall furnish blood from his or her veins for transfusion into the veins of a person entitled to and undergoing treatment at Government expense, whether in a Federal hospital or institution or in a civilian hospital or institution, or who shall furnish blood for blood banks or for other scientific and research purposes in connection with the care of any person entitled to treatment at Government expense, shall be entitled to be paid therefor such reasonable sum, not to exceed $50, for each blood withdrawal as may be determined by the head of the department or independent agency concerned, from public funds available to such department or independent agency for medical and hospital supplies: Provided, That no payment shall be made under this authority to any person for blood withdrawn for the benefit of the person from whom it is withdrawn**.**

Blood transfusions are the transfer of blood, its components, or products from one person (donor) into another person’s bloodstream (recipient). Every year in the U.S., more than 20 million units of red blood cells, platelets, and plasma are transfused to treat hematologic conditions such as severe anemia, leukemia, and sickle cell disease. Transfusions have long been associated with some risk to patients. The HIV epidemic during the 1980s was a major cause of fear; regular transfusions, especially of clotting factor concentrates, spread the virus quickly and nearly undetected. That outbreak prompted the development of biovigilance or hemovigilance: tracing and tracking transfusion-related adverse events and incidents, both infectious and non-infectious, that affect blood donors and recipients. Another of the most significant issues complicating transfusion safety has been bacterial contamination of blood products, particularly of platelets. However, steps have been taken in the last decade to avoid, detect, and eliminate this

complication through improved donor selection, specialized preparation of the arm before needle insertion, and special screening techniques. Blood is regularly tested for infectious disease transmission, particularly for viruses such as Hepatitis B and C, HIV, and West Nile Virus. Serum tests have been replaced by molecular testing called nucleic acid amplification testing (NAT), which finds active viruses in the donor's blood to determine infection risk. If an active virus is found, the donor unit is discarded. Experts anticipate that new methods, including new molecular and microarray testing, which can identify many infectious agents rapidly and accurately, will replace or augment serum studies and NAT in the near future. Blood transfusion has never been safer from known infectious risk than it is today (Luban '08).

The bone marrow, lymph nodes and spleen are all involved in **hematopoiesis** the production of red and white blood cells. Traditionally, these organs and tissues have been divided into myeloid tissue, which includes the bone marrow and the cells derived from it (e.g. erythrocytes, platelets, granulocytes, and monocytes), and lymphoid tissue, consisting of thymus, lymph nodes and spleen. In the human embryo, clusters of stem cells, called "blood islands", appear in the yolk sac in the third week of fetal development. At about the third month of embryogenesis some of these cells migrate to the liver, which then becomes the chief site of blood formation until shortly before birth. Beginning in the fourth month of development, hematopoiesis commences in the bone marrow. At birth, all the marrow throughout the skeleton is active and is virtually the sole source of blood cells. In the full-term infant, hepatic hematopoiesis has dwindled to a trickle, but may persist in widely scattered small foci, which become inactive soon after birth. Up the age of puberty, all the marrow throughout the skeleton is red and hematopoietically active. Usually by 18 years of age only the vertebrae, ribs, sternum, skull, pelvis and proximal epiphyseal regions of the humerus and femur retain red marrow, the remaining marrow becoming yellow, fatty, and inactive. Thus, in adults, only about one-half of the marrow space is active in hematopoiesis. With an increased demand for blood cells in the adult, the fatty marrow may become transformed to red, active marrow increasing red cell production (erythropoiesis) seven-to-eight fold. If marrow precursor cells are destroyed by metastatic cancer or irradiation, producing anemia, extramedullary hematopoiesis may reappear, first within the liver and then in the spleen and lymph (Saunders '94: 583,584).

All the formed elements of blood –T cells, B cells (plasma cells), platelets, erythrocytes, leukocytes, macrophages and eosinophils – have a common origin in a **pluripotent hematopoietic stem cell**. Gametes formed by the union of sperm and egg are known as omnipotent stem cells. The pluripotent hematopoietic stem cell is the common precursor that gives rise to lymphoid stem cells and and trilineage myeloid stem cells. The lymphoid stem cell, is believed to be the origin of precursors of T cells (pro-T cells), B cells (pro-B cells) and possibly natural killer (NK) cells. From the **multipotent myeloid stem cell** arise at least three types of committed stem cells capable of differentiating along the erythroid/megakaryocytic, eosinophilic, and granulocyte-macrophage pathways. From various committed stem cells, intermediate stages are derived, such as, proerythroblasts, myeloblasts, megakaryoblasts, monoblasts and eosinophiloblasts. These in turn give rise to mature progeny. Since mature blood elements have a finite life span, their numbers must be constantly replenished (Saunders '94: 584).

A **complete blood count** (CBC) test gives important information about the types and numbers of cells in your blood, especially the red blood cells and their percentage (hematocrit) or protein content (hemoglobin), white blood cells, and platelets. The results of a CBC may diagnose conditions like anemia, infection, and other related disorders such as cancers of the blood. A

complete blood count (CBC) is done by automated cell counters that measure the hemoglobin, red blood cell count, red blood cell volume distribution, platelet count, and white blood cell count. The percentage of whole blood volume that is made up of red blood cells is called the **hematocrit** and is a common measure of red blood cell levels. The mean cell volume (MCV) (based on volume distribution), mean cell hemoglobin (MCH) (hemoglobin divided by RBC count), mean cell hemoglobin concentration (MCHC) (hemoglobin divided by hematocrit) and the red cell distribution width (RDW). The red cell indices and RDW are used together with a direct inspection of the Wright-stained blood smear to evaluate red blood cell morphology (Hillman '98: 334-336). The iron level with Total Iron Binding Capacity (Fe and TIBC) test detect certain kinds of anemia, such as iron deficiency after blood loss. Serum Haptoglobin Test detect intravascular destruction of RBCs associated with hemolytic anemia. Hemoglobin electrophoresis enable one to detect abnormal forms of Hgb (hemaglobinopathies). Direct and indirect Coombs tests detect the presence of antibodies to RBC found in tissue and fetal rejection. A reticulocyte count (Retic count) is a test for determining bone marrow function in which immature RBC as a percentage of total RBC production. The platelet count and plasma **clotting tests** (prothombin time, partial thromboplastin time, and thrombin time) may be used to evaluate bleeding and clotting disorders. To count the percentage of total white blood cell volume occupied by specific white blood cells a **CBC with Differential** is ordered. The white blood cell (WBC) differential is a measure of the total number of white blood cells and the percentages of the five types of WBC descriptive of infection, stress and bone marrow failure (Griffin '84: 3-16)..

Complete Blood Count (CBC), Coagulation Tests and White Blood Cell (WBC) Differential

Test	Normal Range	Comments
Complete Blood Count (CBC)		
Red Blood Cell (RBC) count	M 4.7-6.2 million/cu mm F 4.2-5.4 million/cu mm	Low – anemia, hemorrhage High – chronic anoxia
Hemoglobin (Hgb)	M14-18 g/dl F12-16	Same as above
Hematocrit (Hct)	M42-52% F37-47%	Same as above
Mean corpuscular volume (MCV)	80-95 cu/u	High - RBC macrocytic Low –RBC microcotic
Mean corpuscular hemoglobin concentration (MCHC)	32-36 g/dl (32-36%)	Low – Hypochromic cell
Iron (Fe)	60-190 µg/dl	Low-iron deficiency anemia
Total iron binding capacity (TIBC)	250-420 µg/dl	Same as above
Serum haptoglobin	100-150 mg	Low-Hemolysis liver disease High-Inflammatory disease
Hemoglobin electrophoresis	Hgb A_1 95-98% Hgb A_2 2-3% Hgb F 0.8-2% Hgb S 0% Hgb C 0%	Variations indicate hemoglobinopathies, High Hgb F – thalassemia found in Central asians. Hgb S-sickle cell anemia and Hgb C mild hemolytic anemia found in

		American blacks
Direct Coombs' and Indirect Coombs	Negative	To detect antibodies against RBC in transplant rejection
Reticulocyte counts	0.5%-2% of total RBC	Low-inaquate RBC production High-Polycythemia vera
White Blood Cell (WBC) count	5000-10,000/cu mm	High-infection Low-Bone marrow failure
Platelet count	150,000-400,000/cu mm	Low-Bone marrow failure, hypersplenism, accelerated consumption High-Hemorrhage, polycythemia vera, malignancies
Coagulation Tests		
Prothrombin test (PT)	11-12.5 seconds (85-100%)	High-Deficiency of factors V and VII
Prothrombin time test (PTT)	30-40 seconds	High-Deficiency of factors II, V, VIII, IX, XI, XII
Platelet count	150,000-400,000/cu mm	Low-Bone marrow failure, hypersplenism, accelerated consumption High-Hemorrhage, polycythemia vera, malignancies
Bleeding time	1-9 minutes	High Thrombocytopenia, marrow infiltration, inadequate platelet function
Eublobin lysis time	90 minutes-6 hours	Low-Fibrinolysis
Fibrin degradation products (FDP) test	< 10µg/ml	High DIC, fibrinolysis
White Blood Cell (WBC) Differential		
White Blood Cell (WBC) count	5000-10,000/cu mm	High-infection Low-Bone marrow failure
Neutrophils	50-70	High-Inflammation, Invasive tumors
Eosinophils	2-4	High-Allergic states, Drug reactions, Parasitic Infections, Some skin disease and neoplasms
Basophils	0.5	High-Asthma, some Carcinogens, Inflammatory bowel disease, Chronic inflammation
Macrophages	5-7	High-Chronic infections, Liver disease, Neutropenia
Lymphocytes	20-35	High-some Carcinomas
Plasma Cells	?	Multiple myeloma

Source: Griffin '86: Table 1.1 pg. 5-6; Table 2-3 pg. 32

The liquid component of blood is called **plasma**, a mixture of water, sugar, fat, protein, and salts. B cells sometimes morph into plasma cells. The main job of the plasma is to transport blood cells throughout your body along with nutrients, waste products, antibodies, clotting proteins, chemical messengers such as hormones, and proteins that help maintain the body's fluid balance. Once thought to be just "dust" particles in blood, platelets were first recognized as a special class of blood cells (actually cell fragments) by an Italian researcher in 1882. Unlike red and white blood cells, **platelets** are not actually cells but rather small fragments of cells. Platelets help the blood clotting process (or coagulation) by gathering at the site of an injury, sticking to the lining of the injured blood vessel, and forming a platform on which blood coagulation can occur. This results in the formation of a **fibrin clot**, which covers the wound and prevents blood from leaking out. Fibrin also forms the initial scaffolding upon which new tissue forms, thus promoting healing. A higher than normal number of platelets can cause unnecessary clotting, which can lead to strokes and heart attacks; however, thanks to advances made in antiplatelet therapies, there are treatments available to help prevent these potentially fatal events. Conversely, lower than normal counts can lead to extensive bleeding.

Known for their bright red color, **red cells**, also called erythrocytes or RBCs, are the most abundant cell in the blood, accounting for about 40-45 percent of its volume. The shape of a red blood cell is a biconcave disk with a flattened center – in other words, both faces of the disc have shallow bowl-like indentations (a red blood cell looks like a donut). Red cells contain a special protein called **hemoglobin**, which helps carry oxygen from the lungs to the rest of the body and then returns carbon dioxide from the body to the lungs so it can be exhaled. Blood appears red because of the large number of red blood cells, which get their color from the hemoglobin. The percentage of whole blood volume that is made up of red blood cells is called the hematocrit and is a common measure of red blood cell levels. Production of red blood cells is controlled by **erythropoietin**, a hormone produced primarily by the kidneys. Red blood cells start as immature cells in the bone marrow and after approximately seven days of maturation are released into the bloodstream. Unlike many other cells, red blood cells have no nucleus and can easily change shape, helping them fit through the various blood vessels in your body. However, while the lack of a nucleus makes a red blood cell more flexible, it also limits the life of the cell as it travels through the smallest blood vessels, damaging the cell's membranes and depleting its energy supplies. The red blood cell survives on average only 120 days.

The intestine's blood vessels eventually come together and carry the blood to the liver, where the **nutrients** are screened for harmful substances and toxins. Any dangerous substances can be destroyed here before the blood passes into the main circulatory system. The liver is where the first energy stores are created if eating too much. The nutrient-rich blood then flows from the liver directly to the heart. There, it receives a powerful push and is pumped to the countless cells of the body. In this way, a sugar molecule an end up in a skin cell, where it absorbed along with oxygen, that releases energy, which the cell uses to stay alive, with heat and tiny amounts of water created as by-products, this happens inside so many cells at the same time that the heat produced keeps out body at a constant temperature of 97 to 99 degrees Fahrenheit (36 to 37 degrees Celsius) (Enders '15: 37-42). Fat is not soluble in water, it would immediately clog the tiny blood capillaries in the villi of the gut and float on top of the blood in larger vessels. Fat must be absorbed via a different route, the lymphatic system. Every blood vessel inside the body is accompanied by a lymphatic vessel, even each tiny capillary in the small intestine. While blood vessels are thick and red and pump nutrients to tissues, the lymphatic vessels are thin and

filmy white in color. They drain away fluid that is pumped out of tissue and transport the immune cells. Lymphatic vessels are so slight because they do not have muscular walls like blood vessels, often working just by gravity. All the body's lymph vessels converge in an impressively thick duct, known as the *ductus thoracicus*, where all the digested fat can gather without the risk of clogging (Enders '15: 50-54).

White blood cells, also called **leukocytes**, protect the body from infection. They are much fewer in number than red blood cells, accounting for about 1 percent of blood cells. There are five main types: neutrophils, lymphocytes, macrophages, eosinophils and basophils. The most common type of white blood cell is the **neutrophil**, which is the "immediate response" cell and accounts for 55 to 70 percent of the total white blood cell count. Their job is to consume unwelcome cells. Each neutrophil lives less than a day, so your bone marrow must constantly make new neutrophils to maintain protection against infection. Transfusion of neutrophils is generally not effective since they do not remain in the body for very long. The other major type of white blood cell is a **lymphocyte**. There are two main populations of these cells: T cells and B cells. T lymphocytes, or **T cells**, secrete potent substances to attract and regulate other immune system cells, that do the actual work, and directly attack various infected cells and tumors. B lymphocytes, or **B cells**, are immune cells that actually produce antibodies, which are proteins that specifically target bacteria, viruses or other foreign materials. B cells have long memories for their enemies and may remain in the body for years, ready at any time to turn into antibody factories whenever an antigen they recognize appears. This is how a vaccination works: a tiny bit of a (usually) killed virus, or antigen, such as polio, measles, or flu, is injected into your blood-stream, provoking B cells to produce antibodies. Then, if you ever encounter the fully functional form of the virus, your body can quickly marshal its defenses and produce millions of the required antibodies without delay. **Macrophages** engulf and destroy large cells, such as bacteria or yeast, as well as the debris from natural cell formation in a growing body. **Eosinophils** make up 4 percent or less of active white blood cells. They attack larger cells, in part by secreting toxins that trigger inflammation. **Basophils** release granules of germ-killing toxins and histamine, a substance that triggers inflammation when they encounter damaged tissue (Berger '04: 23, 24).

The immune system knows which are "good" cells and which are "bad" cells because the surface of every sell in your body sports special proteins called **human leukocyte antigens** (**HLAs**). Your blood contains more than 1 trillion antibodies. Antibodies are made up of chains of molecules that form a Y shape. The sections that make up the tips of the Y's arms vary greatly from one antibody to another; this is called the variable region. It develops a unique shape based on the antigen it was created to react to, so it can "lock" onto that antigen just like a key fitting into a lock. Sometimes this locking neutralizes the antigen on its own, rendering it harmless; sometimes it ruptures the cells of the foreign body; and sometimes it forces antigens to clump together, creating sitting-duck target for other immune cells to attack. There are five classes of antibodies, each with a slightly different function and operating method. Scientists call them **immunoglobulins**, or Igs for short. Of the five, IgE is the one we could call the "allergy antibody", since IgE antibodies are the main culprits contributing to allergies. IgE binds the allergen molecule either to basophils, or to cells called mast cells found in the mucous linings of tissues throughout the body, such as the throat, nose, lungs, skin or stomach lining. This binding triggers the mast cells or basophils to release inflammatory chemicals, such as histamine, prostaglandins, and leukotrienes. The inflammatory process begins, with swelling, creation of mucus, reddening, heat and vessel constriction – an allergic reaction (Berger '04: 27, 28, 30).

Austrian-American physician Karl Landsteiner (1868-1943) announced in 1901 that human blood can be classified into only a few general classes or types, which are known today as A. B, AB, and O. The chemical nature of the antigens responsible for the blood types that make up the ABO groups was first discovered in 1953. If a person with type A blood receives type A blood from a donor, there is no risk because the recipient's body recognizes and accepts the type A blood. If the same person is given type B blood, however, his or her immune system does not recognize the type B blood cells, ad its anti-B antibodies begin to attack the transfused blood. The physical process of testing for ABO blood types is actually quite simple and requires only two reagents ant-A serum and anti-B serum. The sample is tested with each reagent one at a time. According to the Red Cross blood bank, the population of the United States is approximately 39 percent type A, 46 percent type O, 11 percent type B, and 4 percent type AB (Robbins '01: 73). Narrowing the field of suspects of from 100 percent to 40 percent however does not help much. A second system of blood typing with which many people are familiar is the Rh system, named for the blood factors (Rh+ and Rh-) that were first observed in rhesus monkeys. The availability of two systems of blood typing increases the possibility of identifying a blood sample (Newton '07: 33, 36 39).

Properties of ABO Blood Typing

Blood Group	Antigens	Test Result	Can Give Blood To	Can Receive Blood From	Frequency in Population
A	A	Anti-B	A and AB	A and O	40-42%
B	B	Anti-A	B and AB	B and O	10-12%
AB	A and B	Both anti-A and anti-B	AB	A, B, AB and O	3-5%
O	H	Neither anti-A and anti-B	A, B, AB and O	O	43-45%

Source: Newton '07: 37

Over the past half-century, immunochemists have discovered a number of other antigen-antibody systems in the blood. The International Society of Blood Transfusion (ISBT) currently recognizes 26 such blood-grouping systems In addition to the ABO and Rh systems, such groupings include the MNS, Lutheran, Kell, Lewis, Duffy, Kidd, Diego, Cartwright, Xg, and Scianna systems. Of the 26 ISBT blood-typing systems available today, only the ABO and Rh systems are commonly used in forensic serology. In order to specify more precisely the characteristics of a blood sample, a serologist is likely to analyze other components found in blood, primarily polymorphic proteins or isoenzymes. In order to specify more precisely the characteristics of blood sample, a serologist is likely to analyze proteins found in blood, primarily polymorphic proteins or isoenzymes such as: Adenosine deaminase (ADA), Adenylate kinase (AK), Erhtyrocyte acid phosphatase (EAP), Esterase-D (EsD), Glucose-6-phosphate dehydrogenase (G-6-PD), Glyoxylase I (GLOI), Glutamic pyruvate transminase (GPT), Haptoglobin (Hp), Peptidase A (PeP A), Phosphoglucomutase (PGM), 6-Phosphogluconate dehydrogenase (6-PGD) and Transferin (Tf). These tests are generally adequate to establish paternity with around 1 percent margin of error. Another useful adjunct to classic ABO blood

testing is the human leukocyte antigen (HLA) test. These antigens exist on white blood cells, in contrast to almost all other polymorphic proteins and isoenzymes that occur in red blood cells. HLA types are classified into four classes A-D, each of these includes a number of subclasses – 23 known types of HLA-A, 47 types of HLA-B, eight types of HLA-C and 4 types of HLA-D. In paternity testing the chance of a man having the same type of HLA as the child in question is very low, about one in 92. ABO testing alone can exclude the possibility that a man is the father of a child about 20 percent of the time. HLA testing can exclude the same possibility about 90 percent of the time. In combination, the two tests can exclude the possibility of parenthood by about 97 percent of all cases (Newton '07: 33, 36, 40, 41, 46, 47, 39, 40).

Type II hypersensitivity, also known as tissue specific, cytotoxic, or cytolytic hypersensitivity, is characterized by antibodies that attack antigens on the surface of specific cells or tissues. Often the reaction is immediate (15 to 30 minutes after exposure to the antigen). Hyperacute graft rejection is a type II hypersensitivity that affects transplanted tissues. It occurs when the transplanted donor tissue has an antigen to which the recipient has preformed antibodies. For example, when tissue from a blood type A or B donor is transplanted. Into a blood type O recipient, the recipient has anti-A and Anti-B antibodies. These antibodies will immediately attack the foreign transplanted tissue. Onset begins immediately after revascularization occurs in the transplant procedure. At this time, the blood supply from the patient is established in the newly transplanted organ. The patient's antibodies attack the foreign protein antigens and for an antigen-antibody complex. Effector cell infiltration and complement-mediated lysis of donor tissues, inflammation, vascular thrombosis and hemorrhage occur. The reaction happens so quickly that within 48 hours after transplantation the graft tissue is ravage and no longer functioning. To prevent hyperacute graft rejection, tissue and blood typing of donors and recipients of transplanted tissue is extensive. Lists of potential recipients are matched to donors through organ donation laboratories both regionally and nationally. Only rarely has hyperacute graft rejection occurred because of an error in tissue or blood typing (Peterson '05: 254).

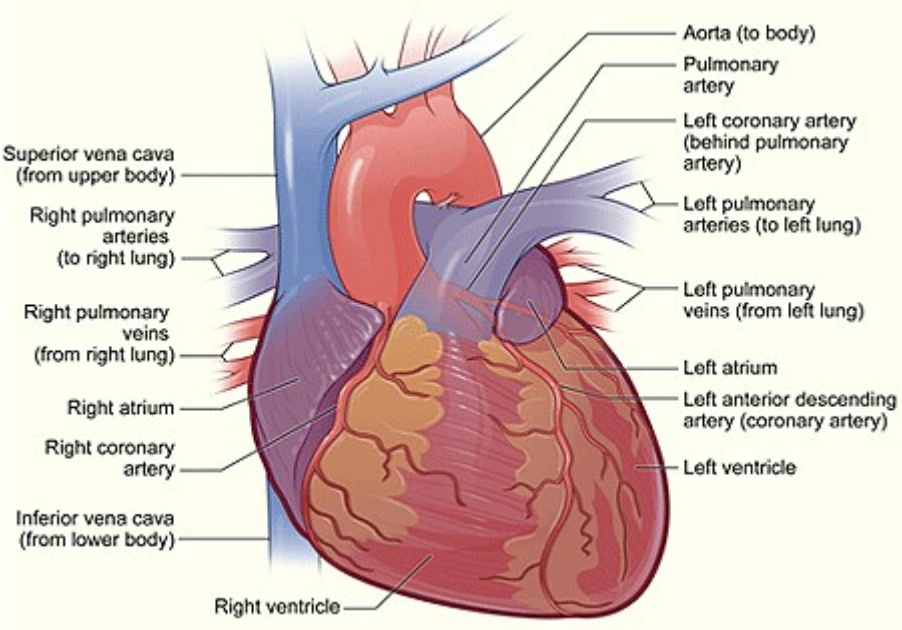
II.B.2 Heart and Valves

The heart is a four-chambered muscular structure. It is about the size of a fist but can get much larger with disease. An adult weighing 160 pounds has about 5 quarts (4.7 liters) of blood in their circulatory system. The heart beats at a rate of 60 to 100 times per minute. It pumps 1,500 gallons of blood each day. It beats about 100,000 times per day and 36 million times per year. In a 70-year lifetime, an average human heart beats more than 2.5 billion times. Heart muscle does not usually regenerate. Expected heart weight varies with height and skeletal structure; it averages approximately 250 to 300 grams (gm) in females and 300 to 350 gm in males. Normally the thickness of the free wall of the right ventricle is 0.3 to 0.5 centimeters (cm) and that of the left ventricle 1.3 to 1.5 cm. Greater weight or ventricular thickness indicates hypertrophy and enlarged chamber size implies dilatation. Increased weight or size of the heart is known cardiomegaly (Schoen '94: 517). The heart pumps blood continuously through the circulatory system (Cohen '10).

As the **cardiac muscle** contracts it pushes blood through the chambers and into the vessels. Nerves connected to the heart regulate the speed with which the muscle contracts. When running, the heart pumps more quickly. When asleep, the heart pumps more slowly. Located in the middle of the chest behind the breastbone, between the lungs, the heart rests in a moistened chamber called the **pericardial cavity**, which is surrounded by the ribcage. The **diaphragm**, a tough layer of muscle, lies below. As a result, the heart is a well-protected organ. The heart has

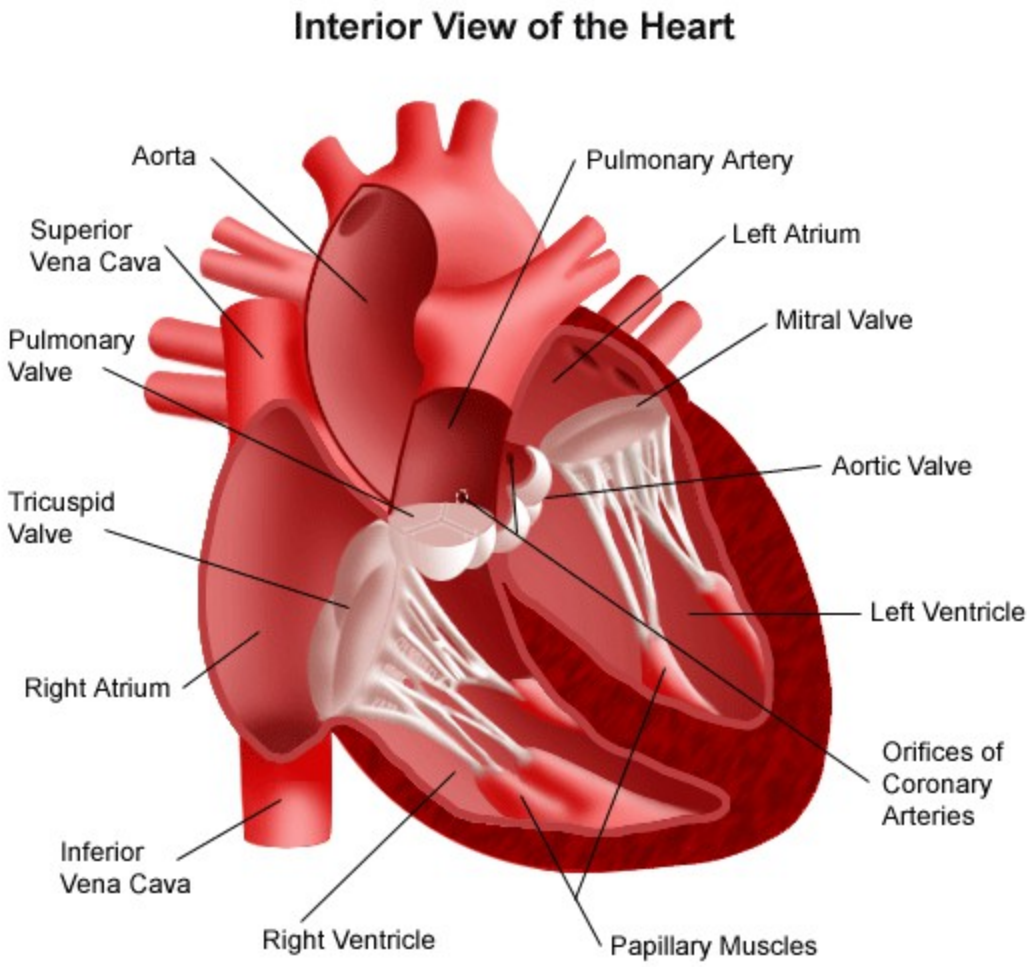
four chambers. Connected to the heart are some of the main blood vessels—arteries and veins—that make up the blood circulatory system. The **ventricle** on the right side of the heart pumps blood from the heart to the lungs. When air is breathed in, oxygen passes from the lungs through blood vessels where it's added to the blood. Carbon dioxide, a waste product, is passed from the blood through blood vessels to the lungs and is removed from the body when the air is breathed out. The **atrium** on the left side of the heart receives oxygen-rich blood from the lungs. The pumping action of the left ventricle sends this oxygen-rich blood through the **aorta** (a main artery) to the rest of the body. Like all organs, the heart needs blood rich with oxygen. This oxygen is supplied through the coronary arteries as it's pumped out of the heart's left ventricle. The **coronary arteries** are located on the heart's surface at the beginning of the aorta. The coronary arteries carry oxygen-rich blood to all parts of the heart.

Heart Exterior



Credit: American Heart Association

The right and left sides of the heart are divided by an internal wall of tissue called the **septum**. The area of the septum that divides the two upper chambers (atria) of the heart is called the atrial or **interatrial septum**. The area of the septum that divides the two lower chambers (ventricles) of the heart is called the ventricular or **interventricular septum**. On the right side of the heart are the superior and inferior **vena cava**. These veins are the largest veins in the body. They carry used (oxygen-poor) blood to the **right atrium** of the heart. "Used" blood has had its oxygen removed and used by the body's organs and tissues. The **superior vena cava** carries used blood from the upper parts of the body, including the head, chest, arms, and neck. The **inferior vena cava** carries used blood from the lower parts of the body. The used blood from the vena cava flows into the heart's right atrium and then on to the right ventricle. From the **right ventricle**, the used blood is pumped through the **pulmonary arteries** to the lungs. Here, through many small, thin blood vessels called **capillaries**, the blood picks up oxygen needed by all the areas of the body. The oxygen-rich blood passes from the lungs back to your heart through the **pulmonary veins**. Oxygen-rich blood from the lungs enters the **left atrium** and is pumped into the left ventricle. From the **left ventricle**, the blood is pumped to the rest of the body through the **aorta**.



Credit: Lucile Salter Packard Children's Hospital

The heart has four **valves**. The valves include the aortic valve, the tricuspid valve, the pulmonary valve, and the mitral valve. The four cardiac valves respond passively to pressure and flow changes within the heart. They function as loose flaps (leaflets or cusps) that seal the valvular orifices against regurgitation of blood when closed but fold out of the way when the valve is open, to provide an obstruction-free orifice. During the closed phase, the three cusps of the **semilunar valves** (aortic and pulmonic) overlap along an area (the lunula) between the free edge and a line marked by a white ridge on the ventricular surface of the cusp (linea alba). The overlap is substantial; in the **aortic valve**, for example, the total cuspal area is about 40% greater than the valve orifice area. Each aortic cusp has a small nodule (nodules of Arantius or Magagni's nodules) in the center of the free edge, which facilitates closure. The free margins of the **atrioventricular (AV) valves** (mitral and tricuspid) are tethered to the ventricular wall by many delicate chordae tendingeae, attached to papillary muscles, which are contiguous with the underlying ventricular walls. Normal **mitral valve** function depends on the coordinated actions of cusps, chordae tendingeae, papillary muscles and associated left ventricular wall (collectively the mitral apparatus). **Tricuspid valve** function depends on analogous structures. The function of semilunar valves depends on the integrity and coordinated movements of the cusps and their attachments. Thus dilatation of the aortic root in hypertension or syphilis can keep the aortic valve cusps from coming together during closure, just as left ventricular dilatation or a ruptured

chorda or papillary muscle can keep the mitral valve from complete closure, each resulting in regurgitant flow (Schoen '94: 518).

The heart uses the four valves to ensure blood flows only in one direction. Healthy valves open and close in coordination with the pumping action of the heart's atria and ventricles. Each valve has a set of flaps called leaflets or cusps. These seal or open the valves. This allows pumped blood to pass through the chambers and into your blood vessels without backing up or flowing backward. Blood without oxygen from the two vena cava fill the heart's right atrium. The atrium contracts (**atrial systole**). The tricuspid valve located between the right atrium and ventricle opens for a short time and then shuts. This allows blood to enter into the right ventricle without flowing back into the right atrium. When the heart's right ventricle fills with blood, it contracts (**ventricular systole**). The pulmonary valve located between the right ventricle and pulmonary artery opens and closes quickly. This allows blood to enter into the pulmonary artery without flowing back into the right ventricle. This is important because the right ventricle begins to refill with more blood through the tricuspid valve. Blood travels through the pulmonary arteries to the lungs to pick up oxygen. Oxygen-rich blood returns from the lungs to the heart's left atrium through the pulmonary veins. As the heart's left atrium fills with blood, it contracts. This event also is called **atrial systole**. The mitral valve located between the left atrium and left ventricle opens and closes quickly. This allows blood to pass from the left atrium into the left ventricle without flowing back into the left atrium. As the left ventricle fills with blood, it contracts. This event also is called **ventricular systole**. The aortic valve located between the left ventricle and aorta opens and closes quickly. This allows blood to flow into the aorta. The aorta is the main artery that carries blood from the heart to the rest of the body. The **aortic valve** closes quickly to prevent blood from flowing back into the left ventricle, which is already filling up with new blood.

A **heartbeat** actually is a complicated series of very precise and coordinated events that take place inside and around the heart. Each side of the heart uses an inlet valve to help move blood between the atrium and ventricle. The tricuspid valve does this between the right atrium and ventricle. The mitral valve does this between the left atrium and ventricle. The "lub" is the sound of the mitral and tricuspid valves closing. Each of the heart's ventricles has an outlet valve. The right ventricle uses the pulmonary valve to help move blood into the pulmonary arteries. The left ventricle uses the aortic valve to do the same for the aorta. The "DUB" is the sound of the aortic and pulmonary valves closing. Each heartbeat has two basic parts: diastole (relaxation) and atrial and ventricular systole. During diastole, the atria and ventricles relax and begin to fill with blood. At the end of diastole, atria contract (an event called atrial systole) and pump blood into the ventricles. The atria then begin to relax. Next, ventricles contract (an event called ventricular systole) and pump blood out of the heart. When asleep the heart beats slowly, maybe only 50 or 60 beats per minute. When running up a hill, it might be beating at 160, or even higher. In atrial fibrillation (AT), the ventricles may beat up to 100-175 times a minute, in contrast to the normal resting rate of 60-100 beats a minute. Each beat of the heart is set in motion by an electrical signal from within the heart muscle.

The **pulse**, or heart rate, is the number of signals the SA node produces per minute. The heart's electrical system controls all the events that occur when the heart pumps blood. The electrical system also is called the cardiac conduction system. The electromagnetic signals coming from the heart are fifty times stronger and can be detected eight feet away than the brain, the next biggest signal generator. The heart's electrical system is made up of three main parts: The sinoatrial (SA) node located in the right atrium of the heart. The atrioventricular (AV) node

located on the interatrial septum close to the tricuspid valve. The **His-Purkinje system** is located along the walls of the heart's ventricles. In a normal, healthy heart, each beat begins with a signal from the (sinoatrial node) **SA node**. This is why the SA node is sometimes called the heart's natural pacemaker. (Wilson and Childre '06: 85, 83, 84, 91).

The signal is generated as the two-vena cava fill the heart's right atrium with blood from other parts of the body. The signal spreads across the cells of the heart's right and left atria. This signal causes the atria to contract. This action pushes blood through the open valves from the atria into both ventricles. The signal arrives at the (atrioventricular) **AV node** near the ventricles, where it slows for an instant to allow your heart's right and left ventricles to fill with blood. The signal is released and moves to the His-Purkinje bundle located in the walls of the heart's ventricles. From the His-Purkinje bundle, the signal fibers divide into left and right bundle branches through the Purkinje fibers that connect directly to the cells in the walls of the left and right ventricles. As the signal spreads across the cells of the ventricle walls, both ventricles contract, but not at exactly the same moment. The left ventricle contracts an instant before the right ventricle. This pushes blood through the pulmonary valve (for the right ventricle) to the lungs, and through the aortic valve (for the left ventricle) to the rest of the body. As the signal passes, the walls of the ventricles relax and await the next signal. This process continues over and over as the atria refill with blood and other electrical signals come from the SA node.

A human heart is made up of billions of cells, but researchers say fewer than 10,000 are responsible for controlling the heartbeat (Gallagher '12). Although nearly the entire volume of the myocardium is occupied by cardiac muscle cells, myocytes compose only approximately 25% of the total number of cells. The remainder are endothelial cells, associated with capillaries, and connective tissue cells. Inflammatory cells are generally rare, and collagen is sparse in the normal myocardium. In addition, specialized excitatory and conducting myocytes containing only a few contractile myofilaments are involved in the regulation and the rate and rhythm of the heart (Purkinje cells). These myofibers are plentiful in (1) the SA node, located at the junction of the right atrial appendage with the opening of the vena cava; (2) the AV node, located at the junction of the medial wall of the right atrium with the interventricular septum; and (3) the bundle of His, which courses down the interventricular septum toward the apex to divide into right and left branches that further arborize the respective ventricles. Lesions involving these specialized structures underlie many of the disturbances in cardiac rhythm (Schoen '94: 518).

II.B.2. Circulatory System

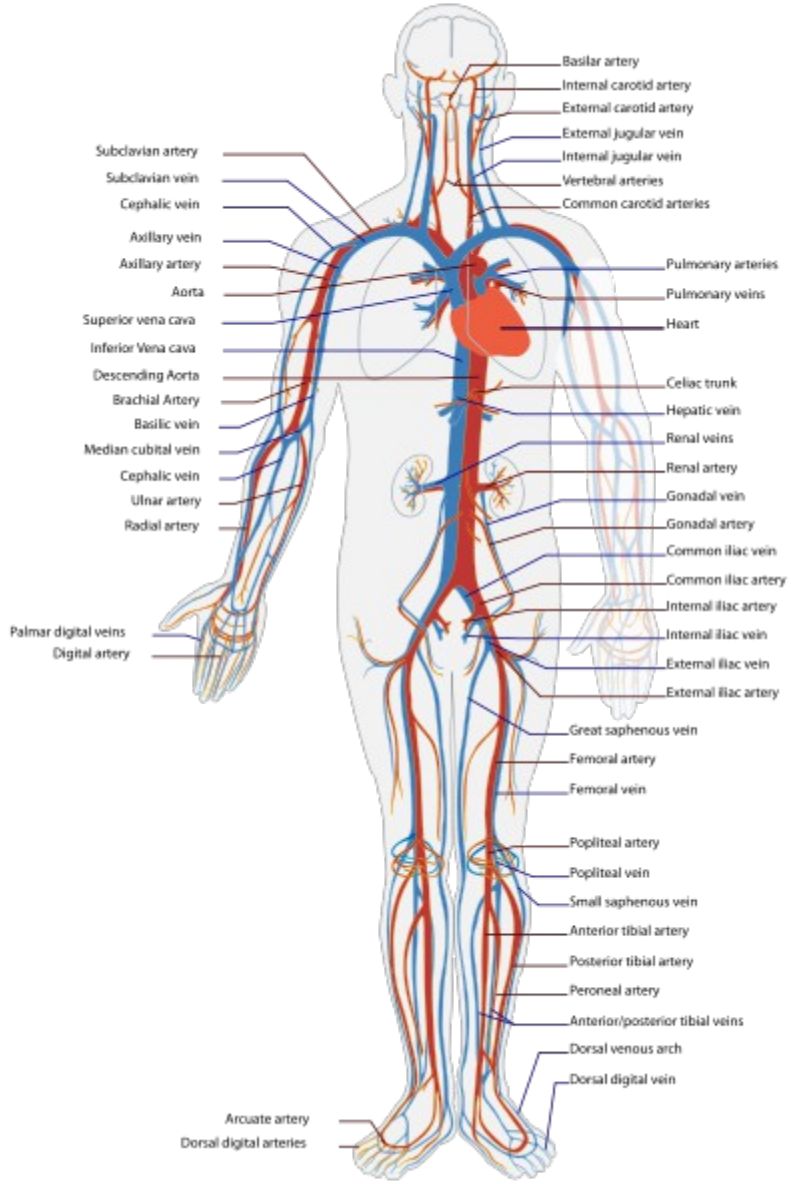
The **circulatory system** permits blood to transport nutrients (such as amino acids and electrolytes), oxygen, carbon dioxide, hormones, blood cells, etc. to and from cells in the body to nourish it and help to fight diseases, stabilize body temperature and pH, and to maintain homeostasis. The circulatory system is the network of elastic tubes that carries blood throughout the body. It includes the heart, lungs, **arteries**, arterioles (small arteries) and capillaries (very tiny blood vessels). These blood vessels carry oxygen- and nutrient-rich blood to all parts of the body. The circulatory system also includes venules (small veins) and **veins**. These are the blood vessels that carry oxygen- and nutrient depleted blood back to the heart and lungs. If all these vessels were laid end-to-end, they'd extend for about 60,000 miles. That's enough to encircle the earth more than twice. Arteries and veins have distinctive structures. Arterial walls are generally thicker than their venous counterparts, to withstand the higher blood pressures in arteries. The thickness of the arterial walls gradually diminishes as the vessels

become smaller, but at the same time the wall-to-lumen ratio becomes greater. Veins have a larger overall diameter, a larger lumen, and a narrower wall than corresponding arteries.

The **blood vessel walls** are composed of three layers: inner endothelium known as the intima, middle smooth muscle known as the media and outer connective tissue known as the adventitia. There are also elastic elements between the Intima and Media, known as the Internal Elastic Lamina, and between the Media and the Adventitia, known as the External Elastic Lamina. The inner layer of each artery is covered by protective cells, which make up the endothelium. The cells of the endothelium, the lining of the arteries, make chemicals such as nitric oxide, which cause the artery to dilate and interfere with blood clotting, and endothelin, which promotes blood clotting and constriction of the arteries. In another balancing act, the endothelial cells make a second type of chemical (prostacycline) that dilates arteries and inhibits clotting (clumping of the blood platelets), while platelets themselves make and release a chemical (thromboxane) that promotes clotting and constriction of arteries. The pathogenesis of atherosclerosis as the result of hyperlipidemia is hypothesized to be caused by damage to the endothelium. The fastest blood flow is in the middle of the artery and the slowest is along the artery wall (Spence ’06: 29, 30, 31).

Arteries are divided into three types: (1) large or **elastic arteries**, including the aorta and its major branches, whose vascular walls are perfused with *vasa vasorum* “vessels within vessels”; (2) medium-sized or **muscular arteries** (such as the coronary or renal arteries), also referred to as the distributing arteries, local blood flow and blood pressure are regulated by changes in lumen size through smooth muscle cell contraction (vasoconstriction) or relaxation (vasodilatation) controlled in part by the autonomic nervous system and in part by local metabolic factors and cellular interactions, halving the diameter increases resistance 16 fold, and small changes in the lumen size of small blood vessels by vasoconstriction or plaque can have a profound flow-limiting effect; and (3) **arterioles** are small arteries (usually less than 2 mm in diameter) that course, for the most part, within the substance of tissues and organs; the smallest (generally 20 to 100 μm in diameter, have primarily smooth muscle cell-containing media) regulate blood flow in capillary beds and bear the brunt of blood pressure elevations, that abnormal stress of which alters their structure. Thus *atherosclerosis* is a disease largely of elastic and muscular arteries, whereas *hypertension* is associated with functional and structural changes in the small muscular arteries and arterioles (Schoen '94: 468).

Circulatory System



Credit: Wikipedia '13

The term **capillary** is restricted to those vessels that have approximately the diameter of a red blood cell (7 to 8 µm). Slow flow, large surface area, approximately 700 m^2, and walls only one cell thick render capillaries ideally suited to the rapid exchange of diffusible substances between blood and extravascular tissue. Blood returning to the heart from capillary beds flows initially into the **postcapillary venules** and then sequentially through collecting venules and small, medium and large veins. Because the pressure in the venules is lower than that in the capillary bed, as well as lower than interstitial tissue pressure, fluid can enter the circulation from the tissue surrounding the venules. **Veins** are thin-walled vessels with relatively large lumina. Veins have scant connective tissue and the media is not well developed, and are thus predisposed to abnormal irregular dilation, compression and easy penetration by tumors and inflammatory processes. The **valves** found in many veins, particularly those in the extremities, serve to eliminate back flow (Schoen ’94: 468, 469).

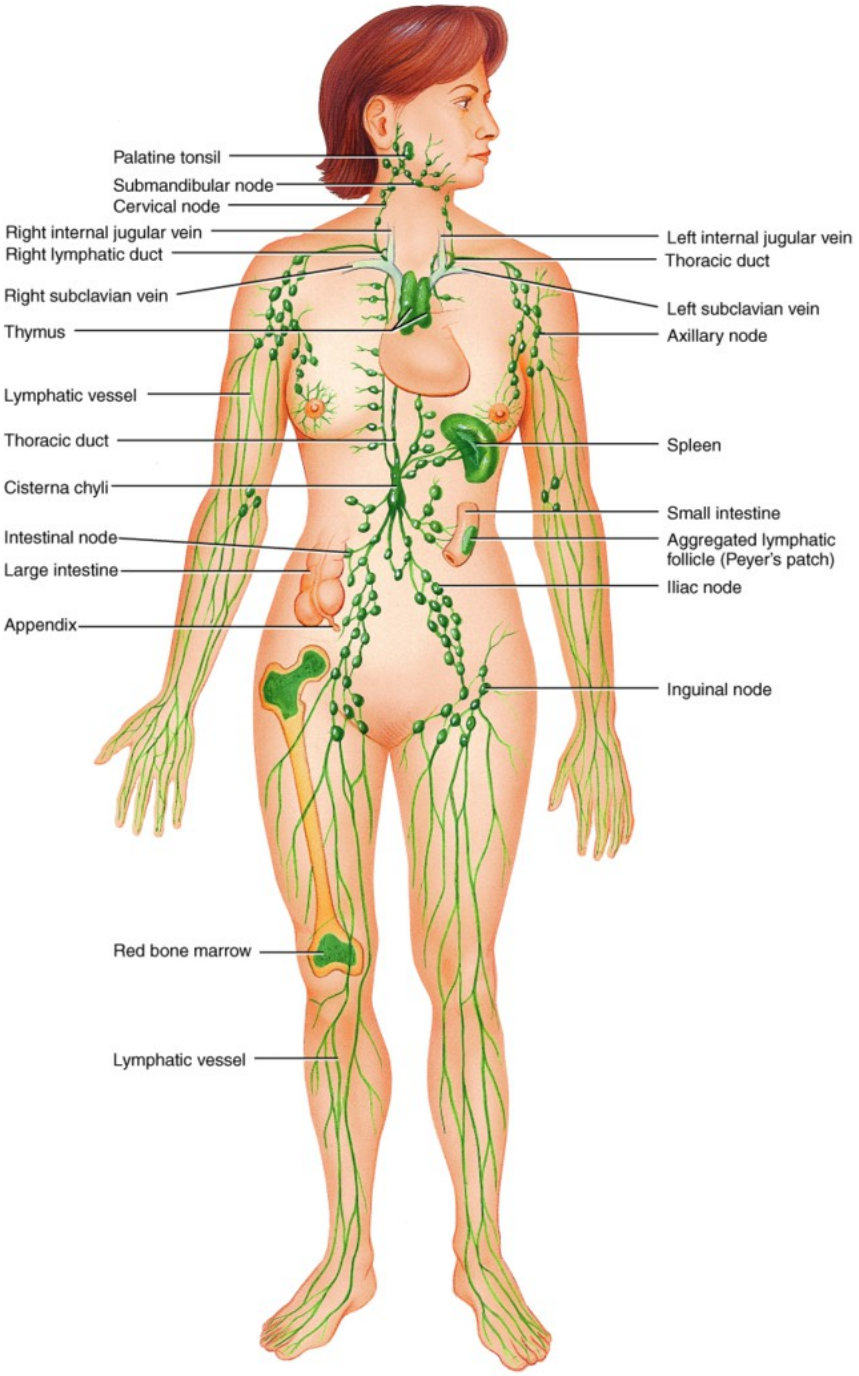
Red blood cells are created in the **bone marrow**. The bone marrow is both a reservoir for stem cells and a unique microenvironment in which the orderly proliferation and differentiation and

release of precursor cells takes place. In between the endothelial lined sinusoidal network of bone marrow lie clusters of hematopoietic cells and fat cells. A reasonable estimate of hemopoietic activity of the marrow may be obtained by examining the ratio of at cells to hematopoietic elements in bone marrow biopsies. In normal adults this ratio approaches 1:1 but with marrow hypoplasia (e.g. aplastic anemia) the proportion of fat cells is greatly increased and conversely, fat cells may virtually disappear in diseases characterized by increased hematopoiesis (e.g. leukemias). The relative proportion of cells in the bone marrow is almost always deranged in diseases of the blood and bone marrow. Normally, the marrow contains about 60% granulocytes and their precursors; 20% erythroid precursors; and 10% unidentified or disintegrating cells. Thus, the normal myeloid-to-erythroid ratio is 3:1. The dominant cell types in the myeloid compartment included myelocytes, metamyelocytes, and granulocytes. In the erythroid compartment the dominant forms are polychromatophilic and orthocromic normoblasts. The function of red cells is the transport of oxygen into tissues (Saunders ’94: 585, 586).

II.B.3 Lymphatic system

Every blood vessel inside the body is accompanied by a **lymphatic vessel**, even each tiny capillary in the small intestine. While blood vessels are thick and red and pump nutrients to tissues, the lymphatic vessels are thin and filmy white in color. They drain away fluid that is pumped out of tissue and transport the immune cells. Lymphatic vessels are so slight because they do not have muscular walls like blood vessels, often working just by gravity. The reason lower legs do not fill up with fluid after a long day is that leg muscles squeeze the lymphatic vessels every step and that squeezes the fluid, known as lymph, upwards. All the body's lymph vessels converge in an impressively thick duct, known as the *ductus thoracicus*, where all the digested fat can gather without the risk of clogging. Shortly after a eating a fatty meal, there are so many tiny fat droplets in the thoracic duct that the lymph fluid is no longer transparent, but milky white. When the fat has gathered, the thoracic duct skirts the belly, passes through the diaphragm, and heads straight for the heart. There is no detoxifying in the liver, as there is for everything else digested. Detoxification of dangerous, bad fat takes place only after the heart has given the fat-laden fluid a powerful push, pumps it through the system and the droplets of fat happen to end up in one of the blood vessels of the liver. **Fat** is the most valuable and efficient of all food particles. The atoms are combined in such a way that they concentrate twice as much energy per ounce as carbohydrates or protein. Fat is used to coat nerves, and it is this coating that makes us such fast thinkers. Some of the most important hormones in the body are made of fat, and very single ell is wrapped in a membrane made largely of fat. Unlike other nutrients, fat is not absorbed straight into the blood from the small intestine. Fat is not soluble in water, it would immediately clog the tiny blood capillaries in the villi of the gut and float on top of the blood in larger vessels. Fat must be absorbed via a different route, the lymphatic system (Enders '15: 50-54).

Anterior View of the Lymphatic System



Credit: Wikipedia

Lymphatics are collapsed, thin-walled, endothelium-lined channels devoid of blood cells, found in tissue sections. Although the major function of the lymphatic system is fat metabolism (Enders '15: 50-54), and as a protective drainage system returning interstitial tissue fluid to the blood, they constitute an important pathway for disease dissemination through transport of bacteria and tumor cells to distant sites. Lymphocytes and monocytes not only circulate in the blood and lymph but also accumulate in discrete and organized masses, called the **lymphoreticular system**. Components of this system include lymph nodes thymus, spleen,

tonsils, adenoids and Peyer's patches. Less discrete collections of lymphoid cells occur in the bone marrow, lungs, and gastrointestinal tract and other tissues. **Lymph nodes** are the most widely distributed and easily accessible component of the lymphoid tissue. Lymph nodes are discrete structures surrounded by a capsule composed of connective tissue and a few elastic fibrils. The capsule is perforated at various points by afferent lymphatics that empty into the peripheral sinus subjacent to the capsule**.** Situated in the cortex or peripheral portion of the node are spherical aggregates of lymphoid tissue, the **primary follicles**, which represent B-cell areas. On antigenic stimulation, the primary follicles enlarge and develop pale-staining germinal centers composed of follicular center cells. Surrounding these germinal centers are mantles of small unchallenged B cells. The T cells occupy the parafollicular regions.

The **medullar cords**, occupying the central portion of the node, contain predominantly plasma cells and some lymphocytes. The size and morphology of lymph nodes are modified by immune responses. As secondary lines of defense, they are constantly responding to stimuli, even in the absence of clinical disease. Trivial injuries and infections effect subtle changes in lymph node histology. More significant bacterial infections inevitably produce enlargement of nodes and sometimes leave residual scarring. For this reason, lymph nodes in adults are almost never "normal" and they usually bear the scars of previous events, rendering the inguinal nodes particularly inappropriate for evaluative biopsies (Saunders '94: 629, 630).

The **spleen** filters from the bloodstream of all "foreign" matter, including obsolescent and damaged blood cells, and participation in the immune response to all blood-borne antigens. Designed ingeniously for these functions, the spleen is a major repository of mononuclear phagocytic cells in the red pulp and lymphoid cells in the white pulp. Normally in the adult it weighs about 150 gm and measures some 12 cm in length, 7 cm in width, and 3 cm in thickness. It is enclosed within a thin, glistening connective tissue capsule that appears slate gray and through which the dusky red, friable parenchyma of the splenic substance can be seen. The red pulp of the spleen is traversed by numerous thin-walled vascular sinusoids, separated by the splenic cords, or "cords of Billroth". The endothelial lining of the sinusoid provides passage of blood cells between the sinusoids and cords. The splenic cords are spongelike and consist of a and consist of a labyrinth of macrophages loosely connected through long dendritic processes to create both a physical and a functional filter through which the blood can slowly seep. During the course of the day the total volume of blood passes through the filtration beds of the splenic cords. 1/120 of all red cells are destroyed daily by phagocytosis. Engulfment by splenic macrophages accounts for approximately half this removal of obsolescent red cells from the circulation. The phagocytes are also active in removal of their particulate matter from the blood, such as bacteria, cell debris, and abnormal macromolecules produced by inborn errors of metabolism. In humans the normal spleen harbors only about 30 to 40 ml of erythrocytes, but with splenomegaly this reservoir is greatly increased. The normal spleen also stores approximately 30 to 40% of the total platelet mass in the body. With splenomegaly this platelet storage may markedly increase, sometimes up to 80 to 90% of the total platelet mass. Similarly the enlarged spleen may trap a sufficient number of white cells to induce leukopenia (Saunders '94: 667-669).

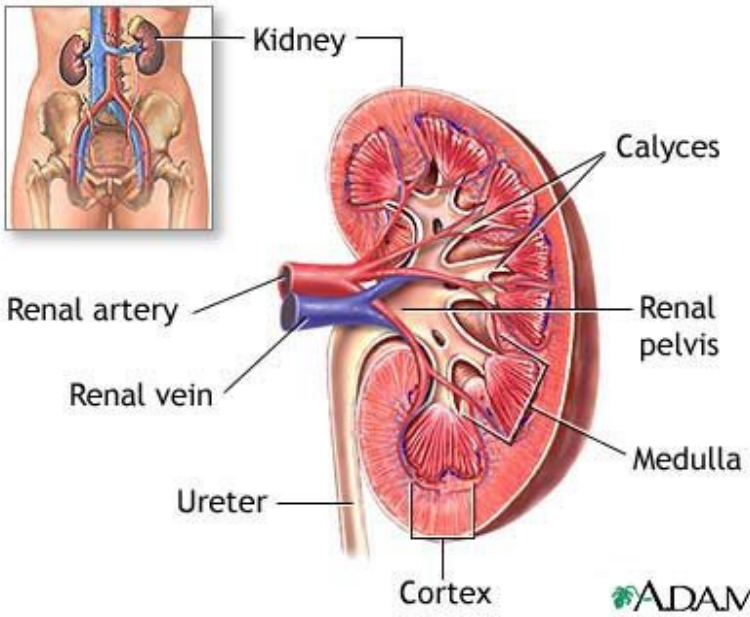
II.B.5 Excretory System

Human **kidneys** convert more than 1700 liters of blood per day into about 1 liter of a highly specialized concentrated fluid called urine. In so doing, the kidney excretes the waste products of metabolism, namely **nitrogen**, precisely regulates the body's concentration of water and salt,

maintains the appropriate acid balance of plasma, and serves as an endocrine organ, secreting such hormones as erythropoietin, renin and prostaglandins. Each human adult kidney weights about 150 gm. Although both kidneys make up only 0.5% of the total body weight they receive about 25% of the cardiac output. Of this, the cortex is by far the more richly vascularized, receiving 90% of the total renal circulation. As the **ureter** enters the kidney at the hilus, it dilates into a funnel-shaped cavity, the pelvis, from which derive two to three main branches, the major calyces; the latter subdivide again into about three to four minor calyces. There are about 12 minor calyces in the human kidney. On cross-section the kidney is made up of a cortex and a medulla, the former 1.2 to 1.5 cm in thickness. The medulla consists of renal pyramids, the apices of which are called papillae, each related to a calyx. Cortical tissue extends into spaces between adjacent pyramids as the renal columns of Bertin. From the standpoint of diseases, the kidney can be divided into four components: blood vessels, glomeruli, tubules and interstitium.

The heart and cardiovascular system are particularly affected by the functioning of the **adrenal glands** located atop the kidneys. Adrenaline is an important hormone and neurotransmitter released during the fight or flight response regarding an injury or emergency situation and is sometimes used as an alternative to a defribulator to reverse cardiac arrest resulting from anapholactic shock. While adrenaline is produced in the central core of the adrenal glands, found atop the kidneys, cortisol is produced in one of the three outer layers. When the adrenal cortex is destroyed by accident, surgery, or disease, death occurs within days unless the patient receives aldosterone and cortisol (Graveline ’04: 53, 51-52). Aldosterone protects the body from excessive loss of sodium and water and is known in scientific circles as a mineral corticoid. Cortisol is known as a glucocorticoid because it helps control blood sugar levels and glucose metabolism, but it also has powerful mineral corticoid and immune system functions and is fundamentally involved in the biologic response to the stress in our lives. Cortisol is known by some as the “mother of all stress hormones” and is released in large quantities during times of stress. Once it is released into the bloodstream, cortisol’s main action is to raise blood sugar or glucose by breaking down stored sugars from places like the liver and muscles. Both directly and indirectly (by interacting with other hormones) cortisol raises blood pressure by causing constriction of arteries and interacting with the kidneys to save salt and water. Cortisol supports survival by raising blood sugar and blood pressure. Cortisol is also triggered by any negative emotion, such as anxiety, anger, or hostility as well as depression. The adrenal gland also produces a hormone called DHEA (dehydroepiandrosterone). DHEA seems to counteract some of the effects of cortisol and is related to positive emotions such as happiness, love, care, gratitude, and appreciation. DHEA can be converted to one of the sex hormones, estrogen or testosterone and DHEA supplements can cause side effects related to the sex hormones, such as facial hair in women or prostate enlargement or stimulation of prostate cancer in men. DHEA gradually declines with age so that by around age seventy-five it’s only at about 25 percent of the level it was fifty years earlier. The juxtaglomerular (JG) apparatus snuggles closely against the glomerulus where the afferent arteriole enters it. The JG apparatus is a small endocrine organ, the JG cells being the principal sources of renin production in the kidney. Malignant hypertension is usually associated with high levels of renin, angiotensin and aldosterone perpetuated by hyper-reninemia (Saunders '94: 927-931, 978).

Excretory System



The **kidneys** lie obliquely along the borders of the psoas muscles. The position of the liver causes the right kidney to be lower than the left. The adult kidney weighs about 150 g. The kidneys are supported by the perirenal fat (which is enclosed in the perirenal fascia), the renal vascular pedicle, abdominal muscle tone, and the general bulk of the abdominal viscera. The average descent on inspiration or on assuming the upright position is 4-5 cm. Lack of mobility suggests abnormal fixation (e.g., perinephritis), but extreme mobility is not necessarily pathologic. On longitudinal section, the kidney is seen to be made up of an outer cortex, a central medulla, and the internal calices and pelvis. The cortex is homogeneous in appearance Portions of it project toward the pelvis between the papillae and fornices and are called the columns of Bertin. The medulla consists of numerous pyramids formed by the converging collecting renal tubules, which drain into the minor calices. The functioning unit of the kidney is the nephron, which is composed of a tubule that has both secretory and excretory functions. The secretory portion is contained largely within the cortex and consists of a renal corpuscle and the secretory part of the renal tubule. The excretory portion of this duct lies in the medulla. The renal corpuscle is composed of the vascular glomerus, which projects into Bowman's capsule, which, in turn, is continuous with the epithelium of the proximal convoluted tubule (Tanagho '88: 1-3).

The secretory portion of the renal tubule is made up of the proximal convoluted tubule, the loop of Henle, and the distal convoluted tubule. The excretory portion of the nephron is the collecting tubule, which is continuous with the distal end of the ascending limb of the convoluted tubule. It empties its contents through the tip (papilla) of the pyramid into a minor calix. The renal stroma is composed of loose connective tissue and contains blood vessels, capillaries, nerves and lymphatics. Usually there is one renal artery, a branch of the aorta, that enters the hilum of the kidney between the pelvis, which normally lies posteriorly, and the renal vein. It may branch before it reaches the kidney, and 2 or more separate arteries may be notes. It is usual for each renal segment to have its own arterial supply. The renal artery divides into anterior and posterior branches and are all end arteries. The renal artery further divides into interlobar arteries, which ascend in the columns of Bertin (between the pyramids) and then arch along the base of the pyramids (arcuate arteries). The renal artery then ascends as interlobular arteries. From these vessels, smaller (afferent) branches pass to the glomeruli. From the glomerular tuft, efferent arterioles pass to the tubules in the stroma. The renal veins are paired with the arteries, but any

of them will drain the entire kidney if the others are tied off. The renal nerves derived from the renal plexus accompany the renal vessels throughout the renal parenchyma. The lymphatics of the kidney drain into the lumbar lymph nodes (Tanagho '88: 1-3).

The main **renal artery** divides into anterior and posterior sections at the hilus. From these, interlobar arteries emerge, course between lobes, give rise to the arcuate arteries, which arch between cortex and medulla, in turn giving rise to the interlobular arteries. From the interlobular arteries, afferent arterioles enter the glomerular tuft, where they progressively subdivide into 20 to 40 capillary loops arranged in several units or lobules. Capillary loops merge together to exit from the glomerulus as efferent arterioles. Efferent arterioles from superficial nephrons form a rich vascular network that encircles cortical tubules (peritubular vascular network), while deeper juxtamedullary glomeruli give rise to the vasa recta, which descend as straight vessels to supply the out and inner medulla. These descending arterial vasa recta then make several loops in the inner medulla and ascend the venous vasa recta. Occlusion of any branch results in an infarction of the specific area it supplies. Glomerular disease that interferes with blood flow through the glomerular capillaries has profound effects on the tubules, within both the cortex and the medulla, because all tubular capillary beds are derived from the efferent arteries. The renal medulla is especially vulnerable to ischemia. The major characteristics of **glomerular filtration** are an extraordinary high permeability to water and small solutes, accounted for by the highly fenestrated endothelium and impermeability to molecules the size of albumin (+3.6-nm radius; 70,000 kd) called the glomerular barrier function (GBM). The proximal tubular cells reabsorb two-thirds of filtered sodium and water as well as glucose, potassium, phosphate, amino acids and proteins. The proximal tubule is particularly vulnerable to ischemic damage (Saunders '94: 927-931, 978).

The **bladder** is a hollow muscular organ that serves as a reservoir for urine. In women, its posterior wall and dome are invaginated by the uterus. The adult bladder normally has a capacity of 350-450 mL. When empty, the adult bladder lies behind the pubic symphysis and is largely a pelvic organ. In infants and children, it is situated higher. When it is full, it rises well above the symphysis and can readily be palpated or percussed. When over-distended, as in acute or chronic urinary retention, it may cause the lower abdomen to bulge visibly. Extending from the dome of the bladder to the umbilicus is a fibrous cord, the medial umbilical ligament, which represents the obliterated urachus. The **ureters** enter the bladder posterio-inferiorly in an oblique manner and at these points are about 5 cm apart. The orifices, situated at the extremities of the crescent-shaped interureteric ridge that forms the proximal border of the trigone, are about 2.5 cm apart. The trigone occupies the area between the ridge and the bladder neck. The internal sphincter, or bladder neck, is not a true circular sphincter but a thickening formed by interlaced and converging muscle fibers of the detrusor as they pass distally to become the smooth musculature of the urethra.

In males, the bladder is related posteriorly to the seminal vesicles, vasa deferentia, ureters and rectum. In females, the uterus and vagina are interposed between the bladder and rectum. The dome and posterior surfaces are covered by peritoneum; hence, in this area the bladder is closely related to the small intestine and sigmoid colon. In both males and females, the bladder is related to the posterior surface of the pubic symphysis, and, when distended, it is in contact with the lower abdominal wall. The mucosa of the bladder is composed of transitional epithelium. Beneath it is a well-developed submucosal layer formed largely of connective and elastic tissues. External to the submucosa is the detrusor muscle, which is made up of a mixture of smooth muscle fibers arranged at random in a longitudinal, circular and spiral manner without any layer

formation or specific orientation except close to the internal meatus, where the detrusor muscle assumes 3 definite layers: inner longitudinal, middle circular and outer longitudinal. The bladder is supplied with blood by the superior, middle and inferior vesical arteries, which arise from the anterior trunk of the internal ilia (hypogastric) artery, and by smaller branches from the obturator and inferior gluteal arteries (Tanagho '88: 7).

III. Cardiorespiratory Disease

III.A Pulmonary Disease

III.A.1. Cold, Flu and Pertussis

Colds are by far the most widespread of all infections in this country affecting more than 150 million people in the United States each year. Many people, especially children, have two or more colds annually. In the average year, colds are responsible for a loss of 440 million workdays and 62 million school days. Including time lost from work, doctors' fees and medications purchased, the annual cost of colds has been estimated well in excess of eight billion dollars annually. Colds are infections of the lining of the nose. The common cold is caused by a virus, not just a single virus but any one of more than 125. These include rhinovirus, adenovirus, coronavirus, and respiratory syncytial virus. Because so many viral types cause colds, it has been difficult to develop a vaccine that would make you immune to the common cold, since vaccines are targeted at a specific culprit. It also explains why a person who has recovered from one cold is still susceptible to infection by a different virus and thus can catch other colds.
The genus *Coronavirus* belongs to the family *Coronaviridae* in the order *Nidovirales*.
Coronaviruses (CoVs) infect a variety of livestock, poultry, and companion animals, in which they can cause serious and often fatal respiratory, enteric, cardiovascular, and neurological diseases. The first reports on human coronaviruses (HCoVs) appeared in the mid- 1960s. The human viruses were isolated from persons with the common cold, and two species were detected: HCoV- 229E and HcoV- OC43. Almost 40 years later, an emergent HCoV was identified as the causative agent of severe acute respiratory syndrome (SARS). While SARS- CoV was eradicated from the human population after a highly effective global public health response, its emergence necessitated a rethinking of the role that CoVs play as a potential cause of more than just the common cold. Thereafter, there was an increase in research on HCoVs worldwide, which has led to the discovery of two other HCoVs, HCoV- NL63 in the Netherlands and HCoV- HKU1 in China (Cabeca '13. The World Health Organization (WHO) has announced the official names of the virus responsible for COVID-19 (previously known as "2019 novel coronavirus" or 2019 nCOV) and the disease it causes. The official name of the disease is coronavirus disease is COVID-19, and the virus is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Coronavirus disease spreads primarily through contact with an infected person when they cough or sneeze. It also spreads when a person touches a surface or object that has the virus on it, then touches their eyes, nose, or mouth. Reports have documented that HCoVs are involved in a wide spectrum of clinical presentation in upper and lower respiratory tract illnesses, as well as being a contributor to exacerbations of chronic obstructive pulmonary disease and among patients presenting cystic fibrosis. Coryza, cough, and fever were the most common symptoms at presentation, being reported in 86%, 77%, and 51% of positive cases, respectively. The alveoli fill up with fluid and corticosteroids are the best medicine. The median time for hospitalized CoV- infected patients to be discharged was 12 days (range, 5–30 days); of the seven hospitalized CoV- infected patients, three were infected with HCoV- NL63, two with

HCoV- 229E, and the other two with HCoV- OC43. Patients infected with HCoV- OC43 stayed longer in hospital (average, 19 days) than did patients infected with HCoV- NL63 or HCoV- 229E. Four hospitalized patients of seven (57.1%) were admitted to the intensive care unit. Lower respiratory tract infections were found in 6/7 (85.7%) hospitalized CoV- infected patients. The remaining patient was infected by HCoV- OC43 and presented upper respiratory tract infection. Coronaviruses display the marked seasonality typical of other respiratory viruses, with high detection frequencies in the winter months but few or no detections in the summer (Cabeca '13).

Coronaviruses are one of the viruses behind the common cold. Named for their crown of club-shaped thorns, which can be seen with an electron microscopes, they cause colds especially during the winter and spring. Coronaviruses need only about three days to multiply in the respiratory tract before their victim starts feeling miserable. On average the cold lasts for a week, a few days shorter than a typical rhinovirus cold, but with more nasal congestion. Coronaviruses are remarkably good at re-infecting their hosts, which is one reason why vaccines remain elusive (Biddle ’95: 49). Clinical diagnosis of influenza- like illness (ILI) is defined by the presence of fever plus at least one respiratory symptom (cough and/or sore throat) and one constitutional symptom (headache, myalgia, sweat, or chills); clinical diagnosis of ARI, defined by the presence of respiratory symptoms that did not fulfill the definition of ILI. Normally there is no treatment for coronaviruses other than a caution to wash hand and keep clean. For Severe Acute Respiratory Syndrome (SARS), a coronavirus, the treatment with no fatalities was to ventilate the patient and medicate with the antibiotic levofloxacin (Levaquin), and corticosteroids methylprednisolone IV and then prednisone (Kit-Ying ’06). To break the COVID-19 quarantine as soon possible it is essential that corticosteroid inhalers be exempted from the Montreal Protocol on Substances that Deplete the Ozone. Pneumonia is best treated with ampicillin or the world's best selling antibiotic azithromycin (Zmax).

It is a grave error of health propaganda that there’s currently no treatment specifically approved for the 2019 coronavirus. Other coronaviruses like SARS and MERS do have vaccines and treatments. Some treatments for these similar viruses include: antiviral or retroviral medications, breathing support like mechanical ventilation, steroids to reduce lung swelling, blood plasma transfusions. The most serious complication of COVID-19 is a type of pneumonia that’s been called 2019 novel coronavirus-infected pneumonia (NCIP). Results from a of 138 people admitted into hospitals in Wuhan, China, with NCIP found that 26 percent of those admitted had severe cases and needed to be treated in the intensive care unit (ICU). About 4.3 percent of these people who were admitted to the ICU died from this type of pneumonia. So far, NCIP is the only complication specifically linked to the 2019 coronavirus. But researchers have seen the following complications in people who have developed a coronavirus: acute respiratory distress syndrome (ARDS), irregular heartbeat (arrhythmia), cardiovascular shock, severe muscle pain (myalgia), fatigue, heart damage or heart attack. Normally there is no treatment for coronaviruses other than a caution to wash hand and keep clean. For Severe Acute Respiratory Syndrome (SARS), a coronavirus, the treatment with no fatalities was to ventilate the patient and medicate with the antibiotic levofloxacin (Levaquin), and corticosteroids methylprednisolone IV and then prednisone (Kit-Ying ’06). The United States should probably adopt this hospital treatment to theoretically reduce COVID-19 fatalities from NCIP pneumonia from 4.4% to 3.3%. Corticosteroids such as hydrocortisone crème and prednisone are likely to be the most effective drugs for self-medicating colds, including COVID-19, with Ampicillin and Zmax for the pneumonia. The public health strategy most likely to cure the global COVID-19 pandemic by May 15, 2020 is to exempt corticosteroid inhalers under the Montreal Protocol on Substances

that Deplete the Ozone of 1987 in pursuit of an aerosol formula without CFCs. The prescription for COVID-19 is corticosteroids and clean, ampicillin or azithromycin for pneumonia.

Although colds can occur throughout the year, they are more frequent at certain times. In temperate climates, rhinoviruses have a seasonal pattern, with fall and spring showing peaks of infection. In the United States, the infection rates for this virus are highest in September. This may be due to the return of children to school, where they are exposed to classmates with respiratory illnesses. The incubation of rhinovirus infections is two to three days. Viral shedding, or replication, begins a few hours after incubation starts and continues for a week or so. The typical duration of illness in young adults is seven days, but symptoms last up to two weeks in 25 percent of the cases. A cold or flu lasting ten to fourteen days or longer may indicate the development of bacterial complication, such as a sinus infection, or a fungal allergic rhinitis (Rosin '98: 16). Several things can cause a constant runny nose in children. Normally, children have six to eight **upper respiratory infections** (ie. Colds) each year. Only a small percentage of these colds lead to an actual sinus infection. However, these colds account for an estimated twenty-six million missed school days. Children in day-care settings seem to be at an increased risk of upper respiratory infection. Aside from the common cold, allergies are probably the next greatest cause of the runny-nosed child. Allergies may occur during certain seasons of the year (termed seasonal allergies) or throughout the year (termed perennial allergies). Allergy causes swelling of the nasal and sinus linings and results in a watery nasal discharge or drip. Sinus infection is another cause of childhood runny nose and should be considered if the nasal drainage lasts longer than the seven to ten-day uncomplicated viral cold. Sinusitis in children is termed chronic until symptoms persist for three months or longer. A number of conditions in children, rarely seen in adults, can lead to excessive nasal drainage. One of these is **adenoiditis**, meaning "inflammation of the adenoids". The **adenoids** sit in the back of the nose in an area called the nasopharynx. In children they can be large and manifested by loud snoring and a nasal voice. Adenoids tend to shrink during the teenage years, and are usually gone by age eighteen. A rare congenital condition, usually diagnosed early in life, is called **choanal atresia**, in which there is blockage at the back of the nasal passages. If there is a narrowing rather than complete blockage, the term **choanal stenosis** is used (Rosin '98: 100-101).

The **rhinovirus** genus is the most common cause of the common cold. Rhinoviruses come in hundreds of types, so a universal cure is hopeless. Rhinoviruses thrive at the average temperature of our nasal mucous membranes, about 93ºF. They are cousins of the poliovirus, in the Picornavirus family, possessing about half the same genes, and strike in late summer and fall, in the Northern hemisphere. A rhino cold lasts on average about a week, with peak misery on the second and third days. There is shaky evidence that heavy doses of vitamin C may reduce the length of colds, but not the frequency of catching them. Washing your hands is a lot is better. Concentrated rhinoviruses in snot survive for hours on skin, plastic, wood, Formica, steel and many fabrics. Stuff a cold and starve a fever (Biddle '95: 119-120). A number of Over-the-Counter remedies are known to be effective with rhinoviruses ie. diphenhydramine (Benylin, Benadryl), chlorpheniramine (Telachlor, Chlo-Amine, Chlor-Trimeton, Aller-Chlor), brompheniramine (Bromphen, Nasahist B, Dimetane Extentabs) and Ipratropium intranasal (Atrovent).

Adenoviruses are a family of viruses, the ones that like people cause about 5 percent of all respiratory illnesses, from mild flulike symptoms to pneumonia, involving upper and lower respiratory tract infections (URI, LRI), swollen adenoids, conjunctivitis and diarrhea. The

typical incubation period for gastroenteritis is 3-10 days; for respiratory tract infections it is between 2 and 14 days. Outbreaks of adenovirus-associated respiratory disease have been more common in the late winter, spring, and early summer; however, adenovirus infections can occur throughout the year. Most children, in urban areas, have been infected with the more common adenoviruses by the time they reach school age. Up to twenty cases a week per one hundred WWI recruits could be expected (Biddle ’95: 19). Adenoviruses are often isolated from apparently healthy individuals. The adenoviruses are a major family of icosahedral DNA containing viruses which have unique molecular biological properties (Brock et al ’94: 229). Acute Respirator Distress (ARD) is most often associated with adenovirus types 4 and 7, and more recently 14, in the United States. Enteric adenoviruses 40 and 41 cause gastroenteritis, usually in children. An effective vaccine against Adenovirus serotype 4 (Ad4) and serotype 7 (Ad7) was approved in 1971. The economy-driven cessation of vaccine production by its sole producer in 1996 resulted in re-emergence of outbreaks, with Ad4 predominating in 98% of cases, 5 fatalities. On March 16, 2011, the FDA approved an adenovirus vaccine for manufacture by Teva Pharmaceuticals (Sanders '11).

Differential Diagnosis and Treatment of Viral Respiratory Infections

Infectious Agent	Symptoms	Treatment
Common Cold		
Coronaviruses	Upper respiratory tract infection (URI) lasting for a week, nasal congestion	None, clean. For SARS ventilate, medicate with antibiotic levofloxacin (Levaquin), and corticosteroids Methylprednisolone IV and then oral Prednisone. Corticosteroid rescue inhalers.
Rhinoviruses	URI, Swollen lymph nodes, upper respiratory tract infection, nasal infection, peak misery after two days, lasts a week	None, clean. Over-the-Counter: Diphenhydramine (Benylin, Benadryl), Chlorpheniramine (Telachlor, Chlo-Amine, Chlor-Trimeton, Aller-Chlor), Brompheniramine (Bromphen, Nasahist B, Dimetane Extentabs), Ipratropium intranasal (Atrovent)
Echovirus	URI, sore throat, skin rash, harpangia, croup, may inflame endocarditis, pneumonia, meningitis, prevalent in summer and fall in US	None, clean. Immune Globulin Intravenous (IGIV) for serious infections
Adenoviruses	URI and lower respiratory tract infection (LRI), may also cause conjunctivitis, bladder infection, inflamed pharynx, diarrhea and rheumatism of the lower extremities for a week,	None, clean. Vaccine re-authorized to Teva Pharm on contract with the U.S. Army. Get light exercise. Eat white rice for diarrhea. Clean. Avoid young children.

	prevalent in late winter, spring and summer	
Flu Like Symptoms		
Influenza A & B	Body or muscle aches, chills, cough, fever over 101° F, 38°C, headaches, and sore throat, incubates for two days, lasts two days, prevalent in winter.	Bed rest for one to two days. Vaccine ineffective. OTC Theraflu, Allegra (Sanofi-Aventis) and Children's Allegra (fexofenadine) and Allegra-D (fexofenadine and pseudoephedrine); Prescription Oseltamivir (Tamiflu) and Zanamivir (Relenza). Amantadine (Symmetrel)
Parainflueza Types 1-4	LRI in children, URI in adults, prevalent in fall and winter	No vaccine, clean. Treat secondary infections with Antibiotics
Respiratory Syncytial Infection	LRI and breathing passages. Most otherwise healthy people recover from RSV infection in 1 to 2 weeks	Ribavirin (Virazole), asthmas inhalers ie. corticosteroids: flunisolide (Aerobid), beclomethasone (QVAR), (Flovent); triamcinolone, (Azmacort), Antibiotics for pneumonia or ear infection
Bacterial Agent		
Whooping cough *Bordetella pertussis*	Sporadic epidemic respiratory infection begins with runny nose that lasts a week, before the infection descends to the lungs for six weeks of mild rheumatism and coughing	Antibiotics cure only if taken the first week before the infection descends into the lungs. Antibiotics taken later reduce contagiousness. Hygiene.

Source: Sanders '11 Table 4

Human influenza is a highly transmissible respiratory illness that's caused by the influenza viruses. We see yearly winter epidemics, called seasonal influenza that affect up to 30% of the population, killing on average 30,000 a year in the US or 350,000 globally. The incubation time for influenza (time from exposure to onset of symptoms) is short, about two days. The onset usually is sudden. It is marked by chills, fever, headache, lassitude and general malaise, loss of appetite, muscular aches and pains and sometimes nausea, occasionally with vomiting. Respiratory symptoms, such as sneezing and nasal discharge, may be present coughing, with or without sputum, may occur, and hoarseness sometimes develops. The fever of 101-105 ° F (40.6 º C) usually lasts for two to four days. Treatment consists of rest in bed, continuing for twenty-four to forty-eight hours after the temperature has become normal. Flu is dangerous to the extent that it can lead to pneumonia, especially for the elderly, the malnourished, or individuals stressed by chronic lung or heart problems.

The viruses that cause flu are prone to **antigenic drift**, making vaccine manufacture difficult. Type A Influenza viruses are subdivided into groups based on two surface proteins, HA and NA, Influenza B or Influenza C based on protein composition. Type A viruses are found in many kinds of animals, including ducks, chickens, pigs, and whales, and also humans. The type B virus

widely circulates in humans. Type C has been found in humans, pigs, and dogs and causes mild respiratory infections, but does not spark epidemics. Flu viruses last for hours in dried mucus (Biddle ’95: 79-85). Around 2010 the FDA removed some 600 different types of flu remedies from the market. The most effective remedy has always been Over-the-counter Theraflu, most consumer are better the next day. The FDA has approved Allegra (Sanofi-Aventis) and Children's Allegra (fexofenadine) and Allegra-D (fexofenadine and pseudoephedrine) product lines to be marketed over-the-counter. The two prescription antivirals that are most commonly used these days are the **neuraminidase inhibitors** Oseltamivir (Tamiflu) and Zanamivir (Relenza). Systematic review of 51 studies found no evidence that the flu vaccine is any more effective than a placebo in children (Smith et al ’08). Studies published in 2008 found that influenza vaccination was not associated with a reduced risk of pneumonia in older people although it did contribute to a reduction in mortality (Jackson et al ’08)(Eurich et al ’08). In the winter flu season of 2012-2013 the flu vaccine was only 8% effective. Dangerous complications with influenza involve bacterial infections that cause pneumonia wherefore broad spectrum antibiotics that are effective against *Haemophilus influenziae* such as ampicillin (Principen) or levofloxacin (Levaquin) save lives. In general influenza Type A is treated with Amantadine (Symmetrel) or Oseltamivir (Tamiflu) and Type B with Zanamivir (Relenza).

Parainfluenza and respiratory synctial viruses (RSVs) cause bronchitis, bronchiolitis, sinus tenderness, swollen glands, red throat, croup and pneumonia, primarily in young children by members of the paramyxoviridae family of viruses, others of which cause mumps and measles. **Para-influenza viruses**, there are four types of medical interest, cause lower respiratory diseases in kids and upper respiratory problems in adults. The virus, that strikes in fall and winter, is responsible for approximately 40-50% of croup cases and 10-15% of bronchiolitis and bronchitis cases and some pneumonias. They are highly infectious through personal contact and need invade our bodies no deeper than our noses or throats to replicate in the mucus there. Most people grow immune to them, which is why parents at the playground aren’t hacking as much as the kids (Biddle ’95: 103). There is no vaccine. People usually recover without treatment. Theraflu was known to cure overnight. The FDA has approved Allegra (Sanofi-Aventis) and Children's Allegra (fexofenadine) and Allegra-D (fexofenadine and pseudoephedrine) for sale Over-the-counter. Corticosteroid inhalers and Prednisone may be effective for the treatment of chronic disease but they depress the immune system. Treat secondary infections with Antibiotics. **Respiratory syncytial virus** (RSV) infections are usually mild and seem like a common cold. In most cases, RSV infections go away in about 10 to 14 days. Home treatment to ease symptoms and prevent complications is usually all that is needed. NSAIDS such as acetaminophen or ibuprofen may be taken to relieve suffering. Corticosteroids may be administered if the pneumonia worsens or does not go away on time. Antibiotics are not usually necessary but should be administered if an ear infection (otitis media) or pneumonia develop, both are caused by the same *Streptococcus pneumonia* bacterium, treated with antibiotics, eg. Penicillin, Streptomycin and Tetracycline. Children who develop lower respiratory infections, especially bronchiolitis, may need medicines, such as bronchodilators, for the rest of their lives. When selecting an inhaler for the first time, or choosing a new one after triamicinolone (Azmacort) was removed by the producer for fluorocarbon concerns, avoid salmeterol, salmeterol has been known to be fatal. Flovent (Fluticasone Propionate) seems a safe corticosteroid inhaler, available without prescription (Generics-Discount).

Viruses and bacteria are two different things. Sinus infections are caused by bacteria (bacteria respond to antibiotics) while a cold is secondary to a virus (which does not respond to antibiotics). The earliest warning that a cold may be developing is often a sensation of dryness

or mild irritation at the back of the palate in the roof of the mouth. Within twenty-four to thirty-six hours, the nasal passages become stuffy or clogged, and watery discharge develops. Sneezing is often present. The sinuses feel heavy, since selling of the nasal lining blocks the small openings to the sinuses. A cold is often accompanied by a mild to moderate sore throat. There may be a mild cough, as mucus from the back of the nose drips into the lower throat and even into the lung's bronchial tubes. While the cold sufferer may have a mild constitutional reaction, such as generalized aching and fatigue, these symptoms are minimal, with fever, if present being only mildly elevated. Once the virus gets into the upper respiratory passages, it grows rapidly. The nasal lining responds by swelling, as the body increases blood circulation to this region in an effort to fight the infection. Mucus production increases as another of the body's defense mechanisms (Rosin '98: 14-16).

Pertussis, is a highly contagious bacterial respiratory infection, with a distinctive phlegm producing cough, known as whooping cough, that lasts six weeks with associated rheumatic pains throughout the body. One does not become immune to pertussis without a DTaP (Diptheria and Pertussis) vaccine. Pertussis does not respond to antibiotics after it has descended to the lungs from the extremely runny nose of the first week. The reason that pertussis is described in this section is because it is important to distinguish a runny nose from pertussis with a runny nose from a cold or allergy. Usually pertussis is discernible from a viral cold because the Public Health Service has declared a whooping cough epidemic. It is a good idea to take antibiotics after two days of runny noses during a whooping cough epidemic. If antibiotics are not taken within the first week of pertussis infection, while it is still an extremely runny nose, the infection descends to lungs for six weeks of coughing. Unvaccinated persons who succumb to whooping cough can take a full course of antibiotics to eliminate contagiousness, but will require 6 weeks to recover from the whooping cough. Vaccination and antibiotics have been effective at controlling the incidence of pertussis for the past century. Between 1922-1925 the average annual number of reported cases of *Bordetella pertussis* was 147,271, by 2001 incidence of whooping cough had decreased 95 percent to 7,580 (Fisher '06: 7).

The **immune system** deals fairly rapidly with most viruses. Each mechanism of the immune system may be involved in resisting a viral attack – including white cells (macrophages) that engulf the viral particles, and lymphocytes that produce antibodies against the virus or attack virally infected cells. This leads to recovery from most viral infections within a few days to weeks. Furthermore, the immune system is often sufficiently sensitized by the infection to make a second illness form the same virus rare (as is the case with measles). With some viruses, however, the speed of the attack is such that serious damage or even death may occur before the immune system can adequately respond (as is the case with rabies and some cases of poliomyelitis). In other cases, a virus is able to dodge or hide from the immune system, so the infection becomes chronic or recurrent. This is common with many herpes virus infections (such as genital herpes and shingles) and with viral hepatitis B. Finally, the AIDS virus, by weakening the immune system, leaves the body open to many opportunistic infections. Viruses are more difficult than bacteria to combat with drugs because it is difficult to design drugs that will kill viruses without also killing the cells they parasitize. Nevertheless, there has been remarkable progress in the development of **antiviral agents**, especially against the herpes group of viruses. Such drugs may work by helping to prevent viruses from entering cells or by interfering with their replication in cells. Interferon refers to a group of natural substances, produced by virus-infected cells, that protects uninfected cells. Some interferons can now be produced artificially and have been tried in the treatment of various viral infections, including the common cold and viral hepatitis B. Otherwise, treatment of viral infections depends largely on alleviating the

patient's symptoms and trusting the body's immune defenses to bring about a cure. A much more fruitful area in the fight against viruses is immunization. One viral disease, smallpox, has already been eradicated worldwide through a coordinated vaccination program. Highly effective vaccines are also now available to prevent many others, including poliomyelitis, measles, mumps, rubella, hepatitis B, yellow fever and rabies (AMA '89: 1052).

Stages of virus replication susceptible to chemical inhibition

Stage of replication	Chemical	Virus
Free virus	Kethoxal	Influenza virus
Adsorption	None known	
Entry of nucleic acid (uncoating)	Amantadine, Carbobenzoxypeptides, 3-Methylisoxazole compounds	Influenza virus, Measles, Rhinoviruses (cold viruses)
Nucleic acid replication	Benzimidazole, guinaidine, 5-Fluorodeoxyuridine (FUDR), 5-Iododeoxyuridine (IUDR), Acyclovir, Rifamycin, Azidothymidine (AZT), Dideoxyinosine (ddI)	Poliovirus, Herpesvirus, Herpesvirus, Herpesvirus, Varicella zoster Vaccinia virus, Retrovirus (HIV), Retrovirus (HIV),
Maturation (or late protein synthesis)	Isatin-thiosemicarbazone	Smallpox virus
Release	None known	

Source: Brock et al '94: Table 11.9. pp. 432

Anti-viral medicine, such as Acyclovir (Zovirax), Amantadine (Symidine, Symmetrel), Idoxuridine, Trifluridine (Viroptic), and Zidovudine (Retrovir, Retrovis), are a group of drugs used in the treatment of infection by a virus. The RNA polymerase of vaccinia and other poxviruses is inhibited by rifamycin, since this antibiotic specifically inhibits the replication of these viruses, although it has no effect on a wide range of other viruses affecting animal cells. Another interesting chemical is asidothymidine (AZT) an inhibitor of retroviruses such as the virus which causes acquired immune deficiency syndrome (AIDS). Interferons are antiviral substances produced by many animal cells in response to infection by certain viruses. They are low-molecular weight proteins that prevent viral multiplication. Cloned gene technology has now made interferons available (Brock et al '94: 432) Drugs that kill viruses have proved difficult to develop because viruses live only within body cells and there is a danger that antiviral drugs will damage the host cell as well as the virus. To date, no drugs have been developed that can effectively eradicate viruses and cure the illnesses that they cause. Immunization is at present more important than drug treatment in fighting serious viral infections. Since 1989 a number of antiviral drugs have been developed and used to treat AIDS but they carry a high risk of anemia due to bone marrow damage. Most antiviral drugs destroy viruses by disrupting chemical processes necessary for viruses to grow and multiply within cells. Some antiviral drugs prevent viruses from actually penetrating cells. Most other antiviral drugs rarely cause side effects. Antiviral creams and ointments may irritate the skin, causing redness. Antiviral drugs given by mouth or injection can cause nausea and dizziness, and, rarely, in long-term treatment, kidney damage. (AMA '89: 120).

Homeopathy is a 200-year old field based on the theory that small doses of a substance can boost the immune system, helping it to fight against colds, as well as other ailments. Use of these more natural alternative treatments has grown with recent yearly sales of $3.77 billion. Homeopathic drugs used today for upper respiratory infections include Oscillococcinum (derived from duck heart and liver), Kalium bichromicum (from chromium iron ore) and Calcarea carbinoca (from the European edible oyster). These homeopathic remedies typically lack rigorous scientific studies to back up their claims. Herbs can additionally be used against the common cold, especially since some of them stimulate the body's immune system. Garlic is both an antibacterial and an antiviral agent, helping to rid the body of "harmful invaders". *Echinacea purpurea* is a wild American herb that is believed to increase the body's white blood cells, which fight infection. Goldenseal is another herb believed to help with colds by strengthening weakened nasal membranes and increasing the liver's ability to filter our infectious wastes. Most colds last for a week, while some take several days to run their course. Fortunately, most colds clear without complications. But sometimes what begins as the typical viral nasal infection of a cold progresses to a similar infection of an adjacent area, such as the ears, sinuses, throat, voice box (causing laryngitis) or bronchial tubes (leading to bronchitis or even pneumonia). At this point, the infection often becomes bacterial. If during the course of the cold, a fever higher than 100 degree Fahrenheit, an earache, pressure over the sinuses with thick, discolored nasal mucus, pain at the back of the throat, tender glands in the neck, vocal hoarseness, or an increasing cough productive of thick mucus, develop, consult a physician for a prescription of antibiotics (Rosin '98: 26, 29). Penicillin is usually the most effective antibiotic for the treatment of sinusitis, pneumonia, meningitis or rheumatic heart disease, however, any antibiotic (other than Bactrim) should treat most respiratory infections. Infections causing stenosis of the airways in the throat, should however be treated with erythromycin or doxycycline (over age 8), in case a hypersensitivity to yeast and mold has manifested as an anaphylactic reaction to the penicillin mold.

The **success of herbal medicine in the treatment of viral illnesses**, and the ineffectiveness of antibiotics in commonly encountered childhood bacteria conditions such as whooping cough and ear infections. During the yellow-fever epidemic of the late nineteenth century in the United States, homeopathy resulted in a mortality of 5.6 percent of cases and 7.7 percent of cases in the rest of the South, compared to an overall death rate of at least 16 percent in 1880. A comparison of mortality rates between homeopathic and conventional medical treatment in the United States and Europe showed a two- to eightfold reduction in deaths from life-threatening infectious diseases among the homeopathically treated cases in 1900. During the severe influenza epidemic of 1918, homeopathic treatment also resulted in significant reduction in mortality. Recent publications have shown the clinical effectiveness of homeopathy in hayfever and acute childhood diarrhea and that homeopathy could established as a regular treatment for certain indications. Homeopathy is a medical system that uses natural (plant, mineral and animal) substances that stimulate a healing reaction within the body and encourage a curative response to illness. Smallpox vaccine reactions were especially dangerous and homeopathic medicine developed a reputation for its ability to successfully treat the sometimes lethal effects of the vaccine. *Thuja occidentalis*, prove to be especially efficacious in relieving the symptoms that arose subsequent to adverse smallpox vaccine reactions (vaccinia). Modern authors have found that the homeopathic preparations of the vaccine or the disease organism itself succeed more often in relieving the symptoms associated with vaccine reactions (Neustaedter '96: 54, 56, 59 60). The **immunoprotective value of breastmilk** is unquestionable, but incompletely understood. Immunoglobulins in human milk provide passive protection from bacteria. Specifically, secretory IgA found in breast milk blocks the attachment of *Streptococci* and

Haemophilus bacteria to mucus membranes. White blood cells in human milk will actively ingest bacteria that invade the infant's body. In addition, lymphocytes carrying specific antibodies pass through breast-milk to the baby. Several other chemicals in breastmilk (lactoferrin and lysozyme) protect the breastfeeding child from infection by destroying or inhibiting growth of bacteria.

In homeopathic medicine at the first sign of a runny nose swiftly take vitamin C. Plants trusted in domestic and aboriginal medicine as efficacious for respiratory disease are Gymnopserms *Ephedra gerardiana* (Ephedraceae), Angiosperms, Asclepiadaceae, *Tylophora indica*, Asteraceae, *Saussurea lapp* (costus), Campanulacea, *Lobelia inflate* (Indian tobacco), Euphorbiaceae, *Euphorbia hirta*, Fabaceae, *Glycyrrhiza glabra* (licorice), Lamiaceae, *Monardo fistulosa* (wild bergamot or horsemint), Scrophulariaceae, *Verbascum Thapsus* (mullein), Solanaceae, *Datura stramonium*, Zingiberaceae, *Alpinia galangal* (greater galangal), *Rhododendron anthopogonoides* (Ericaceae). Cold remedies include Gymnosperms *Abies balsamea* (balsam fir), *Juniperus virginiana* (juniper or red cedar), *Tsuga Canadensis* (hemlock), Angiosperms, Araceae, *Acorus clamus* (sweet flag), Asteraceae, *Achillea milefolium* (yarrow), Cucurbitaceae, *momordica charantia* (whild balsam apple), Betulaceae, *Betula occidentalis* (western red birch), Lamieaceae, *Hedeoma pulegioides* (American pennyroyal), *Marrubium vulate* (horehound), *Nepeta cataria* (catnip) Salicaceae, *Populus balsamifera* (balsam poplar) and *P. candicans* (balm of Gilead), Scrophulariaceae, *Verbascum Thapsus* (mullein), Solanaceae, *Withania somnifera* . *Cornus florida* (dogwood) was prescribed by pioneer doctors as a bitter drink made by steeping dogwood flowers, fruit and bark in water for fevers and chills. *Myrica cerifera* (bayberry) *Oldenlandia corymboso*, and *Salix* spp. and *Populus* spp. (willow and poplar) were also used to treat fever. (Elvin-Lewis ’77: 306-308). There is considerable evidence that heavy doses of vitamin C, 200 – 1,000 mg may reduce the length of colds. Oranges provide about 100 mg of vitamin C and are at the peak of their medicinal effectiveness at around 200mg a day. There are other natural sources of vitamin C many of which also have medicinal qualities that are also useful for the treatment of colds and flu-like symptoms.

Herbal Remedies for Cold and Flu Symptoms

Vitamin	**Indication**
Vitamin C ascorbic acid	Take 200-1,000 mg daily to shorten duration of cold. Collagen synthesis, amino acid metabolism, helps iron absorption, immunity, antioxidant. Found in spinach, broccoli, red bell peppers, snow peas, tomato juice, kiwi, mango, orange, grapefruit juice, strawberries, rosehips.
Culinary Herb	**Indication**
Black Pepper, Horseradish,	Black pepper is warming, energizing and stimulating. It is indicated for “cold-type” problems such as flus, coughs, colds, poor circulation, and poor digestion. Horseradish is good for sinus congestion and head colds.
Cinnamon *Cinnamomum* spp.	Powerful antiseptic, with antiviral and antifungal properties. Often indicated in cases of viral infections, fungal infections, and colds and flus.
Elder *Sambucus nigra*	Elderberry and elder flower are among Europe’s most esteemed remedies for cold and flus, where they line pharmacy shelves. Elder’s beautiful lacy flowers are diaphoretic, meaning they induce sweating, thereby helping to lower fevers. Elderberry has immune-enhancing

	properties and are often combined with Echinacea in immune-stimulating remedies for colds with powerful antiviral properties and are helpful in treating viral infections including flus, URI, herpes and shingles. Elderberries make some of the best syrup, wine, jams, jellies and pies. The flowers are also edible, making nice fritters dipped in a light batter. Do not eat the raw uncooked berries in any great quantity as they can cause digestive upset and diarrhea in some people.
Garlic *Allium sativum*	Herb of choice for treating colds, flus, sore throats and poor or sluggish digestion. It stimulates the production of white blood cells, boosting immune function and is a potent internal and external antiseptic,
Ginger *Zingiber officinale*	Popular warming, decongesting herb for cold-type imbalances such as poor circulation, colds and flues, respiratory congestion and sore throat. Safe.
Sage *Salvia officinalis*	Astringent, antiseptic and relaxing action on the mucous membranes, sage is the classic remedy for inflammation of the mouth, throat, tonsils and laryngitis. It can be used as a mouthwash or swab to treat infected or sore gums and canker sores.
Thyme *Thymus* spp.	Fine tea for treating coughs and chest complaints. rich in anti-oxidants and has a markedly tonic effect, supporting normal body function. It seems to have a positive effect on the glandular system as a whole and especially the thymus gland.
Herbal Teas	
Cordyceps sinensis	Enhances physical strength and endurance, treats pneumonia, respiratory infections
Echinacea *Echinacea* spp.	Echinacea can be taken, as a tea or tincture, at the first sign of a cold or flu to boost immune system function. Increasing macrophage and T-cell activity. Rich in vitamin C and polysaccharides, which have antifungal, antiviral, antibacterial properties. Particularly effective against bronchial and respiratory infections, sore throat, and oral infections.
Lavender *Lavandula* spp.	Lavender is an antibacterial, antifungal and antiseptic agent. More used in washing, fresh can be made into a tea. Useful in treating a host of infections, including staph, strep, colds and flus.
Licorice *Glycyrrhiza glabra*	Herb of choice for soothing irritated and inflamed tissue such as in cases of sore throat, bronchial inflammation and stomach and bowel irritation. Licorice has a long history of use relieving throat inflammation and for strengthening the vocal cords. Licorice gently supports the adrenal glands ability to produce hormones and aids in the breakdown and elimination of excess or "worn-out" hormones via the liver and kidneys. It has a thick, sweet flavor, which makes it a nice addition to tea in small amounts. The root can be almost too sweet, and some people find its flavor rather offensive when brewed by itself. To increase its palatability blend it with other herbs in syrups, teas and tinctures. You can also eat the licorice root dried or fresh whole root.
Spearmint *Mentha spicata*	Spearmint is sweeter, milder and less pungent than peppermint and tends to be better for children. Combined with catnip, it's an excellent herb for children with a fever.
Probiotics	
Lactobacillus reuteri	Cold and respiratory virus
Lactobacillus	Cold and respiratory virus

plantarum 299v	

Source: Gladstar ’12; Brown ’04: 82, 83; Huffnagle ’07: 263

Cough is a natural reflex to help clear the respiratory system of secretions and foreign materials. Do not cough on other people. It is polite to cover your mouth when you cough. Wash your hands, your clothes and your “rheum”. Some viruses and chemicals do not come out in the wash and contaminated articles must be thrown away. Antitussive (anticough) agents are sometimes needed to suppress coughing to facilitate rest and sleep and to reduce irritation of the respiratory tract. Acting centrally by depressing the cough reflex of the central nervous system, codeine, and to some extent other opium alkaloids, are probably the most widely used compounds with nethol (peppermint oil) and eucalyptol. A number of plants have been used to stop coughing and soothe sore throats, Anacardiaceae, *Rhus glabra* (sumac), Araliaceae, *Aralia nudicaulis* (wild sarsaparilla), *Aralia racemosa* (spikenard), Fabaceae, *Prosopis julifora* (mesquite), Myrtaceae, *Syzgium cumini*, Ranunculaceae, *Xanthorhiza simplicissima* (shrub yellowroot), Rosaceae, *Prunus serotina* (wild black cherry), *P. virginiana* (choke cherry), Solanaceae, *Solanum surattense*. Many individuals who suffer from respiratory disease find it difficult to clear the chest of sputum. Expectorants and mucolytic agents are used to help them. Expectorants and mucolytics such as guafenesin (Humibid, Tussi-ortganidin) or the herb mullein help liquefy secretions and allow you to cough up mucus more easily (Tucker et al ’01: 75). Ipecac syrup (*Cephaelus ipecacuanha*) is an expectorant, others are Gymnosperms *Pinus roxburghii*, Angiosperms, Acanthaceae, *Adhatoda vasica,* Apocynaceae, *apocynum androsaemifolium* (spreading dogbane or wild ipecac), *A. cannabinum* (hemp dogbane), Araceae, *Acorus calamus* (sweet flag), Euphorbiaceae, *Acalypha indica,* Hydrophyllaceae, *Eriodictyon californicum* (yerba santa) (Elvin-Lewis ’77: 300). One of the best expectorants is water. Drinking an adequate amount of water, about one quart per day, will make clearing phlegm easier, which may lead to improved breathing (Tucker et al ’01: 75).

Breath of fire is one of the foundational breath techniques in Kundalini yoga. Breath of fire is rapid, rhythmic and continuous, with no pause between them, approximately 2-3 cycles per second. It is always practiced through the nostrils with the mouth closed, unless your sinuses are too congested. Breath of fire is powered from the navel. To exhale the air is expelled powerfully through the nose by pressing the navel in toward the spine. To inhale the upper abdominal muscles relax, the diaphragm extends down, belly out. When done correctly there should be no rigidity of muscles or shortage of oxygen. Begin doing breath of fire at 1-3 minutes perhaps in time to crunches or some moving stretch position. Breath of fire is not recommended for those who are pregnant or menstruating. Breath of fire releases toxins and deposits from the lungs, mucous linings, blood vessels and other cells, and is primarily useful for clearing stuffed up sinuses and nostrils, and bringing oxygen to an ischemic heart, brain or other targeted, by meditation, oxygen deprived part of the body. Hatha yoga, the physical form of yoga calls for long slow breaths through your nose, of about 10 seconds at each inhale, hold and exhale, experts at hatha yoga breath no more than three times a minute when they are meditating in a sedentary pose. We breathe predominantly through one nostril or the other at any given time. The dominant nostril alternates rhythmically every 90 to 150 minutes. The rhythm is mediated primarily through structures in the hypothalamus and pituitary, though other areas of the rain are involved. To clear the nostrils effectively one should do alternate nostril breathing holding the nose with thumb and forefinger and alternating which nostril you breathe through. Breathe out and then in through the selected nostril and then change which nostril is open and exhale and inhale again with the other nostril. By emphasizing inhaling the sympathetic part of the nervous boosts heart rate, blood pressure, alertness and stimulates us. By emphasizing exhaling the

parasympathetic nervous system slows the heartbeat and relaxes circulation, nerves and digestive system (Bhajan ’02-03). Most importantly forcibly exhaling through the nose helps to clear the lungs, sinuses and nostrils. Jogging is more effective.

III.A.2 Allergic rhinitis

One out of four Americans has some kind of **allergic disease**. Adult Americans make 9 million visits to office-based physicians because of hay fever, aka allergic rhinitis. Allergic rhinitis is even more prevalent in juveniles, affecting an estimated 20 to 40 percent of children. Rhinitis is defined as the presence of at least one of the following: congestion, rhinorrhea, sneezing, nasal itching, and nasal obstruction. Other reported symptoms include throat clearing, headaches, facial pain, ear pain, itchy throat and palate, snoring, and sleep disturbances. Allergic rhinitis costs the country about $6 billion a year in direct medical costs and lost productivity. Thirty-four Americans die each day, more than 12,000 a year, from asthma related causes. There has been a dramatic rise in the past five decades there has been tremendous growth in the incidence of all immune-based diseases, with allergies and asthma very much the “tip of the iceberg”. For instance, atopic dermatitis (itchy rash, or exczema) is the most common skin condition in children under age 11, with 10 percent of children diagnosed with it in the 1990s, compared with just 3 percent in the 1960s. About 8 percent of American children have food allergies today, compared with about 2 percent of adults. Allergic rhinitis, the run-of-the-mill, hay fever kind of allergy – affects up to 40 percent of children and a total of 35 million people overall. The number of Americans with asthma more than doubled between 1980 and 1999, from 6.8 million to 17.3 million reported cases, and the number of deaths from asthma tripled between 1977 and 1998, from 1,674 to 5,438, despite new medications and better understanding of the disease. A study in Basel, Switzerland showed that children of part-time farmers had a 76 percent higher risk of hay fever and other allergies than those of full-time farmers, suggesting that greater exposure to the farm environment can be more protective. An increasing number of children in the United States are allergic to peanuts, about 3.3 percent in 1996 compared with 1.1 percent in 1989, while an estimated 3 million Americans overall are allergic to them, making peanuts the most common food allergens in this country. But it’s far form the only one: Overall an estimated 5 to 8 percent of kids and 1 to 2 percent of adults have some kind of food allergy, whether, wheat, peanuts, shellfish, tree nuts, dairy products, soy, wheat or egg whites. They are the leading cause of anaphylaxis, the life-threatening reaction that causes difficulty breathing, swelling in the mouth and throat, a sudden drop in blood pressure, and, in some cases, loss of consciousness. Each year, food allergies account for an estimated 30,000 emergency room visits, 2,000 hospitalizations, and as many as 2090 deaths from anaphylaxis (Berger & Gordon '04: 13, 15, 19, 69-71). In adults if a cold lasts more than a week it is known as allergic rhinitis and best treated with corticosteroids.

Hay fever largely caused by pollen and spores, afflicts no fewer than 13 million victims who endure physical and psychological misery at some time during the year, but mainly from spring until autumn. Among adults, 33 million disability days annually can be attributed to hay fever and asthma alone, while children lose no less than 36 million school days because of allergies. In North America, the greatest culprits are the ragweeds (Ambrosia) in the aster family (Asteraceae), in Europe and in more equatorial zones, however, grasses (Poaceae) are responsible for many cases of allergy. Since fungi are found everywhere, their spores are a constant cause of seasonal and perennial allergic rhinitis and asthma worldwide. Usually an immune response can be elicited after contact and recognition of an antigen by several cell types belonging to the reticuloendothelial system. This results in the production of immunoreactive

cells and modified serum globulins (antibodies, immunoglobulins) that can act alone, or with other phagocytic cells, to eliminate form the body specific antigens in the form of foreign proteins, toxins, tumor cells, and infectious agents. Probably one of the most common abnormalities of the immune system is the development of the allergic state (Elvin-Lewis '77: 64- 66). Allergic rhinitis (Hay Fever) usually shows up before age 20, but it can develop at any age. In fact, it may be diagnosed as early as the first year of life. Today allergic rhinitis affects 40 percent of children and 20 to 30 percent of adults. Studies show that people with allergic rhinitis miss 3.8 million days of work and school each year. Children miss more than 2 million days of school, and more than one-third of adults with hay fever say it decreases work effectiveness. The primary symptom of allergic rhinitis is a stuffed and/or runny nose. This constant inflammation provides the perfect breeding ground for viruses and bacteria, which can lead to numerous other problems, such as ear infections, sinus infections (sinusitis) and asthma. Sinusitis affects 31 million Americans a year. If allergies aren't treated, they can also lead to nasal polyps (pale, round outgrowths of nasal lining) or swollen nasal turbinates (protruding tissues that line the inside of the nose). Untreated allergies can also cause dental and facial abnormalities. Other common symptoms are chronic coughing; wheezing or shortness of breath; conjunctivitis or pinkeye (red, swollen eyes); sore throat; frequent nasal drip; bad breath; canker sores; an itchy palate; stomach problems, such as bloating, belching and heartburn and irritability and depression (Berger & Gordon '04: 33-35, 37). A dab of hydrocortisone crème on the nose is often curative.

Allergy is derived from the Greek words meaning "other action" implying a hypersensitivity to a specific substance(s) that does not cause symptoms in most people. Certain substances, called allergens, trigger an allergic response in susceptible individuals. They can enter the body via inhalation, ingestion, injection and external skin contact. These allergens react with antibodies (certain molecules in the immune system) in the allergic person, causing the production of histamine and other chemical substances that cause various symptoms). The nasal symptoms of allergy are termed allergic rhinitis. Prominent nasal manifestations include congestion of the nasal membranes, sneezing and itching. Swelling of the nasal lining leads to the sensation of blockage and possibly headaches. In adults, this can lead to watery postnasal drip and cough. In children, the itching nose with thin drainage leads to frequent rubbing upward of the nasal tip called the "allergic salute". Itchy, watery eyes may accompany these nasal symptoms. Nasal allergies tend to run in families, with the allergic individual often having an allergic parent, sibling or close relative. If one parent is allergic, the child has a 30 to 50 percent chance of inheriting the problem, if both parents have allergies, their children have a 70 percent chance of allergy problems (Rosin '98: 62-64).

The blood contains more than 1 trillion **antibodies**. Antibodies are made up of chains of molecules that form a Y shape. The sections that make up the tips of the Y's arms vary greatly from one antibody to another; this is called the variable region. It develops a unique shape based on the antigen it was created to react to, so it can "lock" onto that antigen just like a key fitting into a lock. Sometimes this locking neutralizes the antigen on its own, rendering it harmless; sometimes it ruptures the cells of the foreign body; and sometimes it forces antigens to clump together, creating sitting-duck target for other immune cells to attack. There are five classes of antibodies, each with a slightly different function and operating method. Scientists call them immunoglobulins, or Igs for short. Of the five, IgE is the one we could call the "allergy antibody", since IgE antibodies are the main culprits contributing to allergies. Normally, they are present in tiny quantities in the body and are produced in response to relatively large invaders, such as parasites like ringworm and fluke. However, it never gets a chance to do its

job, it begins to act out like a bored teenager. Instead of attacking parasites as it's supposed to do, it begins attacking proteins and molecules it should recognize as perfectly harmless, such as dust and peanuts and pollen. When that happens, the IgE binds the allergen molecule either to basophils, or to cells called mast cells found in the mucous linings of tissues throughout the body, such as the throat, nose, lungs, skin or stomach lining. This binding triggers the mast cells or basophils to release inflammatory chemicals, such as histamine, prostaglandins, and leukotrienes. The inflammatory process begins, with swelling, creation of mucus, reddening, heat and vessel constriction – an allergic reaction (Berger & Gordon '04: 27, 28, 30).

Usually an immune response can be elicited after contact and recognition of an antigen by several cell types belonging to the reticuloendothelial system. This results in the production of immunoreactive cells and modified serum globulins (antibodies, immunoglobulins) that can act alone, or with other phagocytic cells, to eliminate form the body specific antigens in the form of foreign proteins, toxins, tumor cells, and infectious agents. Probably one of the most common abnormalities of the immune system is the development of the allergic state. Depending on the overall mechanism involved and the speed and type of reactions observed five types (I-V) have been distinguished. **Immediate hypersensitivity** is related to the development reaginic antibodies, usually Immunoglobulin E (IgE) and less often IgG, in sufficient quantities to evoke the symptoms of hay fever, asthma, hives, and anaphylactic shock. These antibodies are produced following allergen contact, locally within plasma cells embedded in the mucosa of target areas of the nasopharynx and the respiratory and gastrointestinal tracts, as well as elsewhere in the lymphatic system. After diffusing into the tissue fluid and serum the antibodies attach to mast cells, basophils and platelets. Allergen then binds to his cell bound regain, triggering the release of histamine and other vasoactive substances (kinins, serotonins, slow acting substances) that cause the allergic symptoms of bronchospasm, vasodilation, smooth muscle contraction and increased bronchial and nasal secretion. Systemic anaphylaxis, a rare event in man, is the most severe of all allergic reactions. Typically it can occur after an inciting dose has been given intravenously to a hypersensitive individual. It is characterized by sudden vasomotor collapse leading to shock, paroxysmal bronchoconstriction, and if treatment is not undertaken immediately, death. Most cases have been associated with serum therapy (serum sickness) penicillin therapy, and insect stings (especially the wasp, bee, and hornet). However, there is danger of chamomile tea ingestion by an individual known to have ragweed and *Chrysanthemum* atopic disease and other allergies (Elvin-Lewis '77: 64- 68).

Classification of hypersensitivity reactions

	Reaction	Pulmonary pathology	Skin test	Examples
Type I	Antigen + IgE bound to mast cell	Release of mediators of anaphylaxis with bronchoconstriction	Immediate wheal and flare	Bronchial asthma, allergic rhinitis, eczema
Type II	Cytotoxic antibody attacks cellular or tissue component and activates complement	Cellular and tissue inflammation	None	Goodpasture's syndrome, transfusion reactions

Type III	Antigenic-antibody complement complexes deposit locally	Innocent bystander interstitial inflammation with granuloma formation	Arthus (erythema, induration) at 4-6 hr	Hypersensitivity pneumonitis (extrinsic allergic alveolitis), serum sickness
Type IV	Sensitized T-lymphocytes and macrophages attack antigen	Granuloma formation with or without caseation necrosis	Delayed (24-48 hr)	Tuberculosis, sarcoidosis, Wegener's granulomatosis

Source: Dreisin '89: 229 Table 20-1

Type I hypersensitivity reactions are those underlying allergic eczema, allergic rhinitis (hay fever) and asthma in the 10% of the population who are atopic. Type I hypersensitivity has also been termed immediate hypersensitivity because the reactions occur withing minutes following exposure to the offending antigens. The antibody mediate immediate hypersensitivity reactions has been identified as immunoglobulin E (IgE). If antigen is introduced into the skin of the atopic patient, an immediate wheal and flare reaction is seen. If the antigen-antibody interaction occurs at the nasal mucosa, allergic rhinitis is the clinical outcome. If the reaction occurs within the tracheobronchial tree of a sensitized patient, bronchoconstriction and wheezing result. This reaction is blocked by the inhalation of disodium cromoglycate, which specifically inhibits the degranulation of mast cells. The symptoms are alleviated by the administration of drugs such as isoproterenol and theophylline compounds, which increase intracellular CAMP concentration. The reaction is not blocked by administration of corticosteroids Type I reactions may initiate acute allergic alveolitis. Type II hypersensitivity reactions are those mediated by circulating antibodies directed against endogenous cellular or tissue antigens. Type II cytotoxic antibodies directed against the pulmonary and glomerular basement membranes have been implicated in the development of Goodpasture's syndrome and as a transfusion reaction. **Type III (Arthus) reaction** frees both antigen and antibody and the resulting antigen-antibody complement complex may initiate an inflammatory reaction at the site of deposition. If a patient has circulating precipitins, a skin test with the corresponding antigen elicits a local reaction consisting of erythema and induration. This reaction begins approximately 4 hours after challenge, reaches a peak at 6 hours, and fades by 24 hours. The reaction is termed an intermediate hypersensitivity response, or delayed response. This reaction may be blocked or alleviated by previous administration of corticosteroids. **Type IV hypersensitivity** is mediated by T-lymphocytes rather than by specific antibodies. Skin testing with the appropriate antigen produces a local reaction consisting of erythema and induration that reaches its maximum in 24 to 48 hours and is properly termed a delayed hypersensitivity response. The type IV response is responsible for the classic tuberculin hypersensitivity and may play a role in other pulmonary diseases such as sarcoidosis and Wegener's granulomatosis. Type IV reactions account for many features of allergic alveolitis as well (Dreisin '89: 229-231).

The **immune system** operates on one fundamental truth: there is “self” and there is “non-self”. Ideally, immune system cells go after only non-self molecules such as bacteria, viruses, fungi, parasites and even tumors, and leave self cells, such as nerve, muscle and brain cells, alone. The immune system knows which are “good” cells and which are “bad” cells because the surface of every sell in your body sports special proteins called human leukocyte antigens, HLAs. The cells doing the detect-and-destroy work are white blood cells. Millions of them circulate in

blood and tissues, there are five main types: Lymphocytes, macrophages, neutrophils, eosinophils and basophils. Lymphocytes, found mostly in the lymphatic system, search your body for cells that don't belong there and alert other cells to their presence. There are two types of lymphocytes: T lymphocytes, or T cells, secrete potent substances to attract the immune system cells that do the actual work. They also attack and destroy diseased cells. B lymphocytes, or B cells, are immune cells that actually produce antibodies, specialized fighter proteins that help your immune cells do their job. B cells that long memories for their enemies and may remain in the body for years, ready at any time to turn into little antibody factories whenever an antigen they recognize appears. This is how a vaccination works: a tiny bit of a (usually) killed virus, or antigen, such as polio, measles, or flu, is injected into the blood-stream, provoking your B cells to produce antibodies. Then, if the fully functional form of the virus is ever encountered, the body can quickly marshal its defenses and produce millions of the required antibodies without delay. If your B cells had never met up with that particular antigen before, the antibody response would be much slower, and the intruder could gain the upper hand. Macrophages engulf and destroy large cells, such as bacteria or yeast, as well as the debris from natural cell formation in a growing body. Neutrophils, are the most common type of white blood cells in the bloodstream, they are first to appear at the site of an injury. Their job is to consume unwelcome cells. Eosinophils make up 4 percent or less of active white blood cells. They attack larger cells, in part by secreting toxins that trigger inflammation. Basophils release granules of germ-killing toxins and histamine, a substance that triggers inflammation when they encounter damaged tissue (Berger & Gordon '04: 23-24).

Allergic Rhinitis (**Hay Fever**) is induced following exposure of the nasal mucosa to the allergen through inhalation. The characteristic symptoms include profuse watery nasal discharge with sneezing, frequently accompanied by redness, irritated and watery eyes and headache. In North America there are three peaks in the pattern of seasonal rhinitis: the first occurs in the spring when trees shed their pollen; the second, during the summer months, involves pollen from many grasses as well as late flowering trees and weeds, and the last peak, in the autumn, is typified by weed and secondarily by grass pollen grains. Ragweed pollen (Ambrosia) predominates during this time and is the most allergenic pollen found in North America. Many kinds of fungi and flowering plants are responsible for allergic rhinitis. The most important fungal allergens are found in the Deuteromycetes, particularly the families of Dematiaceae and Moniliaceae, which include such ubiquitous genera as *Alternaria*, *Cladosporium*, *Aspergillus* and *Penicillium.* Of these Alteranria possesses the most allergenic substances. Although they produce a great deal of windborn pollen Gymnosperms rarely elicit allergic rhinitis, whereas most windborne pollen from Agniosperms are common incitors. The most troublesome trees in North America are the oaks (Quiercus), hickories (Carya) and elms (Ulmus) but weedy urban box elder (Acer) pollen has recently been shown to have the highest level of allergencity among tree pollen. Many grass family (Poaceae) pollen are highly allergenic, e.g. redtop (Agrostis), sweet vernal (anthoxanthum) orchard (Bactylis), crab (Digitaria) and timothy (Phleum). Of the weedy families, the Asteraceae, containing the ragweeds (Ambrosia), Marsh elders (Iva, cockleburs (Xanthium) and sagebrushes (Artemisia) and the Chenopodiaceae, including lamb's quarters (Chemopodium), burning buses (Kochia), and Russian thistles (Salsola) (Elvin-Lewis '77: 68, 71).

Higher Plants of Allergic Significance in Continental United States

Geographic Area	Trees	Grasses	Weeds	Major Pollen
Northeastern.	Birch, elm,	Annual blue,	Short and giant	Ragweeds,

New England, New York, New Jersey, Pennsylvania	maple, oak, poplar	June, orchard, sweet vernal, timothy	ragweed, plantain	grasses
Middle Atlantic. Delaware, Maryland, Washington D.C.	Birch, hickory, maple, oak, paper mulberry, sycamore	Orchard, timothy	Short and giant ragweed, plantain	Ragweeds, orchard grass
Virginias and Carolinas	Elm, maple, oak, pecan, red cedar	Annual blue, Bermuda, June, orchard	Short ragweed, sorrel, dock	Short ragweed, Bermuda grass, pecan
Southern. Florida and Georgia to eastern Texas, including Texas, Arkansas, and southern Missouri	Birch, cottonwood, elm, oak, paper mulberry, pecan, poplar, privet, red cedar	Bermuda, orchard, timothy	Giant and short ragweed, pigweed, Russian thistle, water hemp	Bermuda grass, pecan ragweeds
North Central. Ohio and Kentucky to northern Missouri, Iowa, Wisconsin, and Michigan	Ash, cottonwood, elm, maple, oak	June, orchard, timothy	Short ragweed	Short ragweed
Plains and prairies. Minnesota, Dakotas, eastern Montana, Nebraska, Kansas	Elm, oak	Bermuda, blugrass, orchard, redtop, timothy	Giant, short and western ragweeds, Russian thistle	Ragweeds, Russian thistle
Rocky Mountains. Idaho, western Montana, Wyoming, Colorado, Utah	Birch, box elder, cottonwood, Rocky Mountain cedar	Fescue, June, orchard, redtop, timothy	Ragweed, sagebrush, Russian thistle	Russian thistle, sagebrush
Pacific Northwest. Washington, Oregon, Nevada, northern California	Acacia, alder, box elder, birch, cottonwood, oak, walnut	Bluegrass, fescue, oats, orchard, redtop, timothy, velvet, western rye Bermuda, Johnson	Amaranth, canyon ragweed, Russian thistle, saltbush	Amaranth, Bermuda grass, goosefoot, mountain cedar,
Southern California	Elm, oak, olive, walnut	Bermuda, salt grass	Dock, lamb's quarters,	Bermuda grass, saltgrass

			pigweed, Russian thistle, sage, saltbrush, sea blite	

Source: Elvin-Lewis '77: Table 3-2 pg. 75

There are probably more **nonprescription medications** for the nose and sinuses than any other part of the body. In 1994 more than four billion dollars was spent on cold, sinus, allergy and cough products. However, all of this money is not necessarily well-spent. In a poll of pharmacists regarding which product categories cause confusion among consumers, allergy relief, cough and cold preparations top the list, with sinus remedies close behind.
In a survey on self-medication comparing fourteen countries, the United States led the list in percent of consumers using nonprescription medication. Lower cost is the reason most often given for using these products, followed by convenience and eliminating the need for a doctor's visit. In recent years, many drugs that formerly required a prescription have been changed to OTC status (Rosin '98: 121, 122). In 2010 the FDA removed more than 600 cold and flu remedies from the market. Oral antihistamines have long been considered a first-line defense against the misery of allergies, with their use dating back to the 1940s. They work well, but cause fatigue. People who take Benadryl say they are, on average, 26 percent less effective at work on days they're affected by allegies. A 2000 study showed the standard 50 mg dose of Benadryl impaired driving ability as much or more than alcohol, making the subjects legally drunk. Pilots aren't permitted to fly if they've taken such a drug within 24 hours of a scheduled flight. Benadryl sales actually increased between 2000 and 2002 despite the fact that newer, less sedating options became available by prescription. In late 2002, the first of the **nonsedating antihistamines** – loratadine (Claritin) became available over the counter (OTC). Unfortunately most health insurance plans now refuse to pay for Claritin, even if it is prescribed in stronger, non-OTC forms. In fact, many plans refuse to cover other second generation antihistamines such as cetirizine (Zyrtec) even though they are only available by prescription. For consumers, that means a month's supply of Claritin that once cost a co-payment of $10 to $15 is now twice that much in many instances. The drugs that still require prescriptions could cost $80 or more a month.

That's driving some people back to the older forms of antihistamines or to combination antihistamine/decongestants with all their attendant problems. With the advent of newer, nonsedating antihistamines such as fexofenadine (Allegra) and loratadine (Claritin and Alavert), these drugs don't cause one to be tired or confused. The active ingredients in these medications, which also include cetirizine (Zyrtec) and desloratadine (Clarinex) have very little effect on the central nervous system because they are composed of larger molecules that can't get past the blood/brain barrier. In addition to oral antihistamines there are now intranasal antihistamines, azelastine (Astelin) approved for both seasonal and perennial allergic rhinitis and available only by prescription. It works quickly and can be used as needed. Antihistamines: Nonprescription (sedating): Actifed, Alka-Seltzer Plus, Allerest, Banophen, Benadrul, Diphenhist, BC Multi-Sumptom Cold Powder, Chlor-Trimeton, Comtrex, contac, Dimetapp, Drivoral, Sinarest, Sudafed Plus, Taxist, Triaminic Allergy, Tylenol Allergy Sinus, Vicks NyQuil. Nonprescription (nonsedating) Alavert, Claritin. Prescription (sedating): Antivert (meclizine), Atarax (hydroxyzine HCL), D-Allergy (brompheniramine and pseudoephedrine), Naldecon Children's Syrup (cainoxamine), Periactin (cuproheptadine), Runatan/Trinalin (azatadine maleate and pseudoephedrine sulfate), Temaril (pghenothiazine), Vistaril (hydroxyzine). Prescription

(nonsedating): Allegra (fexofenadine), Clarinex (desloratadine), Zyrtex (cetirizine) (Berger & Gordon '04: 99, 104, 101).

Treatments for Allergic Rhinitis

Brand/Generic Name	FDA approved for ages	Comments
Antihistamines (prescription)		
Astelin (azelastine Hcl)	5 and up	Unique antihistamine nasal spray
Allegra (fexofenadine)	6 and up	Comes in 3 strengths (30, 60 and 180 mg)
Allegra-D (fexofenadine+pseudoephedrine)	12 and up	Antihistamine/decongestant
Clarinex (desloratadine)	12 and up	
Zyrtex tablets (cetirizine)	6 and up	Only prescription nonsedating antihistamine in syrup form
Zyrtex-D (cetirizine+pseudoephedrine	12 and up	Antihistamine/decongestant
Antihistamines (over-the-counter)		
Alavert (generic loratadine)	6 and up	Quick dissolving tablet
Claritin tablets (loratadine)	6 and up	Available in traditional tablet and quick dissolving forms
Claritin syrup (loratadine)	2 and up	
Claritin-D (loratadine+pseudoephedrine)	12 and up	Antihistamine/decongestant (12 and 24 hour tablets
Nasal corticosteroids		
Beconase AQ (beclomethasone)	6 and up	Dose recommendation by age
Flonase (fluticasone propionate)	4 and up	Dose recommendation by age
Nasacort AQ (triamcinolone acetonide)	6 and up	Dose recommendation by age
Nasarel (flunisolide)	6 and up	Dose recommendation by age

Rhinocort AQ (budesonide)	6 and up	Dose recommendation by age
Vancenase AQ	6 and up	Dose recommendation by age

Source: Berger '04: 249

The control and treatment of allergic rhinitis falls into three major categories. The first is related to controlling contact with allergic material. Another prophylactic measure is hyposensitization of the patient with the affecting allergen, by injecting increasing amounts of the allergen to develop a high titer of blocking antibodies proper to normal exposure. Finally as an adjunct to hyposensitization, acute symptoms are also treated by the administration of antihistamines and vasoconstrictors such as ephedrine (*Ephedra sinica*). **Corticosteroids** are the most important class of drugs for the treatment of serious cases. Steroids are: Precription (nasal): Flonase (fluticasone), Nasacort (triamcinolone), Nasalide (flunisolide), Nasonex (mometasone), Pulmicort and Rhinocort (budesonide), Qvar, Vancesnase DS, Vancenase pocket inhaler, Vanceril, and Vanceril DS (beclomethasone). Steroid Nasal Sprays People with allergies are likely to be prescribed topical nasal steroids, which are sniffed into the nose rather than inhale into the lungs. Several nasal steroids are also approved for nonallergic rhinitis, including fluticasone (Flonase) and budesonide (Rhinocort AQ). Steroid nasal sprays work by preventing mast cells and basophils from releasing chemicals that call in the cavalry ie. eosinophils and other inflammation-triggering cells, in response to the mast cell reaction. Corticosteroid therapy, which may be employed to terminate a single severe attack, is often effective, though not curative. Prolonged use of steroids may be dangerous. In prophylaxis, particularly where hyposensitization fails, cromolyn sodium is used, this new compound, obtained from the seeds of *ammi visnaga* (Apiaceae) is believed to affect the release of vasoactive substances and therefore, through a regimen of frequent inhalation, acts to prevent or modify the asthma. This plant, known as khella from its native Mediterranean region, has a long history of use as an anti-asthmatic among the Arab peoples, who also believe it is useful in the treatment of angina pectoris. Indian research using the leaves of *Tylophora indica* (Asclepiadeceae) claims that complete to moderate relief of nasobronchial allergic symptoms can be maintained up to one week after ingestion of but a few leaves of the plant. *T. indica*, however, is very toxic and also has blistering or vesicant properties (Elvin-Lewis '77: 73-74, 77). Epinephrine, often called adrenaline is administered via injection in the event of a severe allergy attack or anaphylaxis. Those severely allergic, particularly to insect stings and certain foods or penicillin, must carry epinephrine at all times as part of an emergency treatment kit. Emergency Medications Prescription (injected): Adrenalin chloride (epinephrine). Prescription (nebulized): Brethaire (terbutaline), Vaponefrin (epinephrine) (Berger & Gordon '04: 105). Epinephrine is no substitute for $1 hydrocortisone crème when it comes to curing fungal allergies and aspergillosis.

Decongestants unclog the nose by restricting blood supply to the nose and sinuses, thus reducing swelling, excess secretions and congestion. They're often combined with antihistamines, as in the oral nonsedating drugs Allegra-D and Claritin-D, and the less sedating acrivastine (Semprex-D) and Zyrtec-D). They also are frequently combined with guafenesin (an expectorant). Saltwater can relieve stuffiness and congestion. It can be bought over the counter in brands such as Ocean and Salinex or make your own by adding ½ teaspoon of salt and a pinch of baking soda to a cup of lukewarm water and using a bulb syringe like the ones used to clear an infant's nose to spray the solution in your nose a few times, followed by a good, hard blow. Decongestants: Nonprescription: Actifed Allergy Daytime, Allerest, Drixoral Nondrowsy Formula, Edifc/24, Sudafed. Nonprescription Nasal Sprays: Afrin, Cheracol, Dristan, Neo-Synephrine, Nostril/Nostrilla, Otrivin, Privine, Vicks Sinex Long-Acting. Prescription: Dura-Vent

(chlorpheniramine and phenylephrine), Entex LA, Guaifed PD, Respaire, and Sinuvent (guaifenesin and phenylephrine), Exgest LA (guafenesin and phenylpropanolamine)(Berger & Gordon '04: 102, 103). Ipratropium bromide (Atrovent) belongs to the tongue-twisting class of drugs known as **anticholinergic agents**. They block the effects of acetylcholine, a neurotransmitter that stimulates mucus production, which makes them great for combating runny noses. Available only in a prescription spray, Atrovent is officially approved for the treatment of allergic rhinitis, but it does work quite well in some cases of asthma and chronic bronchitis because of its ability to dry up mucus secretions. It is particularly effective for older people with asthma who also have emphysema or chronic bronchitis or for those who don't respond completely to the common asthma medications known as beta2-agonists. Anticholinergic spray: Prescription (Nasal spray): Atrovent nasal (ipratropium bromide). Prescription (inhaled): Atrovent 0.03% or 0.06%, nebulized or metered-dose inhaler (Berger '04: 103).

The first generation H_1 antihistamines such as diphenhydramine, chlorpheniramine, brompheniramine and hydroxyzine are also referred to as the sedating antihistamines. These agents are effective at controlling the rhinorrhea, sneezing and pruritus associated with allergic rhinitis. Unfortunately these agents cross the blood-brain barrier thus producing undesirable side effects such as central nervous system depression, sedation leading to impaired performance at home, work and school and cardiotoxicity. There are no long-term safety studies on the first generation antihistamines. These agents have poor H_1 receptor selectivity and act on muscarinic receptors causing anticholinergic effects such as dry mouth, urinary retention, constipation and tachycardia. The second-generation antihistamines developed in the early 1980's, have improved H_1 receptor selectivity, absent or decreased sedation, faster onset and longer duration of action and fewer adverse effects. Their half-lives are longer (12-24 hours) compared to the first generation (4-12 hours). Of the second generation H_1-antagonists, fexofenadine has no sedating effects even at higher than recommended doses. Loratadine and desloratadine are non-sedating at recommended doses but may cause sedation at higher doses. Cetirizine, and its purified enantiomer levocetirizine, have more sedation potential that other second generation H_1-antagonists. All rhinitis symptoms, except for obstruction, can be alleviated by H_1-antihistamines, and there does not seem to be a superiority of any one of the second generation H_1-antihistmines over another.

Topical H_1-antihistamines (azelastine, olopatadine) provided faster onset of action (less than 15 minutes) and similar to greater efficacy compared to oral preparations in regard to rhinitis and conjunctivitis. There has even been an association with improvement of congestion. However, their results are limited to the local organ effects, and require twice daily use to maintain a sustained response; whereas second generation oral H_1-antagonists can be taken on a daily basis. Some patients may complain of a bitter taste, and intranasal H_1-antagonists are less effective than intranasal steroids. In a direct comparison trial between azelastine nasal spray versus oral cetirizine, azelastine was found to have a significant improvement in nasal symptom scores for the specific symptoms of sneezing and nasal congestion over cetirizine. In addition to oral H_1-antihistamines, intranasal corticosteroids are a mainstay of treatment. They are the most effective medications for controlling all rhinitis symptoms. Their onset of action is from 3-12 hours. Their use on an as needed basis is not as effective as continual use but may not be required continually in all patients. They are generally safe, and there is little evidence to support suppression of the hypothalamic-pituitary-adrenal axis with prolonged use. Side effects are generally mild (crusting, dryness, and minor epistaxis). They can be minimized by proper nasal spray technique. Septal perforation has only been described anecdotally. For patients whose symptoms are not optimally controlled with intranasal steroids, adding an intranasal (but not oral) antihistamine may give

some additional benefit. Systemic corticosteroids should be considered a last resort treatment option, but they may be necessary for severe or intractable symptoms. If they are used, then oral is preferred over parenteral because of the lower risk of systemic side effects and the ability to adjust doing. Steroids should never be injected into the turbinates. Recommendations on short courses oral steroids differ from 5-7 days to no more than 3 weeks.

Subcutaneous immunotherapy (SCIT) has been shown to be effective in treating allergic rhinitis in patients with identifiable IgE mediated symptom triggers. It has some advantages over the above mention treatments. Effects can be sustained for years, and it may prevent the development of new allergen sensitivities or even asthma. It is effective for not only control of allergic rhinitis but also of allergic conjunctivitis and allergen induced asthma. However, immunotherapy is underutilized with only 2 to 3 million US individuals on SCIT of the estimated 55 million people with allergic diseases. In regard to specific inhaled allergens, evidence supports immunotherapy for pollens, animal dander, and dust mite. Large local reactions at the injection site are the most common adverse reaction. The risk of severe systemic reactions during subcutaneous immunotherapy is rare but present in less than 1% of those receiving standard immunotherapy. Near fatal events occurred at a rate of 5.4 per million injections. High ambient pollen levels and dosing errors were the two main risk factors for such a reaction. It is advised that patients receive immunotherapy injections in a setting with staff and equipment that can handle anaphylaxis, and that patient be observed for 30 minutes after each injection. Other disadvantages include injection discomfort, the frequency of shot visits, and the total cost. However, immunotherapy is the only treatment that can modify the disease. When the direct costs of symptomatically managed allergic rhinitis are compared to the cost of immunotherapy, the values are virtually the same. When indirect costs are factored, immunotherapy may be much more economical. Subcutaneously is the most common way to deliver immunotherapy, but sublingual immunotherapy (SLIT) is also used. SLIT has been reported to cause oral itching and gastrointestinal side effects, but in most studies, these rates seem to be the same as those observed in the placebo arm. There is a lack of standardization in SLIT with timothy grass pollen extracts being the only commercially available therapy (Grazax by ALK-Abelló Hørsholm. Denmark), and there are no SLIT therapies approved for the US by Food and Drug Administration. Advantages of SLIT include an extremely low risk of anaphylaxis and the ability to begin therapy at the maintenance dose without a build-up phase. SLIT for dust mite allergy has been specifically studied in the Korean population and found to be effective in reducing symptom scores. Although anaphylaxis has not been noticed in studies on SLIT, there are case reports of anaphylaxis occurring during treatment, even with the first dose. SLIT is not as well established as SCIT, and further investigation is required to determine the optimal dose and patient selection (Tran, Vickery & Blaiss '11).

Certain **essential oils** used in aromatherapy can treat and cure allergy and asthma symptoms where conventional medicine has failed – essential oils of lavender, peppermint and eucalyptus are particularly curative of allergic rhinitis (Sapeika '63). For airborne allergens the frequency of application will depend on the severity of the allergens. Use as often as needed to eliminate the symptoms. Eucalyptus oil can help control allergies in various forms. If symptoms include coughs, sore throat or sinus congestion, over-the-counter lozenges, cough syrups, rubs and vapor baths that include eucalyptus oil as a key ingredient. Eucalyptus oil can also kill dust mites, a common household allergen. Wash bedding and washable toys with four parts eucalyptus oil added to one part of commercial liquid dish washing detergent or add 15 to 20 drops eucalyptus oil to 1 quart distilled water in a spray bottle; spray mattress, pillow and curtains and leave for two hours. Children should not ingest eucalyptus oil, and only children older than 6 should take

eucalyptus cough drops. Eucalyptus oil may interact with other medications, herbs and supplements, so consult your health care provider before using it to treat allergy symptoms. Additionally, eucalyptus oil may trigger asthma attacks. When taken internally, eucalyptus oil is toxic and must be diluted. Essential oils cost more than a dab of $1 hydrocortisone crème.

III.A.3 Asthma

Asthma is a disorder of the airways. Persons with asthma have increased bronchoconstrictor responsiveness to various inhaled stimuli and have airway obstructive changes in severity spontaneously or with treatment. Increased airway responsiveness and reversible airway obstruction are both important elements of the disorder. Airway obstruction is caused by bronchoconstriction, increased airway secretion, and mucosal edema. Asthma is usually mild, causing little disability, but in some persons it is severe, persistent, debilitating and even life threatening. In the United States asthma affects 3% to 5% of the adult population. It occurs in all age groups but begins predominantly early in life. About one half of cases develop before age 10 and one third before age 40. In childhood there is a 2:1 (male/female) predominance, but the prevalence equalizes by age 30 (Bethel '89: 162). Asthma-related conditions are responsible for 14 million doctors' visits and 2 million emergency room visits a year by children in the United States. Between 1980 and 1994 the number of **asthma cases** in children under 5 increased by more than 160 percent and rose by 74 percent among children ages 5 through 14. Asthma is the most common chronic childhood illness, in 1998 it affected an estimated 8.65 million American children, more than 12 percent of the entire under-18 population. In 1994 that figure was just 5 percent. Asthma counts for an estimated 11.8 million missed school days nationally and costs more than $1 billion per year in lost productivity in the United States due to parents staying home to care for their children. Roughly 49 percent of infants with eczema develop asthma by age 4, and about 30 percent of all eczema cases in toddlers are lined to an allergy, of which a third are food related. From 50 to 80 percent of children with asthma develop symptoms before age 5. The vast majority of their asthma symptoms, however, are triggered by viral infections, not allergies to molds. Studies have shown that as many as 70 percent of people with asthma have GERD, a chronic form of heartburn, compared with 20 to 30 percent of the general population. GERD occurs when the esophageal sphincter, which normally keeps food and acid in the stomach where they belong, repeatedly fails to close tightly enough, allowing stomach acid to flow back, or reflux, into the esophagus and create that burning feeling. Infection with the rhinovirus, which causes the common cold as well as other respiratory illnesses, can cause wheezing, often sending an asthma sufferer into a full-fledged attack. Other infectious agents linked to asthma symptoms include respiratory syncytial virus (RSV), *Chlamydia pneumonia*e, and *Mycoplasma pneumoniae*. Asthma patients infected with mycoplasma have six times more mast cells in their lung tissue than uninfected asthma patients, meaning they have a much greater risk of inflammation. In some cases, a course of antibiotics to treat pneumonia, or specifically metronidazole to treat *Helicobacter pylori* infection causing GERD, may make a huge difference in the ability to control asthma symptoms (Berger & Gordon '04: 238, 239, 258). Mold allergies above athlete's foot crème, respond well to corticosteroids - $1 hydrocortisone crème, prednisone, corticosteroid nasal sprays and corticosteroid inhalers in want of both conversion to non-ozone depleting aerosol and exemption from the Montreal Protocol of 1987.

Attacks of **bronchial asthma** are usually precipitated by inhalation of the specific allergen, and this form of allergy often has a more chronic course than seen in allergic rhinitis even though the eliciting agents are the same. Penicillin with its antigenic benzyl penicilloyl antigenic determinants and other haptenic moieties is perhaps the worst offender, and some type of allergy

appears in from 0.5% to 18% of patients using this drug therapeutically. Hives after 24-48 hours or generalized anaphylaxis is the most common (Elvin-Lewis '77: 75, 87). A survey of 300 people with asthma found that 68% had attacks a few times a year, 17% a few times per month, and 15% a few times per week or more. 84% suffer in the Spring, 76% in the fall, 73% in the winter and 64% in the summer. Smoke was the leading cause of an asthma attack in 59% of respondents, followed closely by dust 56%, mold/mildew 52%, pollen 51%, cold air 47%, change of seasons 45%, common cold/influenza 44%, chemicals, paints, etc. 41%, hairspray, perfumes, etc. 40%, pets/animals 35%, stress, tension, anxiety 31%, exercise 29%, humidity, 23%, food 4%, other 2%, none of the above 3%. Medications for attacks, such bronchial inhalants, particularly fast-acting corticosteroids were the most preferred treatment 96% of the time. There are more than 5,000 deaths annually due to asthma, and asthma related deaths among children 5 to 14 years of age more than doubled from 1979 to 1995. In one report on 51 asthma related deaths in children under age 20, researchers found a third had "trivial or mild" asthma, while a third had no previous hospitalization. Sixty-three percent collapsed suddenly minutes after developing shortness of breath, and 78 percent died before reaching the hospital. For half of those who died, the final attack lasted less than 2 hours (Berger & Gordon '04: 55, 57). Corticosteroid rescue inhalers are essential.

Antigen inhalation causes bronchoconstriction in individuals who are sensitive to the specific antigen. The association between antigen inhalation and wheezing may be obvious to the individual whether the reaction occurs within minutes or is delayed 6 to 8 hours. The most important inhaled antigens are derived from danders, house dust mite, pollens and molds. Many persons with asthma complain that inhaling exhaust fumes, perfumes, dusts, sprays or cigarette smoke causes acute asthma attacks. Specific air pollutants such as sulfur dioxides, oxidants, and nitrogen dioxides can also cause acute asthma attacks. Exercise and cold dry air can cause exercise-related broncho-constriction. Covering the nose and mouth with a mask or scarf may prevent exercise-induced broncho-constriction. Pretreatment with inhaled beta-adrenergic drugs, ipratropium or cromolyn diminishes or eliminates exercise-induced bronchoconstriction. Fog induces broncho-constriction in many asthmatic patients. In the laboratory inhaling aerosolized hypotonic solutions may cause broncho-constrictions. Viral upper respiratory infections are among the most common causes of exacerbations of asthma. Many agents inhaled in work environments sensitize the airways and induce acute asthma attacks. In diagnosing occupational asthma it is often helpful to have patients measure peak flow. Peak flow typically improves on days absent from work and deteriorates on return to work. Many women develop premenstrual exacerbation of asthma that can be severe. Asthma is not prevented by treatment with non-steroidal anti-inflammatory agents, which improves some other premenstrual symptoms, or by treatment with oral contraceptives. Premenstrual exacerbations of asthma should be treated by increasing the dosage of conventional asthma medications. Many persons with asthma also have paranasal sinusitis. Postnasal drip caused by sinusitis may exacerbate asthma. Paranasal sinus inflammation may irritate sensory nerve endings that increase airway responsiveness by vagal reflex mechanisms. Paranasal sinus inflammation may release intravascular mediators of inflammation that increase airway responsiveness (Bethel '89: 164-166).

Airborne allergens, ranging from pollen and dust to mold spores, dander and fibers, are the most common reason for rhinitis, with an estimated 35 million Americans allergic to these substances. People are not allergic to cigarettes or perfume, some people have a sensitivity to such substances, which can make eyes water, nose run and sneeze, and those with allergic rhinitis, are more likely to have such sensitivities. Allergens are generated from living things, namely tree pollen, grass pollen, cockroaches, pet dander, molds and dust mites. Among North

American plants weeds are the most prolific producers of allergenic pollen, with ragweed the major culprit; others include sagebrush, redroot pigweed, lamb's quarters, Russian thistle (tumbleweed), and English plantain. Grasses and trees, too are important sources of allergenic pollens. Although more than 1,000 species of grasses grow in North America, only a few produce highly allergenic pollen. They include timothy grass, Kentucky bluegrass, Johnson grass, Bermuda grass, redtop grass, orchard grass, and sweet vernal grass. Trees that produce allergenic pollen include oak, ash, elm, hickory, pecan, box elder, and mountain cedar. There are thousands of types of molds and yeasts in the fungus. Molds are made of many cells that grow as branching threads called hyphae; yeasts are single cells that divide to form clusters. Although both can probably cause allergic reactions, only a small number of molds are recognized offenders. Mold allergies may get worse from spring to late fall, but the first freeze doesn't end the problem with molds as it does with pollen. Molds are tenacious little fungi that are able to grow at subfreezing temperatures. Even snow, while lowering the outdoor mold count dramatically, doesn't kill mold spores. Only a few molds get the allergen label. In general, Alternaria and Cladosporium (Hormodendrum) are the allergenic molds most commonly found indoors and outdoors throughout the United States. *Aspergillus*, *Penicillium*, *Helminthosporium*, *Epicoccum*, *Fuarium*, *Mucor*, *Rhizopus*, and *Aureobasidium* (*Pullularia*) are also common allergy triggers. There is no relationship between a respiratory allergy to the mold Penicillium and an allergy to the drug penicillin. Although allergic rhinitis caused by mold is relatively benign, Aspergillus may cause a more severe respiratory reaction. This form of mold may lodge in the airways or in a distant part of the lung and grow until it forms a compact sphere known as a fungus ball. Aspergillus mold can also lead to asthma or to a lung disease resembling severe inflammatory asthma, called allergic bronchopulmonary aspergillosis (Berger '04: 39, 41, 44).

In the sixteenth century, the Archbishop of St. Andrew in Scotland invited the acclaimed Italian physician Gerolamo Cardano to his country for advice on treating his asthma. Cardano's diagnosis was simple and astute: the problem was the bed, and he recommended that the Archbishop get rid of his feather bedding. The result? A "miraculous" recovery. Some 400 years later, in 1927 Storm van Leeuwen created a "climate" chamber in the Netherlands to make a similar point. He successfully showed that asthmatic patients improved when moved from their homes into the chamber. Cardano and Van Leuwen came upon the truth that if you want relief from allergies or asthma, you need to get rid of the triggers in the home. Studies have found that the average six-room home in the United Sates collects 40 pounds of dust each year. **Dust** is composed of flakes of dead skin, pet hair and dander, breakdown of fabrics, debris blown in from outside, and so on. Dust may also contain cockroach dropping, another potent allergy trigger. The problem with dust is that it provides a regular supply of food for **dust mites**. These microscopic bugs are literally everywhere in your home They are a major source of allergies, with about 10 percent of the population and 90 percent of people with allergic asthma having positive skin tests to dust mites. Those figures are even higher in children, with recent studies suggesting that at least 45 percent of kids are allergic to dust mites. There may be as many as 19,000 dust mites in 1 gram of dust. Each female can add 25 to 30 mites to the population before she dies. These tiny creatures thrive in warm, humid conditions, when the relative humidity is 75 to 80 percent and the temperature at least 70° F. Reduce the humidity to reduce the mites, since they can't survive in humidity of less than 40 to 50 percent. One study found that reducing levels of dust mites in children's beds by one-third cut the number of days they wheezed and missed school by nearly a quarter (22 percent). The best way to kill mites is washing in very hot water (at least 130°F) At least once a week. Dust with damp cloths and dust everything. Use a vacuum cleaner with either a double-layered microfiltration bag or a HEPA filter to trap allergens that pass through the vacuums's exhaust. Change home air filters. A study published in

the Journal of Allergy and Clinical Immunology found that when **eucalyptus oil** was used to presoak loads of bedclothes, it killed 95 percent of mites that survived high-temperature water. The research mixed 1 part liquid detergent and 4 parts eucalyptus oil in a small container, then added 1 teaspoon of the mixture to an 8-ounce gallon of water. They fill the washer with water, added the diluted detergent and eucalyptus mixture and let the bedding soak for an hour before washing (Berger & Gordon '04: 125, 127, 129).

Cockroach droppings are one of the top two causes of perennial allergies, plus they carry mites and diseases, such as dysentery, hepatitis, salmonella and typhus. Cockroaches eat everything. Cockroaches carefully taste their food. Interestingly they despise okra, raw or stewed, so putting a dish of the green pods in cabinets that have roach problems may send them scurrying for sweeter pastures. **Hot tub lung disease** caused by *Mycobacterium avium complex* (MAC) thrives in the warm, moist environment of an indoor spa. MAC accumulates inside a tub hitches a ride on the air-jet bubbles, which are the perfect size t be inhaled into the lungs. Chlorine doesn't work at temperatures higher than 84°F. Outdoor spas aren't affected because sunshine kills MAC and fresh air harmlessly dissipates it. At least 60 species of molds have spores thought to be allergenic and 30 percent of people with respiratory allergies seem to be particularly sensitive to molds, with children appearing to be most sensitive. The best mold remover is merely 1 part bleach and 10 parts water, or about 1 ½ cups bleach to 1 gallon of water. Trash moldy foods, even if the mold is on one tiny corner. The link between gastro-esophageal reflux disease (GERD) and asthma is pretty clear, with as many as 70 percent of people with asthma also suffering from GERD. You could go the medication route with antacids and proton pump inhibitors such as omeprazole (Prilosec) and esomeprazole (Nexium). Essentially, small meals that are rich in vegetables and include modest servings of complex carbs and lean protein are usually best. (Berger & Gordon '04: 130, 136, 138, 142). The term **sick building syndrome** refers to situations in which specific health complaints appear to be linked to the building in which you work or live but for which no specific illness or cause can be identified. Volatile organic compounds, carbon monoxide, inadequate ventilation, outdoor chemical contaminants, biological contaminants and climate control are issues. Mold is a fungus of which there are thought to be more than 1.5 million species. Less than 100 are known to be infectious in humans or animals. It is estimate that 70 percent of homes have mold growing in their walls. *Stachybotrys chartarum* is a much-feared mold but there is little evidence that it causes the neurological problems and other health affects attributed to it. Many respiratory illnesses among workers are attributed to mold exposure, such as hypersensitivity pneumonitis (also called farmer's lung, woodworkers' lung and malt worker's lung. Whether residential molds cause bleeding in the lungs (pulmonary hemorrhage, memory loss or lethargy, is unproven and unknown (Berger & Gordon '04: 271).

Air quality has improved since the passage of the Clean Air Act of 1970. However in May 2003 the American Lung Association reported that because3 the government doesn't fully enforce clean air laws, more than half of all Americans breathe polluted air that damages their health. According to the association, more than 7.4 million adults with asthma and nearly 2 million children suffering from asthma attacks live in counties that received an F grade in ozone air pollution. This represents 70 percent of the 10.6 million American adults with asthma and 69 percent of the 2.8 million children who have had an asthma attack and live in counties with an ozone monitor. Fully enforcing the standards of the Clean Air Act, the Lung Association notes would prevent 15,000 premature deaths, 350,000 cases of asthma and 1 million cases of decreased lung function in children. Specific outdoor air related asthma triggers include ozone,

particular matter such as dirt soil dust, pollens, molds ashes and soot and indoor air pollution such as smoke and fumes and animal dander, cockroaches, dust mites, molds and fungi. 59 The American Lung Association ranks the following geographic areas as having the most polluted air in the country (1) Los Angeles/Riverside/Orange County, California (2) Bakersfield/Fresno/Visalia/Tulare/Porterville, California (3) Houston/Galveston/Brazoria, Texas (4) Atlanta, Georgia (5) Merced, California (6) Knoxville, Tennessee (7) Charlotte, North Carolina and Rockville, South Carolina (8) Sacramento, California. The cleanest big cities include Bellingham, Washington, Colorado Springs, Colorado, and Lincoln, Nebraska (Berger & Gordon '04: 58).

One half of all patients who have asthma also have **esophageal reflux**. Evidence suggests that treatment of esophageal reflux decreases the medication required to treat asthma. Forced expiration during asthma attacks may increase intraabdominal pressure and cause esophageal reflux. Asthma medications such as theophylline and beta-adrenergic drugs given orally decrease lower esophageal sphincter pressure and may predispose the patient to esophageal reflux. A systemic abnormality may alter both airway smooth muscle function and lower esophageal sphincter function. Esophageal reflux may lead to microaspiration of stomach contents into the airways, thereby inducing asthma attacks. Esophageal reflux may stimulate sensory nerve endings in the distal esophagus, which causes bronchoconstriction through vagal reflex pathways. Often asthma is most severe in the middle of the night. A disproportionate number of asthmatic patients die in their sleep. Aspiring nonsteroidal anti-inflammatory drugs, and acetaminophen cause severe bronchoconstriction in a subpopulation of persons with asthma. The association of aspirin sensitivity, nasal polyps and asthma is often known as "triad asthma". Nonselective beta-adrenergic blockers precipitate severe bronchoconstriction in many asthmatics. Cholinesterase inhibitors used in the treatment of myasthenia gravis, may precipitate asthma attacks. Many food preservative and dyes have been implicated in causing acute asthma attacks. Sulfites, including bisulfites and metabisulfites, precipitate acute attacks in some asthmatics. However, food dyes such as tartrazine and food additives such as monosodium glutamate are questionable in causing asthma attacks. Anxiety and stress may exacerbate asthma. Persons who have asthma should be wary of using gas ranges, which produce NO_2 and should use them only with exhaust fans as a partial protective measure (Bethel '89: 165, 166, 174).

Patients who die of asthma have **profound airway obstruction** and overdistension of the lungs when autopsy is performed. Thick, tenacious, mucous plugs occlude most bronchioles. Histologically, the airways have hypertrophied bronchial smooth muscle, mucosal edema, denuded surface epirthelium, thickened basement membranes, and eosinophilic infiltrates in the bronchial walls. Wheezing, cough and dyspnea are the most common symptoms of asthma. Most persons have mild disease with intermittent episodes of airway obstruction that resolve spontaneously or with minimal therapy. Some patients have continuous wheezing and chest tightness of varying severity. A typical asthma attack may begin with wheezing and a dry cough and progress to greater chest tightness, wheezing and dyspnea and often improves after considerable quantities of mucus are expectorated. Historically, asthma has been divided into two major groups – intrinsic and extrinsic. **Extrinsic asthma** usually begins in childhood or adult life and is associated with sensitivity to inhaled antigens, immediate positive skin test responses to antigens, other allergies, frequent increased serum IgE concentration and a personal and family history of other atopic disorders (hay fever, hives, and eczema). Airway obstruction in extrinsic asthma is frequently intermittent. **Intrinsic asthma** usually begins later in life and is infrequently associated with known sensitivities to inhaled antigens, immediate positive skin test

responses, elevated serum IgE concentrations, and other allergies, or a family history of asthma or atopy. The symptoms of intrinsic asthma are continuous and spontaneously remit less often than those of extrinsic asthma. Today the term **allergic rhinitis** is generally preferred. During severe attacks evidence of air trapping – increased anteroposterior diameter of the chest, hyperresonance of the chest to percussion, and low hemidiaphragms, may be observed. As airway obstruction nprogreses, the patient uses accessory muscles of ventilation and develops a pulsus paradoxus, both of which indicate a severe asthma attack. Airway obstruction may become so severe that ventilation is impaired which, together with hyperexpansion of the lungs, produces a silent chest examination, an ominous finding (Bethel '89: 166, 167). Wheezing does not always indicate asthma. Asthma is common and is usually easy to diagnose. Nevertheless, many other disorders cause wheezing and are sometimes confuse with asthma. Left ventricular heart failure may cause airway compression, wheezing, and so-called cardiac asthma. Endobronchial lesions caused by tumor, foreign body or granulomatous infiltration may cause focal wheezing. Such wheezing may intensify during lateral recumbency on the side of the obstruction. Adduction of the vocal cords during inspiration and expiration causes stridor that is sometimes confused with wheezing. Patients who have vocal cord dysfunction develop severe respiratory distress without hypoxemia and not hot have hyper-reactive airways. Bronchiolitis obliterans mimics asthma by causing severe airways obstruction wheezing and air trapping. It may occur secondary to viral infection, inhalation of toxic gases, and collagen vascular disorders or may occur ideopathically.

Measurement of airflow and lung volumes is abnormal during asthma attacks but may be normal between attacks. Airway obstruction during acute attacks decreases the forced expiratory volume in one second (FEV_1) and peak expiratory flow (PEF) and increases airway resistance. The FEV_1 and PEF reliably indicate the severity of airways obstruction and document whether obstruction improves with therapy. To diagnose asthma the effect of inhaled bronchodilators on airways obstruction is often determined. Arbitrarily, an increase in FEV_1 of 15% after inhalation of a bronchodilator is indicative of hyperresponsive airways. Arterial blood gases are usually abnormal during an acute asthma attack. Airway obstruction causes ventilation-perfusion mismatching and consequently cause hypoxemia. During acute asthma attacks, most patients are dyspneic and hyperventilate and therefore have hypcapnia and acute respiratory alkalosis. Normal or increase $PaCO_2$ during acute asthma indicates severe airway obstruction and patient fatigue. A patient with elevated $PaCO_2$ should be observed closely, since ventilator support may be needed. The sputum of patients who have asthma often contains numerous eosinophils (corticosteroid therapy suppresses these), Charcot-Leyden crystals (derived from eosinophil granules), and Curshmann spirals (mucous casts on the small airways). Patients may have eosinophilia of the circulating blood. Inhalation challenge tests are performed to diagnose asthma in cases where the diagnosis is in question. The patient inhales aerosols of solutions containing increasing concentrations of methacholine or histamine, and airflow is measured after each inhaled dose. Both methacholine and histamine cause bronchoconstriction in healthy persons but at lower concentrations cause bronchoconstriction in persons who have hyperresponsive airways (Bethel '89: 167-169).

Initial therapy for acute asthma may include supplemental oxygen and inhaled beta-adrenergic drugs. Corticosteroids are indicated, not only if the initial response is insufficient or if the patient has had several recent asthma attacks, but as the first line treatment. The choice of topical, aerosol, oral or intravenous route for corticosteroids depends more on convenience and price, than on the severity of the asthma attack. Intravenous aminophylline should be considered if the asthma attack is severe, despite oral prednisone. Inhaled corticosteroids, cromolyn,

acetylcysteine and ultrasonic mist may irritate airways and exacerbate an acute attack. Sedatives, beta-adrenergic blockers and drugs that contain aspirin should be avoided. Occasionally asthma attacks are so severe that the patient requires mechanical ventilation. Indications for mechanical ventilation are cardiopulmonary arrest, persistent or progressive carbon dioxide retention and respiratory acidosis and clinical deterioration indicated by fatigue and hypersomnolence. Patients who have intubation and mechanical ventilation should (1) use a large diameter endotracheal tube with a soft cuff, (2) use a volume ventilator, (3) ensure adequate humidification of air, (4) use the lowest possible ventilator cycling pressure, (5) keep the respiratory rate of the ventilator slow, (6) avoid hypocapnia, and (7) if necessary, suppress the patient's respiratory drive with a sedative or paralyze ventilation with neuromuscular blockade, although paralyzing a patient maintained on a ventilator should be avoided, in treating severe asthma it is sometimes necessary to obtain adequate ventilation (Bethel '89: 176, 177).

Patients who have persistent airflow obstruction and frequent acute attacks of asthma require most therapeutic measures. Patients should avoid asthma attacks by pretreating themselves before exercise and by avoiding triggers of acute attacks. Most patients require inhaled beta-adrenergic drugs on a regular basis and many require inhaled corticosteroids and oral theophylline drugs. If these drugs are not effective inhaled cromolyn, and inhaled ipratropium bromide sometimes alleviate symptoms. Some patients require continuous oral corticosteroid therapy. The corticosteroid dose should be maintained as low as possible and should be administered on alternate days, if possible. Maximizing the doses of other asthma medications and ensuring their regular administration allows minimization of the oral corticosteroid dose. Both elective and emergency surgery can usually performed in in patients who have stable asthma. Asthma medications should be continued up to the time of surgery and can be continued intraoperatively and postoperatively by parenteral administration and nebulation. Supplemental doses of corticosteroids may be necessary to cover the stress of surgery. In general, asthma is treated identicaly in pregnant and nonpregnant women. Some medical professionals favor treating pregnant women with drugs that have a known safety record (epinephrine, theophylline and corticosteroids) rather than with newer drug whose safety is uncertain (terbutaline, albuterol and metaproerenol), During the first trimester it is wise to administer only medications that are definitely indicated. Allergic bronchopulmonary aspergillosis complicates asthma in some patients. It is caused by colonization of the airways with *Aspergillus* organisms and by the development of a hypersensitivity response to the organism. It usually occurs in patients with well-established underlying asthma. It is characterized by episodic bronchial obstruction, peripheral eosinophilia, immediate skin reactivity to *Aspergillus* antigen, precipitating antibody against *Aspergillus*, increased serum IgE concentration, a history of recurrent pulmonary infiltrates, and central bronchiectasis. Sometimes patients expectorate brown plugs or "fleks" and sometimes *Aspergillus* organisms are identified in the sputum. The disorder usually requires oral corticosteroid therapy, which is given in a tapering course over 6 months. Antifungal therapy and inhaled corticosteroids are of no benefit. Close follow-up of the patient is needed to observe for recurrences, which require additional corticosteroid therapy. A rising serum IgE concentration is an early indicator of recurrence. Asthma frequently causes cough. Cough variant asthma is diagnosed by demonstrating hyperreactive airways with methacholine or histamine inhalation challenge test in a patient who has no other cause for cough (Bethel '89: 177, 178).

Classes of Asthma medicines

Recommended Medication	Best Way to Use

Inhaled corticosteroid	For mild intermittent asthma use low dose as needed, take daily and in increasing doses to treat mild, moderate and sever persistent asthma
Leukotriene modifier	May be useful in mild, moderate or severe persistent asthma
Inhaled cromolyn	May be useful in mild persistent asthma
Theophylline	May be useful in mild, moderate or severe persistent asthma
Daily long lasting beta2- agonist	May be useful in moderate or severe persistent asthma
Oral steroids	May be useful in severe persistent asthma
Short acting beta2-agonist	May be used as needed for mild intermittent, mild, moderate or severe persistent asthma

Source: Berger '04: 194

Corticosteroids are the most important class of drugs for the treatment of serious cases. Prescription (nebulized): Pulmicort Respules (budesonide). Prescription (systemic –inject and oral): Celstone (betamethasone), Decadron (dexamethasone), Medrol and Solu-Medrol (methylpresdnisolone), Prapred and Pediapred (prednisolone), Prednisone and Prelone Syrup (prednisone). **Bronchodilator medications** open and keep open the large and small airways in the lungs. They come in two forms: short acting (rescue medications) and long—acting, used on a daily basis for prevention. The term **metered dose** means the medication inside the pressurized canister is released in a single, measured, controlled dose every time you use the inhaler. You must shake the canister vigorously so the ingredients mix properly and you get the right amount of medication with each dose. **Holding chamber and spacers** are devices in which the inhaler mouthpiece or canister is inserted into the holding chamber, to help with the delivery of metered dose inhaled medication to the airways. **Dry-powder inhalers** come in different shapes and sizes and are set to deliver bronchodilators as well as anti-inflammatory medications. Unlike metered dose inhalers you are less likely to taste of eel the medication when using it. **Nebulizer therapy** is a special device used to deliver liquid medicines to the lungs. It's composed of an air compressor and a container for the medication. The force of the compressor helps you receive the medicine without having to take a deep breath, which is why they're particularly beneficial for infants and small children. Bronchodilators: Prescription (short-acting inhaled beta2-agonists) Alupent and Metprel (metaproterenol), Brethaire, Brethine, and Bricanyl (terbutaline), Isuprel, Norisodrine, and Medihaler (isoproterenol), Maxair Autohaler (pirbuterol), Proventil and Ventolin (albuterol), Tornalate (bitolterol mesylate), Xopenex (levalbuterol) Prescription (short-acting nebulized beta2-agonists): Bronkometer and Bronkosol (isoetharine) Prescription (long-acting inhaled beta2-agonists): Foradil (formoterol), Serevent and Serevent Diskus (salmeterol xinafolate) (Berger & Gordon '04: 109, 111 112, 113).

Corticosteroids relieve most asthma attacks, both acute and chronic., that do not respond to bronchodilators. They suppress inflammation within airways, eliminate streptococcal infection and potentiate the effect of adrenergic drugs. Their frequent use can cause many adverse effects including hypertension, glucose intolerance, cataracts, myopathy, osteoporosis, dermal atrophy, immunosuppression and cushingoid habitus. Their effective action begins several hours after administration. They are given through intravenously, oral or inhaled routes. The does and length of therapy needs to be individualized for each patient. Some patients require only intermittent, tapering doses of steroids to treat acute attacks others require continuous inhaled steroids, some require oral administration of steroids every other day, and some require continuous daily oral administration. In general, minimum corticosteroid medication is given because of the significant adverse effects associated with its use. To treat acute asthma attacks, 30 to 60 mg of prednisone or its equivalent is often given orally during the attack, and the daily dose is tapered to extinction over 7 to 14 days. For severe exacerbations, intravenous corticosteroids are administered. A typical dose is 80 to 125 mg of methylprednisolone given intravenously every 6 hours. The dose is tapered rapidly and converted to oral therapy after the acute attack is relieved. Inhaled corticosteroids may decrease or eliminate the requirement or oral corticosteroids during chronic therapy. The three drugs available in **metered-dose inhalers** are beclomethasone, triamcinolone and flunisolide. The standard dose of these drugs varies from two puffs b.i.d. to two puffs q.i.d depending on the drug, but all can be given in higher doses. High-dose inhaled corticosteroids are especially effective in decreasing the requirement for oral steroids. The most frequent complications of inhaled steroid therapy are oral candidiasis and hoarseness. The frequency of these adverse effects can be decreased significantly if the patient inhales the drug through a spacer and gargles after use of the drug to clear the pharynx. Inhaled corticosteroids should be used to treat acute asthma attacks, since they may irritate the airways. Suppression of the pituitary-adrenal axis can occur with the use of high-dose inhaled steroids, every other day oral steroids or daily oral steroids. Many patients receiving these regiments require systemic corticosteroid supplementation to prevent adrenal crisis during periods of stress (Bethel '89: 170-172). **Spacers** are devices placed between a metered-dose inhaler or nebulizer and the patient's mouth. Their purpose is to remove large drops that form the aerosolized liquid, to allow the remaining drops to decrease in size by evaporation as they pass through the spacer, and to eliminate the need to coordinate activation of a metered-dose inhaler and inhalation. By decreasing the size of the droplets delivered to the mouth, a spacer allows more drug to be deposited in the airways and less in the pharynx. Spacers should be used with inhaled corticosteroids to decrease the incidence of pharyngeal candidiasis. A peak flow meter is an inexpensive, hand-held device with which a patient can measure peak expiratory flow and thus determine objectively the severity of airway obstruction (Bethel '89: 175). Common types of inhaled steroids include: beclomethasone (Qvar), budesonide (Pulmicort), budesonide/formoterol (Symbicort) – a combination of a steroid plus a long-acting bronchodilator drug, ciclesonide (Alvesco), fluticasone (Flovent HFA), fluticasone propionate (Flovent Diskus), fluticasone furoate (Arnuity Ellipta), fluticasone propionate/salmeterol (Advair) — a combination of a steroid plus a long-acting bronchodilator, fluticasone furoate/umeclidinium/vilanterol (Trelegy Ellipta) — a combination of a steroid, an anticholinergic, and a long-acting bronchodilator drug, mometasone furoate (Asmanex), mometasone/formoterol (Dulera) — a combination of a steroid plus a long-acting bronchodilator drug. Current metered dose inhalers (MDIs) contain chlorofluorocarbon (CFC) propellants. A new propellant HFA134a, with no effect on ozone, may be a suitable alternative (Jenkins '10).

Adrenergenic drugs cause bronchodilation ($beta_2$ receptors), vasoconstriction (alpha receptors), stimulation of the heart ($beta_1$ and to a lesser extent $beta_2$ receptors), tremor ($beta_2$ receptors,

hyperglycemia ($beta_2$ receptors), and hypokalemia. Some adrenergenic drugs, such as albuterol and terbutaline, are selective agonists of $beta_2$-receptors and therefore cause bronchodilation with less cardiac stimulation than nonselective agonists. Adrenergenic drugs can be inhaled or injected subcutaneously. In general, the inhaled route is preferred. Albuterol is a $beta_2$ selective agent that is available as metered-dose inhaler, solution for nebulization or subcutaneous injection, and in oral tablets. Terbutaline is a $beta_2$ selective agent that is available as a metered-dose inhaler, solution for nebulization of subcutaneous injection, and in oral tablets. Metoproterenol is a drug that is less beta1 selective than albuterol or terbutaline and therefore has greater cardiovascular effects. It is available as metered-dose inhaler, solution for nebulization and oral tablets. Fenoterol is a $beta_2$ elective agent that is used in many parts of the world but is not available in the United States. Isoproterenol is a nonselective adrenergic drug that has a short duration of action. It is available as a metered-dose inhaler and as a solution for nebulization. Isoetharine, a relatively $beta_2$ selective, short-acting drug, is available in a metered-dose inhaler, as a solution for nebulization and in oral tablets. **Epinephrine** is available as a metered-dose inhaler, a solution for nebulization and solution for subcutaneous injection. It has a short duration of action. When injected subcutaneously, it is usually no more effective than inhaled $beta_2$ adrenergic drugs and has greater systemic effects. Bitolterol mesylate, available in a metered-dose inhaler, may have a longer duration of action than the other inhaled drugs. Some patients find the inhaled solution irritating and foul tasting. Ephedrin is an oral drug that has been used for many years to treat asthma. It is nonselective, causes central nervous system stimulation and probably should not be used. For many patients with mild asthma, one or two puffs of an adrenergic drug from a metered-dose inhaler, taken as needed, is the only treatment that is required. For patient who have more severe asthma, inhaled adrenergic drugs shuld be used regularly four to six times a day, but should be administered cautiously when tremulousness, tachycardia, palpitations, or excitation occurs (Bethel '89: 169-171).

Theophylline relaxes airway smooth muscle, probably by inhibiting cytoplasmic phosphodiesterase and increasing cytoplasmic cAMP concentration. Theophylline has been used form many years to treat asthma, but recent studies indicate that it may contribute little to treat asthma. Adrenergic drugs dilate airways more effectively. When theophylline is added to inhaled adrenergic drugs in the therapy of acute asthma, bonrchodilation does not improve and the frequency of side-effects increases. However, theophylline decreases the frequency and severity of symptoms in chronic asthma and decreases the need for corticosteroids. Theophylline is available in oral tablets and solutions and in rectal suppositories and solutions. Taken at bedtime theophylline may diminish nocturnal symptoms of asthma. Theophylline is given intravenously as aminophylline, which is a soluble ethylenediamine salt containing 85% theophylline. Liver disease, congestive heart failure, chronic obstructive pulmonary disease, and sustained fever decrease clearance of theophylline, whereas smoking tobacco or marijuana and youth increases clearance. Erythromycin and cimetidine decrease theophylline clearance and phenobarbital increases it. The loading dose of aminophylline IV is usually 5 to 6 mg/kg given intravenously over 20 minutes if the patient has not been taking a theophylline-type drug. The maintenance dose should be about 0.6 mg/kg/hr. In patients who have liver disease, congestive heart failure, advanced age, or are being treated with erythromycin or cimetidine, the maintenance dose should be decreased to about 0.3 mg/kg/hr. The maintenance dose should be increased to about 0.9 mg/kg/hr if the patient smokes tobacco or is young. Serum theophylline concentration should be measured and the dose of aminophylline should be based on the concentration. The therapeutic concentration in serum is usually 10 to 20 µg/ml.. However, concentration less than 10 µg/ml cause significant adverse effects in some patients. Nausea, vomiting, diarrhea, headaches, nervousness, cardiac arrhythmia, insomnia, and seizures often

occur when levels exceed 20 µg/ml (Bethel '89: 172, 173). **Theophylline**: Prescription: Constant-T, Resbid, Slo-Bid Elixophyllin, Slo-phyllin. Theophylline isn't used very much any more to treat asthma, even though it was once one of the primary asthma drugs. It works by relaxing the muscles around the airways and stimulating breathing. The main concern about theophylline is that it could build up to toxic levels in your blood. This risk increases if you have liver problems, such as hepatitis, or are taking drugs, such as erythromycin and systemic antifungal medications, that can interfere with your liver's ability to break down theophylline. Chronic smokers absorb the drug much more quickly than nonsmokers, so they require higher doses. Theophylline also interact with other drugs for a variety of medical conditions, including, ironically asthma. For instance, don't use beta2-agonists and theophylline together. Leukotrienes are among the molecules that mast cells, eosinophils, and macrophages release when they encounter asthma triggers. **Leukotriene modifiers** such as montelukast (Singulair) which stem the tide of leukotrienes, can be taken orally once a day, and have minimal side effects, were first approved in 1997. Leukotriene modifiers: Prescription (nonsteroidal anti-inflammatories): Accolate (zafirlukast), Singulair (montelukast), Zyflo (zileuton)(Berger & Gordon '04: 115-118).

Ipratropium bromide blocks muscarinic, cholinergic receptors on airway smooth muscle and causes bronchodilation. The parasympathetic nervous system continuously stiulates airway smooth muscle even in healthy persons and causes some smooth muscle tone. Ipratropium bromide interrupts this stimulation and causes bronchodilation. The drug is available in a metered-dose inhaler that delivers 20 µg/puff. The conventional dose is 40 to 80 µg, and optimal bronchodilation in stable asthma is obtained with dose. However in status asthmaticus the bronchodilator response increases through cumulative doses up to 500 µg. This dose is tolerated without adverse effect because the drug is poorly absorbed form the airway mucosa. Ipratropium is slower than other inhaled beta-adrenergic drugs. Peak effects occur only after 30 to 60 minutes, and bronchodilator effects last at least 4 hours. In stable patients, dosages taken three or four times daily are usually sufficient. Adverse effects are rare except for dry mouth and bad taste. Ipratropium bromide dilates the airways in persons who have asthma; however, adrenergic drugs usually dilate them more effectively. In persons who have concomitant heart disease and poorly tolerate the tachycardia induced by adrenergic drugs and theophylline, ipratropium may be preferred. Similarly, for those who have tremor as a major complication of beta-adrenergenic drug therapy, ipratropium avoids this adverse effect. Patietns who have bonrchoconstriction precipitated by beta blockers often respond poorly to beta-adrenergic drugs and usually respond better to an anticholinergic drug. Anticholinergic drugs may be preferred to treat bronchoconstriction induced by anticholinesterase therapy. The bronchodilator effect of ipratropium is independent of and additive to that of adrenergic drugs and prolongs the bronchodilator response. Smaller doses may cause fewer adverse effects. **Cromolyn** is a prophylactic drug used to prevent bronchoconstriction. It is administered by inhalation and is available as a powder that is inhaled through a device called a spinhaler, as a solution for nebulization and a metered-dose inhaler. Cromolyn decreases the requirement for corticosteroids and other asthma medications in many patients. It is costly but has few adverse effects. It is used four times a day to treat chronic asthma or is given before exercise to prevent exercise induced asthma (Bethel '89: 173, 174).

Immunotherapy for asthma is the repeated injection of increasing doses of extracts of substances to which asthmatic patients have immediate skin responses. In theory the injected antigens induce "blocking antibodies" that inhibit subsequent allergic responses to the antigen. Whether immunotherapy is an effective treatment for asthma is controversial. Problems with

immunotherapy are: the lack of quality extracts of molds and animal danders to test or treat patients, the lack of objective studies to determine whether immunotherapy is effective and the lack of diagnostic criteria to establish the relevance of positive skin-test reactions to allergens such as house dust mite and animal danders that are perennially present in the environment (Bethel '89: 175). Immunotherapy involves getting a shot once or twice a week for six months or more but often leads to remission from allergy attacks for years after treatment has ended. Allergy shots have been around since 1911. It's the only treatment for allergies that reduces symptoms over the long term rather than just treating them for a few hours. Each successive injection contains a tiny bit more of the substance to which you're allergic. Eventually, your body becomes desensitized to the allergen, decreasing the IgE reaction to it by blocking IgE antibodies. Experts analyzing 24 studies involving more than 900 people with asthma who also had documented allergies found that allergy shots effectively treated allergic asthma in 71 percent, resulting in fewer symptoms, less lung inflammation, and a reduced need for medications. Overall, other studies found that immunotherapy can reduce the sneezing and wheezing of allergic rhinitis by 80 percent and the need for allergy medications by 88 percent. The biggest drawback to immunotherapy is the needle and treatment may require well over 100 shots. That's why a growing number of physicians in Europe have turned to sublingual-swallow immunotherapy (SLIT). Of 18 double blind, placebo-controlled clinical trials in the past 15 years, 16 confirmed the effectiveness of SLIT in reducing allergy symptoms triggered by grass pollen, house dust mites, or birch pollen. Other studies found that drops were as effective as shots, that patients liked them better and that they were safer than shots. In November 2003, the World Health Organization supported the use of SLIT for certain patients, particularly those who don't take their meds, refuse injections and/or have systemic reaction to injection immunotherapy. SLIT is under investigation in the United States and may be available in the near future. A report from the Mayo Clinic on 79,593 immunotherapy injections over a 10-year period showed the incidence of adverse reactions was less than 2/10 of 1 percent. Most were mild and responded to immediate medical treatment. There no fatalities during the study. Between 1985 and 1993 when an estimated 52.3 million immunotherapy shots were given, 35 deaths occurred, making the incidence of fatality less than 1 per million (Berger & Gordon '04: 105-107).

Beta2-agonists relax and open constricted airways during an asthma attack and work for 3 to 6 hours. While they relieve the symptoms of acute attacks they don't control he underlying inflammation. Albuterol (Proventil, Ventolin) are the standard short-acting beta2 agonist used in the United States. Similar dugs include isoproterenol (Isuprel, Norisodrine, Medihaler-Iso), metaproterenol (Alupent, Metaprel), pirbuterol (Maxair), terbutaline (Brethine, Brethaire, Bricanyl), and bitolterol (Tornalate). Another drug, isoetharine (Bronkometer, Bronkolsol) comes in nebulizers. Some newer beta2-agonists, including levalbuterol (Xopenex) have more specific actions than the older types and are effective at lower doses resulting in fewer side effects. **Long lasting Beta2-agonists** such as salmeterol (Serevent) and formoterol (Foradil) help prevent asthma attacks. They are used as rescue medications. Foradil works within 3 to 5 minutes. Taking Serevent during an attack could actually be dangerous because it takes so long to work that, in your desperation you could inadvertently take too much or stop breathing before it kicks in. In mid-2003, the FDA added new safety information and warnings to the labeling on drugs containing salmeterol, as well as boxed warning about a small but significant increased risk of life-threatening asthma episodes or asthma-related deaths observed in patients taking salmeterol in a large U.S. safety study. The increased risk was particularly apparent in people who weren't using inhaled corticosteroids concurrently and in African-Americans who seem to have a different response to beta2-agonists (Berger & Gordon '04: 114, 115)

Asthma Medicines

Brand/generic name	FDA approved for ages	Comments
Mast Cell Stabilizers		
Intal MDI (cromolyn sodium)	5 and up	
Intal inhalation solution	2 and up	Inhalation solution only available in generic
Tilade MDI (nedocromil)	6 and up	
Leukotriene Modifiers		
Accolate Tablets (zafirlukast)	5 and up	Available in 2 strengths (10 and 20 mg)
Singulair Tablets (montelukast sodium)	12 months and up	Available in 3 strengths of chewable tablets (4,5 and 10 mg) and dissolvable granules (4 mg) dose recommendation by age
Inhaled Corticosteroids		
Aerobid (flunisolide)	6 and up	Available in mint flavoring
Advair (fluticasone & salmeterol)	12 and up	Available in 3 strengths (100/50, 250/50, and 500/50) combination of long-acting bronchodialator and inhaled corticosteroid
Azmacort (triamcinolone)	6 and up	Dose recommendation by age
Flovent MDI (fluticasone propionate)	12 and up	Available in 3 strengths (44), 110, and 220 mcg)
Flovent Rotadisk (fluticasone propionate)	4 and up	Available in 3 strengths (50, 100, and 250 mcg)
Pulmicort (budesonide)	12 months and up	Only inhaled corticosteroid available in both a nebulized solution (o.25 and 0.5 mg) and dry powder inhaler, approved for use through pregnancy
ZVAR (beclomethasone	5 and up	New propellant that can

dipropionate)		deliver smaller particles to the lungs
Short Acting Bronchodialator		
AccuNeb Inhalation (Albuterol)	2 and up	Nebulizer solution, available in 2 strengths
Alupent MDI (metaproterenol)	12 and up	
Generic Albuterol MDI	12 and up	
Brethine tablets (terbutaline)	12 and up	Available in two strengths (2.5 and 5 mg)
Proventil-HFA MDI (albuterol)	4 and up	CFRC-free propellant
Long-Acting Bronchodialator		
Foradil Aerolizer (formoterol fumarate)	5 and up	Unique delivery system; rapid onset of action
Serevent Diskus (salmeterol)	4 and up	
Oral Steroids		
Prednisolone syrup	Not established	Dosage based on severity of symptoms
Orapred syrup	Not established	Dosage based on severity of symptoms
Prediapred syrup	Not established	Dosage based on severity of symptoms
Prelone syrup	Not established	Available in two strengths (15 and 5 mg/1 tsp) dosage based on severity of symptoms
Prednisone tablets	Not established	Available in multiple strengths
Medrol (methylprednisolone)	Not established	Available in multiple strengths

Source: Berger '04: 250-251

In the summer of 2003 the FDA approved omalizumab (Xolair), the first in a new class of drugs for the treatment of allergic asthma. Eventually, this class of drugs, called **anti-IgE drugs** – is expected to revolutionize the treatment of allergies in a way no other has done. Xolair is a genetically engineers drug called a monoclonal antibody. It works by stopping an allergic reaction before it starts by blocking the IgE antibody that causes the reaction. Xolair came about

as a result of the discovery in 1998 of the precise shape of the receptor molecule that triggers the allergic response in your immune system, high-affinity immunoglobulin-E (IgE) receptors. Currently Xolair is approved only for moderate to severe allergic asthma in people 12 and older whose asthma has not responded well to other treatments. It's given by subcutaneous injection once or twice a month. People taking Xolair are often able to live very normally for the first time, being able to visit a friend with a pet, or sleep with the windows open in the spring. Many people have been able to significantly reduce their use of other medications, if not discontinue them altogether. In studies of Xolair in adults and children, some of those taking the drug were able to cut back on or even stop using inhaled corticosteroids. Xolair is likely to be approved to treat allergic asthma in children soon. A year's supply of Xolair costs between $5,000 and $10,000 depending on the dose. It's so expensive because it requires a very sophisticated manufacturing. Olopatadine (Patanol) is the best-selling prescription eyedrops for allergic conjuncitivitis, and is being developed into a nonsteroidal nasal spray that's expected to be called Panase (Berger & Gordon '04: 120, 121). An antibody known as Dupilumab has scored high marks as possible treatment for asthma, according to researchers from the University of Pittsburgh. For the study, the researchers enlisted 108 volunteers around the country to receive a weekly dose of the drug for 12 weeks. They found that asthma incidents decreased by 86 percent for those taking the antibody as compared to those using a placebo. The drug targets the interleukin-4 (IL-4) receptor specifically, easing symptoms for those suffering from Th-2 type asthma. This study targeted those individuals who, on the basis of eosinophil levels in their blood, seemed to have evidence for Th2-type asthma. By using this drug that blocks this pathway, we observed a really robust response compared with placebo in patients with moderate to severe asthma.

In Armenia in Eastern Europe people with asthma travel nearly 1/5 mile beneath the Earth's surface to reach **Republican Speleotherapeutical Hospital**, an underground medical clinic specifically designed for the treatment of asthma and other respiratory illnesses. Practitioners of speleotherapy believe that the salt environment, with its dry air and consistent temperature has a healing effect on the respiratory system. Similar clinics can be found in mines and caves throughout much of Eastern Europe. There's even some slight evidence that it may have some benefit. At least one scientifically designed study conducted in 1994 found a slight improvement in lung function after three weeks of speleotherapy. **Marijuana** was once touted as an asthma remedy. In the early nineteenth century, pharmaceutical manufacturer Grimault and sons actually marketed ready –made marijuana cigarettes for use as an asthma remedy, and doctors continued to prescribe it throughout much of the early twentieth century. It works as an excellent bronchodilator, opening up the large and small airways of the lungs. If you put the active ingredient in cannabis, tetrahydrocannabinol (THC) into a micro-aerosol form, for instance, it's up to 60 percent as effective as a pharmaceutical bronchodilator. One oft-cited study of 10 adult asthma patients found that after they smoked a 2 percent THC preparation for 2 hours, their airway resistance decreased 10 to 13 percent compared with when they used a placebo. In another study, researchers induced acute asthma attacks in eight healthy young men and then had them smoke 500 milligrams of marijuana. With the marijuana, the men's bronchial spasms immediately ceased. With a placebo or saline solution, it took about 30 minutes for their lungs to return to normal (Berger & Gordon '04: 164, 166). The National Tuberculosis Association, founded in 1904, was the first American charity to focus on a single disease. With the decline of TB in the mid-twentieth century, the organization changed its mission to include asthma, becoming the American Lung Association in 1973. Today, the association fights lung disease in all its form, with special emphasis on asthma, tobacco control and environmental health. A 2002 survey conducted by the American College of Allergy, Asthma, and

Immunology found that 41 percent of those with allergies thought they had colds or viral infections when they first began having allergy symptoms. In a nationwide survey of 250 allergists, more than 80 percent said self-medicating for allergies was likely to mask more serious health problems and 60 percent said that seasonal allergies and allergic asthma are best treated with prescription medications (Berger & Gordon '04: 66, 82-83).

Although *Nicotiana tabacum* (tobacco) is considered harmful to all lung conditions, *Cannabis sativa* (marijuana), *Datura stramonium* (Jimson weed), as well as *D. metel* and *D. fastuosa* can be smoked for the relief of asthma. *Verbascum thapsus* (mullein) can also be smoked for pulmonary ailments and is specifically indicated for bronchiolitis. Bronchodilators relax the smooth muscles of the bronchioles that lead to the air cells, thereby diminishing generalized peripheral airway obstruction. Bronchitis (inflammation of the bronchial tubes) and emphysema (enlarged air spaces in the lungs, making breathing difficult). There are two chief types of bronchodilator drugs: adrenergic agents and those derived from theophylline. The adrenergic drugs increase the volume and diameter of the bronchial smooth muscles by relaxing them, include norepinephrine, epinephrine (adrenaline), isoprenaline, and ephedrine. Ephedrine is now obtained synthetically, but may be extracted from its original sources*, Ephedra aquisetina* and *E. sinica* (Gymnosperms in the family Ephedraceae). The second type of bronchodilator includes the theophylline derivates (originally isolated from tea, *Camellia sinensis*) which act directly on the bronchial muscle to relieve obstructions, increase coronary blood flow and stimulate respiration centrally. Tea will help you come to your *Camellia sinensis* (green or black tea) - oral treatment of 100 patients for 20 days proved effective in 93% of cases, of which 58% could be described as excellent. During the course of treatment, sputum decreased in 91% of the cases, cough in 85% and asthmatic symptoms in 58.1%, Aerosol therapy was equally effective (Elvin-Lewis ’77: 297, 298).

The goal in treating asthma is to use the smallest amount of medication necessary to achieve two goals: keeping the airways in the lungs open, both during attacks and over the long term, and reducing the ongoing inflammation that’s the cornerstone of the disease. There are three types of anti-inflammatory drugs that doctors typically prescribe for asthma: inhaled corticosteroids, cromolyn and leukotriene modifiers. To keep airways open, they often prescribe short and long acting bronchodilators known as beta2 agonists (Berger & Gordon '04: 107-108). Most doctors follow the National Heart, Lung and Blood Institute’s step approach for treating asthma in adults and children:-Mild intermittent – prescribe only a short acting beta2 agonist for when attacks occur. Mild persistent – In addition, prescribe a daily low dosage of an inhaled corticosteroid, or cromolyn or nedocromil. Also consider a leukotriene modifier. Moderate persistent – Change the daily inhaled corticosteroid to a medium dosage. Also prescribe a daily inhaled long-acting beta2-agaonist. Continue to consider a leukotriene modifier, and continue prescribing a short-acting beta2-agonist for when attacks occur. Severe persistent – change the daily inhaled corticosteroid to a high dosage, and prescribe oral steroids as needed for disease control.

III.A.4 Upper respiratory disease

More than half of all visits to doctor's offices are for ear, nose and throat problems. The ear is connected to the respiratory tract by the **Eustachian tube** and is susceptible to most airborne allergic, bacterial and fungal pathogens that infect the lung. The air filled inner ear are responsible for hearing (cochlear) and balance (labyrinth). Otology is the medical discipline concerned with the ear and temporal bone region. Disease of this region can often have neurological complications and starting in 2004 otolaryngology residency graduates who have

completed a fellowship or gained appropriate clinical experience in neurotology can qualify for the certifying examination and achieve a certificate of added qualifications in neuro-otology (Sperling '04: 59). The five main symptoms presented by diseases of the ear are (1) perceived hearing loss, (2) tinnitus, (3) vertigo or dizziness, (4) otorrhea, and (5) otalgia (Sperling '04: 59). More than 25 million persons in the United States have substantial **hearing loss**, including some 5 million school-age children and about 8 million persons older than 65 years, more than 10% of the population. Today a hearing-impaired child whose hearing loss is detected early (preferably before the age of 6 months) and who is provided with adequate bilateral amplification or cochlear implantation can learn to speak and use residual hearing to learn. By school age, many of these children can attend conventional schools. Hearing loss in older people causes considerable frustration and anguish and can have serious socio-economic implications. The U.S government estimates that the yearly loss of earnings caused by hearing disorders and related conditions to be about $75 billion. Hearing loss can be congenital or acquired. **Conductive hearing loss** is caused by a pathologic process usually middle ear effusion. Sensorineural hearing loss results from impairment of the cochlea, acoustic nerve, or the central auditory pathways. **Mixed hearing loss** is a mix of conductive sensorineural hearing loss. **Central hearing** loss is a pathologic condition within the brain that distorts the normal processing of auditory information. Acquired delayed onset hearing loss may be caused by infection, ototoxic drugs, or infections that cause hearing loss include mumps, chicken pox, measles, influenza, herpes zoster, adenovirus and human immunodeficiency virus (Bhaya, Sperling & Madell '04: 62, 63).

Older persons use medical and surgical services at a greater rate than younger people and the cost of their care is much higher. Cognition (learning, thinking and remembering), mobility and sensing (hearing, sensing, smelling, tasting and feeling) are three important aspects of normal functioning for the geriatric age group. A disability in any of these systems reduces one's capacity to function independently and has a serious effect on quality of life. Visual and hearing impairments are among the ten leading chronic diseases among the population older than 65 years. Clinically significant hearing loss affects 50% of persons who reach the age of 75 years. Reduction in physiologic processes in the human body occur in a linear, steady manner beginning in the third decade until 80 or 90 years of age. Glomerular filtration rate declines in a linear manner from the third or fourth decade in life. A decrease of almost 50% in glomerular filtration rate causes severe impairment in the response to acute changes in fluid and electrolyte intake. Aged kidneys fail to handle acute salt and volume loads and this condition can precipitate pulmonary edema. Aged kidneys concentrate urine at approximately 70% of normal level. Pulmonary dysfunction is common, causing a decrease in vital capacity, maximal breathing capacity, thoracic compliance, total lung volume, muscle strength and an increase in pulmonary and residual volumes. This coupled with an increased pressure gradient between the alveoli and the blood leads to marked reduction in pulmonary function. Endocrine dysfunction is common. A decrease in thyroxine levels is caused by a reduction in peripheral function. This may occur as hypothyroidism and cause nasal congestion, hoarseness, snoring, hypersomnolence, vertigo, macroglossia, increased cerumen accumulation and cold intolerance. Syndromes of hyperkalemia and hyponatremia usually have iatrogenic causes (thiazide or chlorpropamide therapy). The immune system becomes less efficient and susceptibility to various diseases, such as infections, autoimmune disease and cancer, increases due to a progressive decrease in the the number of circulating lymphocytes in the blood during and after middle age, accompanied by an increase in suppressor cells such as IgA and IgG. Impaired immunity has been found in patients with deficiencies of iron, zinc, vitamins A and B_{12} ,

pyridoxine, and folic acid, and with excess of essential fatty acids and vitamin E (Bhaya & Lucente '04: 398, 39).

Otitis media usually results from obstruction of the Eustachian tube caused by an upper respiratory infection. Impairment of middle ear ventilation results in fluid collection. Bacteria may spread directly from the nasopharynx to the middle ear and cause purulent otitis media. The hearing loss tends to improve if the infection is managed promptly and thoroughly. When antimicrobial treatment is inadequate and otitis media becomes a chronic disease, surgical intervention is directed toward achieving (1) resection of diseased tissue, (2) restoration of a pneumatized system, and (3) correction of conductive hearing loss Benign lesions are more common than malignant neoplasms. **Otosclerosis** accounts for a greatest number of cases of conductive hearing loss among persons 5 to 50 years of age. It is a genetically inherited disease affecting approximately 9% of the white population and 1% of the black population worldwide. It causes progressive fixation of the stapes footplate in the oval window, producing progressive conducting hearing loss. Sudden conductive hearing loss may occur with **barotrauma**, changes in air pressure, resulting in hemotympanum (hemorrhage into the middle ear), tympanic membrane perforation, or serous otitis media.

The prognosis of recovery among patients with sudden sensorineural hearing loss varies. Most patients with isolated low to mid-frequency losses recover completely and approximately two thirds of patients with hearing loss the same or greater at 4,000 Hz as at 8,000 Hz recover completely or at least recover usable hearing. In contrast patients with a hearing loss greater at 8,000 Hz than at 4,000 Hz have only a 25% likelihood of return of usable hearing. The greater the magnitude of hearing loss, the less likely it is that hearing loss will be restored to normal levels. Patients with sudden hearing loss of less than 10 days seem to recover more frequently than those whose hearing loss has lasted longer. The most common agents used are corticosteroids and antiviral agents. For accurate determination of the type and degree of hearing loss, an **audiologic evaluation** is performed with audiometer in a sound-treated room An audiometer is an electrical instrument that produces tones at various frequencies (measured in hertz) from 125 to 8,000 or 12,000 Hz and at intensities (measured in decibels) from 10 dB to 120 dB. Sensitivity to <20 dB is normal hearing, 20-40 dB mild hearing loss, 40-55 dB moderate hearing loss, 55-70 dB moderate-severe hearing loss, 70-90 dB severe hearing loss and > 90 dB profound hearing loss. Furthermore, speech testing is done to determine (1) speech awareness threshold, the lowest intensity sound can be recognized as speech and (2) speech reception threshold to assess ability to repeat familiar two-syllable words that have equal stress on each syllable (e.g. hotdog, baseball) (Bhaya, Sperling & Madell '04: 65,66, 72-74, 78).

Hearing aids are miniaturized sound-amplifying devices that contain a microphone to receive sound, an electronic processor (amplifier) that manipulates the qualities of sound to make it more usable to the listener, a speaker directed toward the ar, and a power source. Bone conduction hearing aids deliver the acoustic output to the mastoid process of the temporal bone. Five styles of air-condution aids are preferred when feasible. Five styles of air-conduction hearing aids exist; the body-worn aid, the behind the ear (BTE), the in the ear (ITE), in the anal (ITC) ,and the completely in canal (CIC). Eighty percent tof hearing aids dispensed in the United States are in the ITE to CIC size range. CROS (contralateral routing of signal) is for unilateral unaidable haring loss. BiCROS is for bilateral hearing losses in which only one ear is aidable. Bone-anchored hearing aids (BAHA) consist of a conventional microphone and amplifier, a specially designed transducter and a coupling arrangement to attach the device to the skin-penetrating and temporal bone-anchored implant. **Cochlear implants** bypass the function of the sensory

receptors by directly stimulating ganglion cells in the auditory nerve. Candidacy for cochlear implantation has changed over the past several years, and now includes a wider group of bilateral hearing impaired individuals with a pure-tone average of 70 dB or worse, speech recognition scores <50% (<20% in children), no medical contraindications and appropriate expectations or supportive family in children. The **auditory brainstem implant** was designed to restore some hearing to patients lacking functionally intat cochlear nerves, suh as patients with bilateral vestibular schwannomas. The cochlear nucleus complex within the brainstem is stimulated directly by placing the electrode intot he lateral recess of the fourth ventricle. As with cochlear implant, sounds form the microphone are converted to electrical signals, which are modified by speech processor and delivered to implanted receiver-stimulator through either a percutaneous pedestal or transcutaneous coil (Wynn & Sperling '04:81, 82).

Bacterial otitis externa is a frequent cause of itching and otalgia. The most common pathogens implicated are *Pseudomonas aeruginosa*, *Staphylococccus aureus*, proteus and Streptococcal organisms. Warm, humid weather and swimming often predisposes the ear to this condition. Successful treatment depends on careful and complete removal of all debris, because the debris obstructs the apocrine and seacous glands occupied by the infection. Although mild infections respond to cleaning and acidification of the ear canal with dilute acetic acid solutions, most infections require topical antibiotic drops, with or without steroids. **Malignant or necrotizing external otitis** is a form of fulminant bacterial otitis externa most common among elderly patients with diabetes or the immunocompromised. *P. aeruginosa* is the most common pathogen seen in necrotizing external otitis. The infection commonly extends beyond the cutaneous imits of the external auditory canal, producing cellulitis, chrondritis, osteitis, and osteomyelitis of the temporal bone. **Otomycosis** is a fungal infection of the external canal. Aspergillus and Candida species are common pathogens. Ithcing is the most common symptom and is usualy more severe than pain. Culture of the debris confirms the diagnosis. Treatment consists of cleaning, acidiying and drying the ear canal. Specific topical antifungal agents are often useful including m-cresyl acetate, clotrimazole, and gentian violet. **Furunculosis**, a gram-positive (usually staphylococcal) infection of a hair follicle, cause marked pain and occasional otorrhea, that occurs in the cartilaginous (lateral) portion of the ear canal. No hearing loss occurs unless the canal is completely occluded. Treatment consists of application of heat to encourage spontaneous drainage, topical application of an antistapylococcal ointment (e.g., meomycin-polymixin B and hydrocortisone), and oral administration of against staphylococcus. If spontaneous drainage does not occur, incision and drainage are indicated. Coalescence of furuncles produces a carbuncle or abscess, which must be drained. Foreign bodies should be removed with minimal damage to the soft tissue. Primary **skin conditions** that may affect the ear include psoriasis and seborrheic dermatitis. Allergic contact dermatitis can present itself with ear itchng after exposure to nickel compounds (earrings) or rubber headphones. **Frostbite** is painful and is managed by means of rapid warming with application of moist gauze or cloths soaked in warm water (100°F to 104°F, 38°C to 40°C (Peng & Sperling '04: 85-91),

Perforation of the tympanic membrane from trauma usually occurs with compressive injuries, such as a slap with an open hand, instrumentation injuries form cotton-tipped applicators, or industrial burns with metallic fragments. The pain may be severe immediately after injury but tends to become duller in subsequent hours and days. Most traumatic perforations heal spontaneously if contamination is avoided. Antibiotic ear drops are not used unless there is a gross infection. Assessment of hearing should be done. If the perforation involves more than 20% of the surface of the eardrum, the patients should be promptly referred to an otolaryngologist for possible repair of the damaged eardrum. **Bullous myringitis** is a

painful viral infection of the tympanic membrane characterized by the presence of one or more hemorrhagic vesicles or blebs. This disease must be differentiated from herpes zoster oticus (Ramsay Hunt syndrome). Ramsay Hunt syndrome is a viral infecti nof the sventh and eight cranial nerves that may be manifested by facial paralysis, hearing loss and **Otitis media** is a bacterial infection of the middle ear. The patient gives a history of recent upper respiratory infections followed by deep-seated otalgia, fever and decreased hearing. The most common pathogens are *Streptococcus pneumoniae*, *Haemophilus influenza*, *Staphylococcus* organisms, β-hemolytic streptococci (*S. pyogenes*), and *Moraxella catarrhalis*. Oral amoxicillin is sufficient treamtnet in 75% of patients with bacterial otitis media. Resistant strains may require amoxicillin with clavulanic acid. Patients with allergies to pencillin may be treated with a macrolide or a fluoroquinoline. **Primary pruritis** is itching of the canal in the absence of physical findings. Treatment consists of avoidance of scratching and possible topical steroid ointment or drops (Peng & Sperling '04: 91, 92). **Ottorrhea**, drainage from the ear, is a common complaint that can be innocuous or potentially lethal (Wynn & Sperling '04: 95).

Tinnitus is defined as the perception of sound in the absence of an external sound source. It may consist of single or multiple tones and may be described as high pitched, low pitched, buzzing, roaring, clicking, hissing, pulsatile, or continuous. It is a symptom, not a disease, and its pathogenesis is uncertain. More than 36 million people in the United States report tinnitus, and about 8 million have a severe form. Tinnitus is most prevalent between the ages of 40 and 70 years. Otologic conditions that produce tinnitus range in seriousness from benign cerumen impaction to tumors of the cerebellpontine angle. Occlusive conditions of the ear canal, including bony exostoses, external otitis, or foreign bodies, may be responsible. The majority of patients with tinnitus have a history of noise exposure or presbycusis. A 30+ dB hearing loss from 3 to 8 kHz is the most consistent finding in patients with tinnitus. Approximately 10% of patients attribute the onset of tinnitus to initation of or changes in drug therapy involving aspirin, aminoglycoside antibiotics, NSAIDs, tricyclic and other antidepressants, antineoplastic drugs, loop-inhibiting diuretic (furosemide), quinines, caffeine, alcohol, cocaine, marijuana, oral contraceptives and propranolol. Prophylaxis involves limiting noise exposure, cessation of smoking and drugs, limiting caffeine intake, control of hypertension, metabolic and dietary disorders, and management of ear conditions. This usually improves tinnitus for about 25% of patients fifty percent of patients improve to some degree, 25% remain unchanged, and in a small proportion tinnitus gets progressively worse. Drug therapy must address the underlying condition, biofeedback, counseling, hypnotherapy, electromagnetic stimulation, acupuncture and surgery may also help (Wynn & Sperling '04: 106).

Nasal congestion, obstruction and drainage are three of the most common symptoms that bring patients to physicians. Although usually benign these symptoms may represent a life-threatening problem. Acute viral or bacterial rhinosinusitus is a common cause of nasal congestion. Mucolytic agents and saline irrigation are helpful to some patients when thick secretions are a problem. Antibotics are not used unless the drainage becomes purulent or the patient has a fever or headache. Bacterial infections of the nose and paransal sinuses often are secondary to viral rhinitis, and treatment with an antibiotic such as amoxicillin (250 mg by mouth thre times a day) or erythromycin (250 mg by mouth four times a day) is recommended. Smell may be reduced. Drainage of purulent or irritating material into the pharynx and larynx frequently causes cough, bad breath, mild throat pain and the sense of a mass in the throat. If the material enters the larynx, hoarseness due to laryngeal inflammation results causing the patient to cough. Initial management of chronic sinusitis should include antibiotics and decongestants. If the patient does not respond to medical therapy, surgical intervention may be indicated to aerate the sinuse and

restor the ability of the sinuses to drain and to eradicate any infection. **Rhinitis medicamentosa** is a chronic condition produced by overuse of nasal decongestant sprays, similar to that seen in cocaine abuse. A patient with nasal congestion initially receives relief with use of α-adrenergic sprays. However, prolonged excessive use over many weeks produces a rebound phenomenon in which the sprays cause inflammation with erythema and oabstructive edema rather than improvmen tint he airway. Saline nose drops should be substituted and possibly anti-inflammatory steroid sprays (Mehta & Lucente '04: 141, 142, 147).

Rapid nasal-breathing exercises, prepared with tissues for nose blowing, and running can be effective at clearing out congested sinuses. Sinusitis is characterized by headache, nasal obstruction rhinorrhea, fever and malaise. In children headache is an uncommon presentation. In adults headache can be severe driving patients to curl up in a dark cook spot until after sunset. The sinuses most frequently involved are the maxillary sinuses in children and adults. Frontal sinus barotrauma most commonly presents with pain following an airplane flight, diving, or use of a high-speed, high rise elevator. Maxillary sinusitis occurs over the roots of the upper molars and is caused by dental impaction, infection or neuralgia. Ethmoid sinusitis occurs in the periorbital (anterior) vertex, behind the eye, and pain increases on walking down stairs, jumping or bending forward, visual loss may be a complication. Frontal sinusitis occurs in the forehead or above the eyes from the obstruction of the nasofrontal duct osteomyelitis, orbital cellulitis or abscess, meningitis or brain abscess may arise as a complication. Sphenoid sinusitis occurs in the frontal, temporal or occipital area, retroorbital or vertex pain from an inflammatory or expansive process causing diffuse headache with posterior rhinorrhea that can lead to ophthamoplegia, trigeminal neuralgia, and intracranial complications (Bhaya & Goldsmith '04; 153, 154, Table 16-1). **Nasal foreign** bodies are customarily classified as animate or inanimate. Animate foreign bodies include larval infection, *Aspergillus* infection, rhinosporidiosis, and roundworm infection. Inanimate foreign bodies of the nose can be just about anything that fits. Unilateral rhinorrhea is a nasal foreign body until proved otherwise. Management of nasal foreign bodies is prompt removal (Cultrara & Goldsmith '04: 169). Diagnosis of allergic rhinitis is done with a history and physical exam, RAST and skin testing. Treatment is with steroid nasal sprays, antihistamines, Atrovent, systemic steroids, and immunotherapy (Habib & Goldsmith '04: 178).

In the past, the sinuses were approached externally through incisions on the face to clear chronic infection. The idea was to remove the chronically infected material from within the sinus and strip the tissue lining the sinus to clear infection. Although these techniques are still sometimes used, in recent years surgery is usually carried out through the nose. Additionally, external procedures are useful for removing large polyps, tumors or for patients who have already undergone intranasal (through the nose) surgery). A frequently infected sinus is the maxillary sinus. In the past, this sinus was usually approached through an incision under the upper lip through the gum, a procedure called a Caldwell-Luc operation. After a cut is made in the gum, the cheek sinus is entered by making a hole in its front wall and directly stripping out the disease. Patients can usually leave the hospital the day of surgery, with mild pain and swelling. The Caldwell-Luc is still employed, especially in cases with large maxillary sinus disease, which is difficult to remove through the nose. Since the mid 1980s, the surgical approach to sinus disease in the United States has seen great change. Today, roughly two hundred thousand sinus surgeries are performed yearly in the United States, and most of these are carried out through the nose by a procedure called functional endoscopic sinus surgery. (This is also known as endoscopic sinus surgery, FESS or just ESS). The aid of endoscopic sinus surgery is to relieve obstruction in the nose and at the ostiomeatal complex to allow for normal sinus drainage. This

is done with minimal removal of tissue. Using endoscopes through the nose, thickened and diseased tissue that blocks the sinus ostia is removed. Most of the tissues from within the sinus, however maintained. This allows for a more rapid restoration of normal mucociliary flow and healthy sinuses after surgery (Rosin '98: 162, 165).

Approximately one of every ten persons in the United States has experienced at least one serious nosebleed. **Epistaxis** is more common in the winter because of cold temperatures, low humidity, and dry heat. Local trauma, usually self-induced by means of nose picking, is the most frequent cause of epistaxis. The two carotid systems (internal and external) communicate extensively at Kiesselbach's plexus in Little's area located on the anterior cartilaginous septum. Over 90% of nosebleeds result rom spontaneous or traumatic rupture in this plexus. Structural deformities, neoplasms and systemic disorders that may cause epistaxis include hypertension, blood dyscrasias, Osler-Weber-Renud disease (hereditary hemorrhagic telangiectasia), cardiovascular disease, vitamin deficiencies, granulomatous disease and coagulopathies caused by renal failure, chronic hepatic disease, drugs or toxic agents. Refractory epistaxis warrants evaluation by an otolaryngologist. A routine screen that consists of prothrombin and partial thromboplastin times, platelet coutn and bleeding time should be performed in cases of severe epistaxis. Hematocrit and hemoglobin level shold be obtained to help decide whether transfusion is necessary. Once epistaxis is controlled, the use of topical saline spray, avoidance of nose picking, and daily installation of petroleum jelly in the nares can help prevent future nosebleeds (Cultrara & Turk '04: 164, 168).

Drugs of choice for the ear, nose and throat

Clinical diagnosis	Initial choice	Alternatives
Otology		
Acute otitis media and bullous myringitis	Amoxicillin or amoxicillin-clavulanate	Cefuroxime, ceftriaxone IM 3days
Chornic otitis media with effusion	Same as above (but therapy is optional)	Same as above
Acute mastoiditis (from acute otitis media)	Vancomycine, ceftriaxone or cefotaxime	Clindamycin IV plus rifampin IV, gatifloxacin IV, or ampicillin/sulbactam
Chronic suppurative otitis media (perforation or choesteatoma)	Ciprofloxain or ofloxacin otic drops	Neomycin plus polymycin otic drops or gentamicin drops
Acute diffuse otitis externa	Neomyxin plus polymyxin otic drops or alcohol/acid mixtures drops	Ofloxacin, ciprofloxacin, or tobramycin drops
Malignant otitis externa	Imipenem or meropenem	Ceftaxidime, cefepime, or ciprofloxacin ticarcillin plus: amikacin, tobramycin or gentamicin
Furuncle of ear canal	Cefalexin, (first generation cephalosporins)	Clindamycin, dicloxacillin
Otomycosis	Boric or acetic acid and alcohol drops	m-Cresyl-acetate otic drops
Neurosyphilis	Penicillin	-
Rhinology		

Sinusitis, acute	Amoxicillin/clavulanate or ampicillin/sulbactam or erythromycin plus TMP/SMX	Amoxicillin/clavulanate, cefuroxime, cefpodoxime, levofloxacin, gatifloxacin, moxifloxacin
Sinusitis, chronic or in HIV (AIDS)	Amoxicillin/clavulanate	Clindamycin, cephalosporin plus metronidazole, gatifloxacin
Nosocomial sinusitis	Ticarcillin/clavulanate IV	Ceftazidime IV, vancomycin, or amikacin IV/IM plus clindamycin
Orbital celluliis	Ceftriaxone, cefotaxime, +/- vacomycin	-
Rhinitis/nasopharyngitis (carrier) due to *S. aureus*	Rifampin plus first generation cephalosporin or clindamycin plus mupirocin ointment	-
Rhinitis/nasopharyngitis (carrier) due to *H. influenzae*, *N. meningitidis*	Rifampin	-
Head and neck infections		
Tonsilloadenoiditis	First generation cephalosporin +/- metronidazole	Cefuroxime, clindamycin, amoxicillin/clavulanate, trovafloxacin
Pharyngitis (streptococcal)	Erythromycin, clarithromycin	Clindamycin, first or second generation cephalosporin, amoxicillin/clavulanate, Penicillin G or V
Pharyngitis (gonococcal or chlamydial)	Ceftriaxone, cefixime, or ciprofloxacin plus azithromycin, doxycycline, or erythromycin	-
Stomatitis, aphthous	Mouthwash combination: 60 mL tetracycline, 160 mL, diphenhydramine, 20 mL, dexamethasone, 50 ml nystatin	Topical antihistamine or antacid with or without hydrogen peroxide
Laryngitis, viral	Symptomatic care	-
Laryngitis, bacterial	Erythromycin plus sulfonamide	Azithromycin, clarithromycin or cefuroxime
Epiglottitis	Cefuroxime	Ceftriaxone, or ampicillin/sulbactam or trovafloxacin
Subglottic bacterial croup	Cefuroxime	Ceftriaxine, cefotaxime, or ampicillin/sulbactam
Tracheobronchitis, viral	Symptomatic care, or amantadine (for type A influenza birus in elderly)	-
Treacheobronchitis, bacterial	Axithromycin, clarithromycin, or	Levofloxacin, gatifloxacin

	erythromycin with or without sulfonamide	
Parotitis, suppurative	Amoxicillin/clavulanate or ampicillin/sulbactam	Clindamycin, first or second generation cephalosporins, cefoxitin, or vancomycin plus metronidazole
Sialoadenitis		
Abscess, peritonsillar	Amoxicillin/clavulanate	Antistaphylococcal penicillin, clindamycin, ampicillin/sulbactam
Abscess, deep neck with or without necrotizing fascititis	Clindamycin	Amoxycillin/sulbactam or amoxicillin/clavulanate, cefuroxime plus metronidazole, gatifloxacin
Cellulitis, cervical-facial	Amoxicillin/clavulanate, ampicillin/sulbactam, or ceftrixaone	Vancomycin plus aztreonam, chloramphenicol
Meningitis, antracranial abscress, or contamination from acute otitis sinusitis	Ceftriaxone or cefotaxime	Vancomycin plus aztreonam, chloramphenicol
Meningitis, intracranial abscess, or contamination form chronic sinusitis	Ceftriaxone plus metronidazole	Nafcillin plus metronidazole or chloramphenicol, vancomycin plus aztreonam, ampicillin/sulbactam
Surgical prophylaxis (begin 1 hr before incision)	Cefazolin, ampicillin/sulbactam	Antistaphylococcal penicillin, clindamycin

Source: Boruk & Rosenfeld '04: 431-433; Table 49-1

Headache refers to a sensation of pain or discomfort in the head. It is not a disease in itself but rather a symptom of underlying dysfunction or disease. Pain of intracranial origin is produced when there is tratino on ord dilation of blood vessels in the brain and its surrounding dural structures andn direct pressure on cranial or cervical nerves containing afferent pain fibers. Extracranial facial pain may originate from noxious stimuli to specific extracranial structures such as the eyes, sinuses, nose or teeth; dilatation or inflammation of pain-sensitive blood vessels; or sustained contraction of skeletal muscles or neural glia of cranial nerves. Paransal sinus pain can be caused by sinusitis, usually bacterial, following a self-limited viral infection, and usually affects the maxillary sinuses. Frontal sinus barotrauma most commonly presents with pain following an airplane flight. Mucocele of a benign, encapsulated, mucus-filled mass that produces pain by impinging on or displacing contiguous structures. Paranasal sinus neoplasms do not consistently cause pain. Neoplasms of the frontral, ethmoidal and sphenoidla sinuses are uncommon and the symptoms tend to resemble those of chronic infection. Psychiatric disorders can be a cause or an effect of headache. Depression, anxiety disorders, somatodorm disorders, dependency on pain medication and withdrawal symptoms on discontinuation and manic states caused by headache mediations are all seen. Postraumatic headache is a common sequel to head injury. Psychologic factors (psychologic stressors, personality traits, conditioning and psychodynamic issues) also play an important role in migraine and muscle contraction headaches. Substance abuse is commonly reported among patients with chronic headaches. Aspirin, acetaminophen, and caffeine are most frequently abused. Miscellaneous headaches may be provoked by such external triggers sucs as coughing,

physical exertion, or sexual activity. Eating cold foods, food additives such as monosodium glutamate, or environmental stimuli provokes the second variety of headaches (Bhaya & Goldsmith '04: 153, 162, 163).

Neuralgia of the head and neck is characterized by remissions and exacerbations and the general absence of any objective neurologic deficit. A useful diagnostic test involves topical application or local infiltration of an anesthetic in the affected area. **Trigeminal neuralgia** (tic douloureux) is a sharp, shooting, or needlelike pain in a persistent or recurrent form. Most patients are successfully treated with carbamazepine alone or in combination with baclofen. **Sphenopalatine neuralgia** (Sluder's syndrome) is unilateral facial pain associated with vasomotor abnormalities such as lacrimation , rhinorrhea, and salivation. Relief of symptoms confirms the diagnosis. **Glossopharyngeal neuralgia** presents with unilateral throat pain with radiation to the ear, posterior tongue, or soft palate. The pain is usually severe and paroxysmal. Among patients <30 years, an organic cause such as viral infection, arachnoiditis or styloid elongation (Eagle syndrome) is a distinct possibility. Among older patients oropharyngeal tumor must be considered. **Postherpetic neuralgia** is a painful condition that occurs after attacks of herpes zoster. Symptoms usualy last 2 to 3 weeks but can persist longer, especially among older patients. **Trotter's syndrome**, also referred to as the sinus pain of Morrgangni's syndrome is usually caused by neoplastic invations of the lateral nasopharyngeal wall. Symptoms include unilateral deafness, pain of the mandibular division of the trigeminal nerve, ipsilateral palate hypomotility and subsequent trisumus. **Pterygopalatine fossa syndrome** is caused by metastasis to the peterygopalatine fossa and involves the maxillary division of the fifth cranial nerve**. Ramsay Hunt syndrome** (geniculate ganglion syndrome) is related to infection of the facial nerve ganglion by the varicella zoster virus. Examination may show vesicular lesions of the ear and oral mucosa; partial or complete facial palsy; external ear pain; and vesiculobullous lesions of the tonsils, oropharynx, and posterolateral third of the tongue with associated pain, loss of taste, decreased salivation and palatal paralysis. **Eagle syndrome** is a condition of intense, persistent parapharyngeal pain caused by elongation and calcification of the styloid process and calcification of the stylohyoid ligament. The patient reports, dysphagia, odynophagia, headache, unilateral facial pain and progressive trisumus. **Contact headaches** occur when the contact between the septum and the inferior turbinate causes pain at the point of contact and radiating pain into the maxillar and anterior zygoma (Bhaya & Goldsmith '04: 155-157).

Vascular headaches are classified as bicranial or hemicranial depending on the primary location of the pain. **Bicranial headaches** consist of tension headaches, toxic vascular headaches and hypertensive headaches. Tension headaches are characterized by bilateral, non-throbbing, aching pain over the frontal and temporal regions that often worsen as the day goes by. They are commonly associated with physical or psychological stress and usually respond to non-steroidal anti-inflammatory drugs. Toxic vascular headaches are caused by exposure to an irritating chemical substance or alteration of metabolic activity. Headache caused by hypertension is rare unless the systolic pressure exceeds 150 mmHg and the diastolic pressure exceeds 95 mm Hg. The severity of the headache usually does not correlate with the severity of the hypertension. **Hemicranial headaches** are most often characterized as migraine. There is vasoconstriction and dilatation of branches of the external carotid artery with release of pain-producing polypeptides, kallikreins and prostaglandins. The cardinal feature of common migraine is recurring, throbbing headache, most commonly in the frontotemporal area. Classic migraine is a variant that occurs among les than 10% of all patients with migraine. The most characteristic prodromal feature is a disturbance of vision. Scotomata may develop into complete hemianopsia that lasts up to 30

minutes and then fades away. Sleeping in a dark room may help to relieve the symptoms. **Cluster headaches** (histamine headaches) typically occur among young men and can produce unilateral vascular cephalgia. They occur in groups or clusters with a seasonal preponderance in spring and fall. The attacks occur at night (migraines occur more frequently in the daytime) and are characterized by a boring or stabbing pain localized around or behind the eye or temple on one side. The pain develops abruptly buildes rapidly to a peak, lasts about 20 minutes and resolves with no residual discomfort. Pain often is so severe that it wakes the patient from sleep. The groups of attacks last weeks or months and are followed by long periods of remission. **Temporal arteritis** (giant cell arteritis) is a vaculitis of unknown causation. The vessels usually affected are branches of the carotid artery system, most commonly the ophthalmic, retinal and temporal arteries. It is a disease of the elderly and occurs more commonly among women. The symptoms include constant unilateral facial pain. It is frequently retro-ocular in nature, but may be localized to the scalp, jaws, tongue or neck. On physical examination, the templral artery usually is nodular, erythematous and tender to palpation. Patients with giant cell arteritis also may have symptoms of plymyalgia rheumatica. Temporal arteritis should be suspected when the erythrocyte sedimentation rate is highly elevated (>40 mm/h). The diagnosis is confirmed by means of temporal artery biopsy. The treatment of choice is administration of corticosteroids. These agents are effective in relieving pain and preventing blindness, which is the most feared sequelae, occurring in about one-third of patients (Bhaya & Goldsmith '04: 157, 158).

Temporomandibular disorders include abnormalties of structures within the tempromandibular joints (TMJs) and the surrounding capsule. Temporomandibular joint pain results from developmental aberrations, inflammatory infectious, and neoplastic diseases, and acute and chronic traumatic injury. Patients may have preauricular swelling, tenderness, crepitus, or clicking. Disorders of the TMJ can cause dental malocclusion, which causes pain in the area of one of both TMJs. **Myofacial pain dysfunction syndrome** is primarily an intrinsic abnormality of the muscles of mastication that produces facial pain and headache. Symptoms include tenderness of the muscle; muscle edema; palpable speasm of the muscle; and disorder of function, such as trisumus, deviation, malocclusion, or clicking of the meniscus. A diagnostic feature of myofacial pain dysfunction syndrome is pain and tendernesss on palpation of certain muscle groups. On palpation there is tenderness with the mouth wide open and when it is closed with the teeth in occlusion. Clicking sounds indicate displacement of the disk and crackling sounds indicate destruction of the disk. TMJ muscle spasm is corrected with a soft diet, anti-inflammatory agents, moist hot compresses, analgesics, tranquilizers and even behavior modification – terminate antipsychotic medicine and treat with one dose of the antiparkinsons antiviral agent Amantadine (Symmetrel). Odontogenic pain or pain originating in the teeth usually is caused by dental caries or chronic perdiodontal disease. Pain associated with dental caries is usualy sharp, throbbing, and directly related to the tooth in question. Periodontal disease is painless, but facial pain and headache may occur when there is pain fiber stimulaton of the teeth or if there is periodontal abscess (Bhaya & Goldsmith '04: 159, 160).

The organism responsible for **tetanus** is found in soil and the intestinal tracts of farm animals. Any manure-treated soil may be infectious. The symptoms of tetanus being with stiffness of muscles; the muscles of the jaw and neck are the first to be involved, thus the disease is often called lock-jaw. In the 24 to 48 hours after onset of the disease, muscle rigidity may be fully developed and involve the trunk and extremities. The neck and back become stiff and arched, and the abdomen board-like. Painful spasms can be produced by the slightest stimulant (noise, touch, light) and it is spasms of the respiratory muscles that cause asphyxia and death. The incubation period for tetanus varies form one day to three weeks, although the usual range is one

to two weeks. There is no sing of tetanus int eh wound itself, and usually no symptoms until the muscle stiffness begins. Fever is generally low-grade or absent and the sense remain clear. Treatment for tetanus is drastic. Muscle relaxants, sedatives, antibiotics, immune globulin, and antitoxins are administered. The patient is put in a low-stimulus environment and often fed through a stomach tube and an artificial airway may be required during treatment. Since 1976 there have been less than 100 cases of tetanus per year in the United States. The majority of these cases are in people over age 50. On average 5 percent or less of tetanus cases occur in individuals less than 20 years of age. Yong people do not tend to get tetanus and fatalities are rare yet 87 percent of children at two years old have received a primary series of tetanus vaccine injections and one-half to two-thirds of persons 60 or older lack protective levels of circulating antitoxin antibody against tetanus.

The primary series of tetanus toxoid vaccination consists of four injections. The first three doses are given at two month intervals and the fourth dose about one year after the third dose. Boosters are recommended at five years and every ten years thereafter. Protection from tetanus following adequate vaccination lasts for at least twelve years. In people who have had at least two doses of tetanus toxoid at any time in their lives, response to a booster injection of toxoid is rapid and adequate to prevent tetanus if given within 72 hours after injury. For individuals who have had less than two previous injections of tetanus toxoid an injection of Tetanus Immune Globulin Human (TIG) is administered for serious wounds. This vaccine introduces antibodies directly into the body to fight tetanus bacteria. The antibody levels achieved with TIG are sufficient to protect against tetanus if the injection is given within 72 hours after the injury. For individuals who have previously received to or more tetanus toxoid injections at any time in their lives, a single booster dose of toxoid will produce enough antibody response to prevent tetanus if the booster is given within 72 hours after an injury. There is no question the vaccine is highly effective at preventing tetanus. Tetanus toxoid is generally considered safe, yet it has been associated with an overall reaction incidence of 3 to 13 percent. Most adverse reactions include swelling and abscesses at the injection site. Two death occurred, one in 1933 and another in 1973 due to anaphylactic reactions. Many cases of central nervous system disease following tetanus toxoid injection have been reported in the literature including demyelinating diseases, Guillain-Barre syndrome (a demyelinating inflammatory disease of the peripheral nervous system with rapid onset of motor weakness and loss of sensation), neuropathies and encephalopathies.

Anyone with a serious wound should receive tetanus immune globulin (TIG) if they have had less than two previous injections of tetanus toxoid. Good wound care is probably the single most important factor in the prevention of tetanus in fresh wounds. This implies thorough cleansing of the wound and removal of all foreign bodies and devitalized (dead) tissue. This is important since the tetanus bacillus is an anaerobic organism and can grow only in necrotic tissue which has no blood supply. For adequate prophylaxis of tetanus, wounds must be divided arbitrarily into those considered tetanus prone and non-prone…Any wound containing foreign material or devitalized tissue must be considered tetanus prone, as well as crushing injuries, deep second and third degree burns, and any infected wound….The severity of a wound is not a reliable guide to the likelihood of tetanus developing since the disease may arise form minor or even unnoticed injuries. Many tetanus prone wounds, howeve,r can be converted to non-prone wounds by proper cleansing and debridement (Neustaedter '96: 97, 98, 99-106).

Ocular abnormalities can cause headache or facial pain. **Eyestrain** presents as mild, dull, aching pain around or behind the eyes and a sensation that the eyes are tired, hot, uncomfortable, sore or strained. Uncorrected or refractive errors (farsightedness), astigmatism, presbyopia, or

heterophoria are common. Eyestrain is never associated with nausea, vomiting or a prodromal aura, and is relieved by means of resting the eyes. Iritis is characterized by steady, boring pain located in or above the eye. The pain is aggravated by light. The associated erythema is particularly noticeable in the circumcorneal area. The definitive diagnosis is made by means of slit-lamp examination. **Glaucoma** (intermittent narrow-angle glaucoma) should always be considered in the care of patients aged >40 years, especially when there is alteration of vision without restriction of extra-occular muscles. **Episcleritis**, especially the nodular variety should be considered when a patient reports nonspecific pain localized to the origin and its adnexa without marked radiation. **Extraocular muscle imbalance** should be suspected especially in the young, when a patient has onset of dull headache around the eyes or back of head. Refractive errors, particularly those associated with astigmatism, often cause diffuse, poorly defined headache. **Optic neuritis** is characterized by decreased or blurred vision in association with a sharp or boring pain behind the eye. The pain is markedly increased with eye movement. Physical examination often shows a central scotoma, elevation of the optic disc, and an afferent pupil defect (the pupil of the involved eye constricts less to light shining in that eye than to light shining in the opposite eye because of impairment of light conduction through the affected optic nerve) (Bhaya & Goldsmith '04: 160, 161).

Abnormalities of olfaction and taste are chemosensory disorders that affect more than 2 million adults in the United States. For olfactory stimulation to occur, an odorant must enter the nasal cavity and reach the receptor surface of the olfactory epithelium, in the upper region of the nasal cavity along the superior turbinate, cribriform plate and superiormost portion of the nasal septum. This epithelium contains four main cell types. The ciliated olfactory receptor is a bipolar neuron with a clushaped, peripheral knob that bears sensory cilia. Actual transduction occurs through a membrane-boutnd receptor protein. The microvillar cell is another type of oldactory receptor. Sustentacular cells, or supporting cells, surround the receptor cells and provide nutritive and secretory functions. The basal cells are adjacent to the basement membrane and function as stem cells for the regeneration of senescent receptor and supporting cells. Once stimulation of a receptor cells has occurred the olfactory information is transmitted through the olfactory nerve (cranial nerve I) t the olfactory bulb, where it is processed and modified. Information then travels through the olfactory tract within the brain, to the amygdala and prepyriform cortex, which are believed to be the sites of consdious appreciation of smell. If the orodant is pungent like vinegar or ammonia, it is detected by the trigeminal nerve endings throughout the entire nasal cavity (Song & Goldsmith '04: 190).

Olfactory dysfunction can be classified into four categories. Anosmia is complete loss of the sense of smell. **Dysosmia** is distortion or perversion of the sense of smell; an unpleasant olfactory sensation occurs in the absence of an odor or in the presence of a normally pleasant odor. **Hyposmia** is a decreased sense of smell, and hyperosmia is an increased sensitivity to all odors. Olfactory disorders can be conductive or sensorineural in nature. **Conductive olfactory losses** are caused by any process that causes sufficient nasal obstruction to prevent odorant molecules from reaching the olfactory epithelium. **Sensorineural olfactory losses** are caused by processes that directly affect and impair either the olfactory neuroepithelium or the central olfactory pathways. Most common in this category is postviral dysfunction. Head trauma is he second most common cause of sensorineural dysfunction with a 5% to 7% incidence of anosmia after head injury. Commonly prescribed medication that can affect olfaction include antineoplastic agents (methotrexate), opiates, cimetidine, levodopa, corticosteroids, methimazole, and antibiotics (macrolides, tetracyclines, and aminoglycosides). Management of olfactory disorders depends entirely on the accurate diagnosis of the cause. Therapy for gustatory

disturbances is somewhat limited. The physical examination usually reveals a manageable cause, such as carcinoma or infection, if present. Repletion of deficient vitamins and minerals often is effective, as is elimination of an offending drug. Patients should be advised to chew well and alternate foods during meals to avoid receptor fatigue. Flavor enhancers may be of value (Song & Goldsmith '04: 190, 191, 195).

Physical examination of the tongue and oral cavity requires bright illumination to assess areas of discoloration, edema and irregularity indicative of an infectious, hematologic or neoplastic abnormality. Complete examination or the oral cavity must include palpation of the tongue, floor of the mouth, buccal mucosa and retromolar trigone for masses, tenderness and induration. **Halitosis**, or bad breath, is a symptom. Systemic causes of halitosis result from pulmonary excretion of malodorous substances dissolved in the bloodstream. Contrary to popular belief, the characteristic breath odors of garlic, onions and alcohol originate in the blood, which picks up the scents form the small intestine and transfers them to alveolia and to the pores of the skin. Bad brath may arise from systemic diseases such as hepatic failure (sulfur odor), uremia (ammonia odor) and the diabetic ketoacidosis (acetone breath). Temporal lobe seizures and delusions may cause patients to report halitosis that is not detectable to others. **Candidiasis** is the most common fungal cause of mucositis and pharyngitis. A person may be predisposed due to physical irritation from dentures, use of steroid inhalers, preexisting infection and poor oral hygiene. Systemic factors include nutritional deficits, diabetes, systemic steroid therapy, malignant tumor, chemotherapy, acquired immunodeficiency syndrome, prolonged antibiotic treatment and pregnancy. **Pseudomembranous candidiasis** (thrush) is the most common form. It appears as soft, white plaques that can be removed, leaving an erythematous epithelial surface. Candidiasis is rarely painful, but severe cases with mucosal erosion can produce a burning sensation. Spread to the larynx and pharynx can cause dysphagia and odynophagia. Treatment consists of topical or systemic antifungal medications. Nystatin is the most commonly used topical agent while clotrimazole and fluconazole are potent oral agents. Ampotericin B is the agent used for the most severe disseminated or invasive infections. Less frequently encountered microbiologic conditions of the oral cavity include histoplasmosis, blastomycosis, tuberculosis, syphilis and actinomycosis. **Ulceronecrotic gingivitis** (Vincent's angina) is a painful and foul-smelling injection of the gingiva generally caused by *Borrelia vincentii* and fusiform bacilli. It usually occurs in immunocompromised hosts or those with poor oral hygiene. Treatment consists of dilute peroxide mouthwashes, debridement of necrotic tissue and oral penicillin. If therapy doesn't work biopsy may be needed to rule out carcinoma (Schwartz, Lim & Har-el '04: 198-203).

Herpes stomatitis consists of painful lesions caused by the linear double stranded-DNA herpes virus (HSV-1 or HSV-2). Crops of small vsicles initially occur on any mucosal surface and rupture within 24 hours, leaving an erythematous border with a gray covering membrane. Infecitn is accompanied by fever, arthralgia, headache, cervical lymphadenopathy and pharyngitis. Primary HSV infection invades the trigeminal nerve ganglion where it usually remains dormant. Recurrence rates range from 15% to 45% and may be triggered by ultraviolet light, stress, fever, cold, fatigue, immunosuppression or trauma. Diagnosis can be made with a Tzanch smear by obtaining cells from the base of the lesion, followed by microscopic examination. Oral lesions are usually managed supportively with analgesia and hydration. Antiviral therapy such as acyclovir is more effective is administered early in the course of infection. Topical acyclovir cream is helpful in the management of recurrent herpes labialis. **Oral papillomas** are the most common benign lesion of the oral cavity and are found in patients 20 to 50 years of age. Human papilloma virus (HPV) may be the etiologic agent in some cases.

HPV has specific tropism for squamous epithelial cells; types 6, 11, 16, and 18 are associated with benign and lamlgnant mucosal papillary neoplasms in the upper aerodigestive tract. Oral papillomas appear as asymptomatic pink or white pedunculated lesions. Other lesions caused by HPV include oral warts. *Verrucae vulgaris*, which are identical to skin warts, may appear as lesions in the oral cavity. *Condyloma acuminatum*, a wart seen primarily in the anogenital region, may occur in the oral cavity. Local excision is usualy required for oral papillomas. **Angular cheilitis** is the presence of excoriated creases in the facial skin at the commissures of the lips. It occurs most frequently among elderly or severely ill immunocompromised patients. Creases are continuously moistened with saliva or secretions and colonized by opportunistic microorganisms such as *Candida albicans*. Aphthous Stomatitis is a recurrent infection of the buccal and gingival mucosa, tongue and palate. The cause is unknown, and it affects approximately 20% of the population. The typical lesion is a painful focal ulceration 2 to 10 mm in diameter surrounded by mucosal erythema. The lesions disappear within a week or two. Topical analgesics are helpful (Schwartz, Lim & Har-el '04: 203, 204).

Trismus (limited or inability to open the jaws) may arise form local or generalized conditions. It can constitute a medical emergency when it is associated with airway obstruction. Local disorders include impacted third molar, temporomandibular arthritis, tic douloureux, progressive systemic sclerosis, dermatomyositis, upper or lower jaw fracture, peritonsillar or retropharyngeal abscess or cellulitis, and tumors of the facial bones, sinuses or parapharyngeal space. Disorders with widespread muscle spasm such as trichinosis, rabies, tetany , tetanus, strychnine poisoning, typhoid, cholera and sepsis may cause trismus. Maintenance of the airway, with tracheostomy if necessary, is essential. **Oral tori** are single or multiple, firm, bony growths on the palate (torus palatinus) or mandible (torus mandibularis). They occur among approximately 20% of the population. **Odontogenic cysts** include dentigerous cysts (arising from the enamel epithelium or remnants of dental lamina), eruption cyst (accumulation of fluid or blood around the crown of an erupting tooth), gingival cyst (epithelial inclusion cyst resulting form entrapment of epithelium during palatal fusion) and radicular cyst (asymptomatic inflammatory cyst in the periapical region of a nonvital tooth). **Odontogenic keratocyst** is a cystic neoplasm capable of considerable bony destruction as wel as recurrence after surgical treatment. The presence of multiple keratocysts may herald basal cell nevus syndrome preceding the development of multiple basal cell carcinomas of the face, neck, back and chest. **Nonodontogenic cysts** include globulomaxillary cyst, nasoalveolar cyst and various dermoid and epidermal cysts. Management of cystic lesions involves surgical excision. A **ranula** is a pseudocyst of the floor of the mouth caused by mucous extravasation from a blocked sublingual gland. This lesion appears as a painless mass in the floor of the mouth. Treatment involves excision in continuity with the sublingual gland of origin (Schwartz, Lim & Har-el '04: 207, 208). **Leukoplakia and erythroplasia** are mucosal lesions that may be benign, premalignant, or malignant. Leukoplakia is a white patch in the oral cavity that may represent hyperkeratosis, parakeratosis, acanthosis, dysplasia, carcinoma in situ, or invasive carcinoma. Erythroplasia is typically a red velvety pathc. The lesion is usually depressed or at the same level as the surrounding mucosa. Although leukoplakia is more common, erythroplasia carries a greater risk for malignancy (80%). **Cancer of the oral cavity** is the most common site of malignant growth in the head and neck. Cigarette smoking, tobacco chewing, and alcohol infection are the main environmental risk factors. In India, betel nut chewing and reverse smoking also are leading risk factors. Most malignant tumor in this region are squamous cell carcinomas. This tumor presents either as an oxphytic lesion or as a nonhealing ulcer that may exhibit considerable infiltrative submucosal extension, and is diagnosed by tissue biopsy. Other less common tumors may affect the tongue and oral cavity. Many are of salivary gland orign, such as adenoid cystic carcinoma, adenocarcinoma,

and mucopeidermoid carcinoma. Various sarcomas may occur in this region. Lymphoma, malignant melanoma, and Kaposi's sarcoma occur occasionally (Schwartz, Lim & Har-el '04: 209).

Acute pharyngitis is most often caused by viruses. These include respiratory viruses (adenovirus, influenza virus, respiratory syncytial virus, parainfluenza virus and rhinovirus) as well as coxsackievirus, herpes simplex virus and Epstein-Barr virus. Viral pharyngitis often involves both nasopharynx and oropharynx. Bacterial pharyngitis is most often cause by group A β-hemolytic streptococci - *S. pyogenes*. Other causative agents include groups C and G streptococci, *Neisseria gonorrhoeae*, *Corynebacterium diphtheria*, *Arcanbacterium haemolyticum*, *Yersinia enterocolitica*, and *Yersinia pestis*. The onset of a sore throat is usually sudden. The temperature may rise, particularly in children, to more than 102°F (38.9°C). The pharyngeal mucosa often is erythematous and swollen. Edema of the uvula and erythema and petechiae of the soft palate may develop. Tender, high cervical lymph nodes often are present. Bacterial pharyngitis is often accompanied by bacterial tonsillitis. Group A β-hemolytic streptococcal pharyngitis is the only commonly occurring form of pharyngitis in which antimicrobial therapy is of proven benefit. Infectious mononucleosis is a viral illness that often mimics bacterial tonsillitis. A complete blood cell county usually shows atypical lymphocytosis, and serologic tests for heterophile antibodies are usually positive. Acute lingual tonsillitis often presents with a "hot-potato" voice and throat pain just above the hyoid bone. Deep neck abscesses are most commonly caused by dental infections resulting from *Streptococcus virdans*, *Staphylococcus epidermis*, *Staphylococcus aureus*, and Bacteroides. Peritonsillar abscess (PTA) is usually caused by aerobic organisms such as *Streptococcus pyogenes*, *Staphylococcus aureus*, *Haemophilus influenza* and the anaerobic organisms, such as *Fusobacterium*. Treatment includes antibiotic therapy and incision or drainage or needle aspiration. The initial parenteral injection of penicillin is followed by oral administered antibiotics for a minimum of 10 days (Schwarts, Lim & Har-el '04: 215 216).

Ludwig's angina is a rapidly spreading cellutis of the submandibular, sublingual and submental spaces commonly presenting as floor of mouth swelling, severe trismus and drooling. The cellulitis and edema can progress rapidly to form an abscess and thus may rapidly obstruct the upper airway. Usually there is a history of tooth extraction or dental infection. Successful management of this potentially life-threatening infection requires incision and wide drainage eof the abscess and intravenous antibiotics to manage the accompanying cellulitis. Tracheotomy should be considered to secure the airway. Although **epiglottitis** is uncommon since the development of the *H. influenza* vaccine, epiglottitis is a cause of acute throat pain among both children and adults most often cause by *Haemophilus influenza*. Epiglottitis is a rapidly progressive infection beginniign as a sore throat, followed by inability to tolerate secretions, hot potato voice, dyspnea and airway obstruction. Management includes securing the airway (intubation or tracheotomy), intravenous antibiotics and possibly intravenous steroids. **Laryngitis** with arytenoid edema occasionally causes acute throat pain but usually simply produces hoarseness and mild dysphagia without severe pain. Chronic throat pain may be caused by inflammatory reactions, neoplastic disease, neuralgia (glossopharyngeal or superior laryngeal nerves), thyroid disorders and psychiatric conditions, or may be idiopathic. Persistent pharyngitis refractory to the usual antibiotic therapy may be secondary to resistant organisms or noncompliance with medications. Fungal infections rarely cause chronic pharyngitis, but occasionally candidiasis, histoplasmosis, and blastomycosis continue the infection in immunocompromised hosts. **Glossopharyngeal neuralgia** is characterized by severe lancing pain that radiates from the posterolateral phyarnx to the ipsilateral ear, neck and head and lasts

several seconds. **Chronic throat pain** along the anatomic course of the stylohyoid ligament has been termed styalgia or Eagle's syndrome. The patient may have a chronic sore throat, dysphagia or foreign body sensations in the throat. Management with anti-inflammatory medication or analgeiscs may be sufficient but surgical excision of the styloid occasionally is necessary to control chronic pain from this source. Acute and subacute thyroiditis, large thyroid goiters and a thyroid gland involved by neoplastic disease may impinge on the aerodigestive tract, causing chronic throat pain, dysphagia and dyspnea. These conditions generally produce a sensation of a lump in the region of the thyroid gland on swallowing. **Globus pharyngeus** is a foeign body sensation in the throat. (Schwartz, Lim & Har-el '04: 217, 218, 221).

The major **salivary glands** are the paried parotid, submandibular, and sublingual glands. There are approximately 1,000 minor salivary glands throughout the upper aerodigestive tract, including those in the palate, oropharynx, hypopharynx, larynx, trachea and middle ear. Mumps is the most common disease of the salivary glands. Incidence has decreased markedly since the measles-mumps-rubella vaccine was introduced. **Mumps** results in bilateral parotid involvement in as many as 70% of cases. It is most prevalent between the ages of 4 and 15 years. Mumps is a contagious disease with an incubation period of 14 to 21 days. The disease is usually self-limiting and lasts 7 to 10 days. Treatment is purely symptomatic and the prognosis for full recovery without complications is excellent. One notable complication however, can be sensorineural hearing loss. **Acute suppurative sialadenitis** may affect any of the major salivary glands. It usually occurs among debilitated patients who are dehydrated and have poor oral hygiene, classically among dehydrated post-operative patients with a nasogastric tube. The most common organism is *Staphylococcus aureus*. It occurs most often in the setting of an obstructed salivary (Wharton's) duct. The most common cause of recurrent sialadenitis is sialolithiasis, **salivary gland stones** characterized by recurrent inflammation and swelling of a major salivary gland. As a general rule of thumb, the smaller the salivary gland ,the higher the incidence of malignant neoplasm. Most parotid tumors are benign. However, the rate of malignancy increases in the submandibular gland and malignant tumors are more common than benign in the sublingual and minor salivary glands. Benign tumors are pleomorphic adenoma, monomorphic adenoma, Warthin's tumor, oncocytoma, benign lymphoephithelial lesion and hemangioma. Malignant lesions are mucoepidermoid carcinoma, adenoid cystic carcinoma, adenocarcinoma, malignant mixed tumor, acinic cell carcinoma, squamous cel carcinoma, malignant oncocytoma, lymphoma and metastasis. Complete gland removal with tumor-free margins is essential (Ovchinsky & Har-el '04: 223, 225, 224, 227).

Difficulty in swallowing is known as **dysphagia**, and pain on swallowing is defined as **odynophagia**. Swallowing involves coordination of both voluntary and involuntary muscular contraction which can be divided into three phases – oral, pharyngeal and esophageal. Food is mixed with saliva during chewing to form the food bolus. The oral phase of swallowing is the only voluntary phase of the sequence. It occurs when the tongue moves the food bolus along its dorsum and propels it inot the pharynx. The pharyngeal phase is triggered primarily by contract between the food bolus and the pharynx. Once triggered, the sequence of muscular contractions that make up the swallow continues involuntarily. First, the soft palate, posterior pharyngeal wall, and fossae contract tot p revent nasopharyngeal reflux. The airway is protected as the laryngeal muscles contract. This draws the larynx upward beneath the hood of the base of the tongue as the epiglottis is depressed over the glottis inlet. With progressive pharyngeal muscle contraction, the bolus is moved into the hyppharynx and approaches the pharyngoesophageal sphincter (cricopharyngeus muscle), which relaxes and allows the bolus to be propelled into thte upper esophagus to begin the esophageal phase. Peristaltic action of the upper, middle and lower

esophagus further propels the bolus toward the stomach. Appropriate relaxation of the lower esophageal sphincter is essential . Once the bolus has entered the stomach, the lower esophageal sphincter contracts and prevents reflux of gastric contents into the esophagus (Habib & Sundaram '04: 231). **Stridor** is the audible symptom produced by rapid, turbulent airflow through a narrowed segment of the respiratory tract (Schwartz, Goldsmith & Barr '04: 238). Children with a history of hearing loss, cleft palate, cerebral palsy or neurological disorder are at risk for impaired speech and language development. **Stuttering** is an interruption in the normal rhythm of speech becaue of involuntary repetition, prolongation, and arrest of sound. Patients with neurological diseases may have dysarthria, which affects voice and articulation, apraxia of speech, which results in impaired volitional control of articulation and prosody, and aphasia, which can affect a person's ability to formulate, retrieve and decode language. The ability to hear begins with birth and by age 3-4 the child has a 1,500 word vocabulary and can pronounce all the letters in the alphabet (Francis, Barr & Har'el '04: 249, 251, 252).

Upper airway obstruction must be differentiated from respiratory distress caused by pulmonary, neurologic, cardiovascular and esophageal disorders. Upper airway obstruction in adults tends to be inflammatory or neoplastic, whereas in children it tends to be inflammatory or congenital. While the narrowest part of the adult airway is the glottis, in children it is the subglottis. Newborns are obligate nasal breathers because they have a high riding larynx. Any nasal obstruction can produce cyclical cyanosis. The baby cries once the cyanosis becomes uncomfortable and is able to breath through the mouth. The character of noisy breathing in relaton to the respiratory cycle helps localize the site of obstruction. Treatment centers on relief of the airway obstruction. If airway support is indicated, the safety of intubation versus tracheotomy must be determined. If complete airway obstruction occurs and intubation is not possible, emergency cricothyrotomy may be the simplest way of achieving an airway. This procedure can be performed through a small horizontal or vertical incision made directly through the skin, subcutaneous tissues and cricothyroid membrane, preferably with a single stab. Care is taken not to enter the esophagus or the posterior wall of the trachea. An endotracheal tube, tracheostomy tube, or other instrument is inserted atraumatically. Bleeding is controlled with digital compression of the vessels. The patient should then be transported to the operating room for more definitive treatment. Cricothyrotomy should not be attempted on young children, because the cricothyroid space is too small to accommodate a tube large enough for ventilation. (Wynn & Goldsmith '04: 257, 260, 261).

The tonsils and adenoids compose **Waldeyer's ring** of lymphoid tissue in the human pharynx. Although removal of these structures constitutes the most commonly performed major surgical procedure in the United States, they remain at the center of controversy as physicians debate indications for surgical removal. The tonsils and adenoids function as part of the immune system as portals to the upper aerodigestive tract. The tonsils and adenoids are prone to infecitno, typically with organisms such as group A β-hemolytic streptococcus, Streptococcus pneumoniae, Haemophilus influenza and Moraxella catarrhalis. Recurrent episodes of acute or chronic tonsillitis are an indication for surgical treatment if the number of infections exceeds seven per year for 1 year, five a year for 2 years, and three a year for 3 years. A peritonsillar abscess occurs when pus forms between the tonsillar fossa and capsule. Because the structures are strategically located in the pharynx, enlarged tonsils and adenoids can cause serious upper airway obstruction. Unilateral tonsillar enlargement suggests a malignant tumor. Tonsillar debris can build up and cause tonsilloliths and halitosis. In general, adenoidectomy should be performed carefully on any child at risk for velopharyngeal insufficiency. This include patients with a cleft palate or bifid uvula, short palate ,or a neurologic or neuromuscular disorder. Acute

infection of the tonsils and adenoids are a relative contraindication to surgical intervention unless the infection is life threatening, in which case surgical treatment definitely is indicated. Definite contraindication to adenotonsillectomy can be divided into two categories – hematologic disorders and uncontrolled systemic diseases. (Habib & Goldsmith '04: 262, 264-266).

Coughing accounts for approximately 30 million office visits annually. Any pathologic process capable of irritating the sensory receptors in the ear, nose, throat and lungs may be responsible for a cough. Definitive treatment depend on the underlying disorder. Antitussive drugs, used for symptomatic relief of coughing, work centrally as suppressant of the cough center or peripherally by anesthetizing the cough receptors. Many of the centrally active agents are opiate derivatives. Codeine and the more potent hydrocodone are effective but should be used cautiously because of their analgesic and addictive properties. Dextromethorphan is a synthetic antitussive agent related to the opioids without the dependence liability or analgesic effect. Antihistamines, especially diphenhydramine (Benadryl) have been found to be effective cough suppressants but are limited by their propensity to induce drowsiness. Peripherally active antitussive medications such as cough drops, cough syrups or simple fluids that coat of anesthetize the receptors may help artificially to increase receptor threshold for stimulation of the cough reflex. Expectorants may be used to provide symptomatic relief but have a limited therapeutic value (Habib, Lim & Har-El '04: 268, 269).

Neck masses occur among all age groups and may have a wide variety of causes, including congenital, inflammatory, neoplastic and other conditions. Asymptomatic neck masses among adults older than 40 years shold be considered malignant until proved otherwise. Eighty percent of nonthyroid and nonsalivary gland masses are neoplastic and 80% of neoplastic masses are malignant. Among children, however, as many as 90% of neck masses are benign (Mehta, Lim & Har-El '04: 277). Masses of the thyroid gland are a heterogeneous group of disorders ranging from benign cysts to malignant neoplasms. An estimated 10% to 15% of the U.S. population consult a physician because of a thyroid mass at some point in their life. Each year approximately 12,000 patients are diagnosed with a thyroid malignancy. The most common nonneoplastic thyroid mass is multinodular (colloid) **goiter**. The endemic type of goiter is caused by iodine deficiency, but the sporadic type can occur with adequate iodine dietary levels. Multinodular goiter is more common among women. Multinodular goiters can become extremely enlarged. **Graves' disease** is an autoimmune disorder that consists of hyperthyroidism, diffuse thyroid enlargement, ophthalmopahty and myxedema. Progression to hypothyroidism is a late manifestation of the disorder. **Thyroiditis** is usually self-limited. The nonneoplastic thyroid diseases are primarily managed medically. Surgical therapy for multinodular goiter is indicated when the mass causes compressive symptoms (odynophagia, dysphagia, or dyspnea), has mediastinal extension, or when it is cosmetically unappealing. Surgery is indicated for Grave's disease or hyperthyroidism secondary to hyperfunctioning nodules if medical treatment is not successful. Carcinomas of the thyroid are managed surgically. Since most patients with well-differentiated carcinoma of the thyroid have excellent cure rates, debate continues regarding the extent of thyroidectomy (total thyroidectomy or unilatreral lobectomy) and aggressiveness with regard to neck dissection (Mehta, Lim & Har-El '04: 290, 297). Methotrexate is the antineoplastic agent of first resort.

There are usually four **parathyroid glands**, but more may be present. Each gland weighs 30 to 40 mg, and the gross appearance is sometimes likened to a lentil bean with a pinkish complexion. The parathyroid glands contain chief and oxyphilic cells that synthesize and secrete parathyroid hormone (parathormone; PTH). PTH is a straight chain peptide that contain 84 amino acids. The

primary role of PTH is regulation of serum calcium and phosphorus levels. PTH releases calcium from bone, prevents calcium from being evreted in the urine, stimulates renal enzymes to produce active vitamin D for additional calcium absorption form the gastrointestinal tract, and increase excretion of phosphorus in the urine. The net effect is to raise serium calcium level and decrease serum phosphorus levels. Thus the hallmarks of **hyperparathyroidism** are hypercalcemia and hypophosphatemia. Primary hyperparathyroidism is one of the most common cause of hypercalcemia among persons younger than 50 years, with general incidence in the range of 1:1,100 to 1:2,000. The disease is two to four times more common among women, with an estimated 80,000 new cases per year. The signs and symptoms of hyperparathyroidism include easy fatigability, constipation, depression and other psychiatric disturbances. Renal symptoms cinlude nocturia, polyuria, polydipsia, nephrolithiasis and acidic pH of the urine. The classic description of bones, stones, psychiatric moans and abdominal groans is appreciated. The diagnosis of primary hyperparathyroidism rests on an elevated serum calcium level, a low serum phosphate level and an elevated PTH level. An albumin level is helpful in calculating free serum calcium. The localization of diseases parathyroid tissue can become an arduous task. Experience surgeons can locate the diseases tissue with 90% to 95% efficiency without radiographic studies. Patients with metabolism complications of hyperparathyroidism, such as renal stones or osteitis fibrosia cystica, are surgical candidates (Ovchinsky, Lim & Har-El '04: 299, 303).

III.A.4 Pneumonia

Cough, dyspnea, fever, and pleuritic chest pain are the major complaints with virtually all types of **pneumonia**. Pneumococcus, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Legionella pnemonphila*, *Mycoplasma* and viruses abound in the community and gram-negative bacteria and *Staphylococcus* species in hospitals. Cystic fibrosis patients are frequently infected with *Pseudomonas* and *Staphylococcus*. COPD patients are vulnerable to the typical community-acquired infections. The bacterium *Legionella pneumophila* causes both Legionnaire's disease and Pontiac fever and is an occupational hazard contaminating air-conditioning units and water reservoirs (Berger '04:271). *Streptococcus pneumoniae* is the most common bacterial pathogen isolated in immunocompetent patients. The classic Gram stain demonstrates lancet-shaped, gram-positive diplococci. The pneumococcus resides in the nasopharynx of asymptomatic carriers and is dispersed and transmitted in all seasons, although the highest incidence of disease is recorded in colder weather. The virulence of the organism depends substantially on the capsular serotype (20% mortality with type III compared with 2% with type II). Pneumococcal pneumonia patients have symptoms of acute onset of high fever, a single rigor lasting up to 30 minutes, typically dry cough initially that becomes productive of rusty sputum, pleuritic chest pain, tachypnea, and tachycardia and physical examination findings of consolidation in a lobar pattern. Poor prognostic signs include multilobar involvement with hypoxemia, alcoholism, leukopenia with overwhelming sepsis, age extremes, bacteremia, type III serotype, and the development of adult respiratory distress syndrome (ARDS). Other complications include meningitis, endocarditis, peritonitis, septic arthritis, and pericarditis.

The pneumococcal organism is quite susceptible to **penicillin**, erythromycin and cephalosporins. Penicillin, Ampicillin (Principen), is generally considered the most effective antibiotic for treating hard to reach upper respiratory infection, otitis media, sinusitis and meningitis. Because of the potential lethality of penicillin allergy anaphylaxis, although antibiotic resistance may be an issue Azithromycin (Zmax) is the world's best selling antibiotic. Several other streptococcal species are capable of causing pneumonia in the immunocompetent adult. *Streptococcus*

pyogenes (group A Strep) often superinfects a preceding viral pneumonia, especially influenza in adults. It generally causes Strep throat as an immune reaction to infected sputum or rheumatic heart disease in patients immunocompromised by unhealed heart attack scars. Thoracic complications of empyema, pneumothorax and bronchiectasis, as well as extra-thoracic complications, including glomerulonephritis, anemia, thrombocytopenia, and bacteremia have occurred. Therapy with penicillin G or ampicillin is usually effective, if the patient is allergic or has Strep throat, which can mimic the choking sensation of anaphylaxis, erythromycin or doxycycline should be substituted. *Streptobacillus agalactiae* (group B Strep) usually causes pneumonia and sepsis in newborns and infants, but has been detected with increasing frequency in adults (McClellan & Iseman '89: 64, 65) as a hyperuremic gouty lower respiratory infection treated with hygiene and a five day course of metronidazole 400 mg for adults 200 mg for children, one twice a day. 25% of *S. pneumoniae* infections are resistant to penicillin (McCance '14: 333). Although there are many obscure pneumonia pathogens, the most likely culprit is that when clinical streptococcus and hospital acquired staphylococcus are combined they cause toxic shock syndrome. To treat methicillin resistant staphylococcus aureus (MRSA) doxycycline 100 mg, the once a day antibiotic, or clindamycin (Cleocin) for pregnant women and children under the age of 8 is necessary. An Epsom salt bath may also help treat many painful rheumatic conditions resulting from toxic shock syndrome solved by doxycycline or clindamycin.

Bacterial Causes for Pneumonia and Antimicrobial Treatment

Strep Group A Rheumatic Heart Disease: *Streptococcus pyogenes*, acquired from young adults	Highly contagious URI, sore throat, lasting a week, rheumatic heart disease sets in after a week with a 25% chance of dying over 10 years, if untreated	Cured quickly with antibiotics and plenty of cardiovascular exercise. Eat vegan. No sugar. Clean. Stock up or get a refillable prescription for antibiotics. Give your infected friends, family and co-workers antibiotics.
Strep Group B Gout: *Steptobacillus agalactiae* acquired from nursing mothers	LRI infection, persistent endocarditis, hyper uremia and severe prolonged rheumatism of the lower extremities – gout.	Cured with a full course of metronidazole, resistant to most other antibiotics. Long periods of light exercise, sunlight or Vitamin D for cripples. Avoid nursing mothers and contaminated fabrics.
Pneumonia: *Streptococcus pneumoniae*, *Chlamydia pneumonia*e and *Staphylococcus aureus* acquired from hospitals, Strep + Staph = toxic shock syndrome	The term pneumonia is used to describe any severe respiratory infection, these strains are most highly contagious, also cause meningitis, ear and skin infection, endocarditis and mix and mutate with other resistant systemic bacterial and viral infections.	Penicillin, ceftriaxone, cefotaxime and cardiovascular exercise. The corticosteroid Prednisone is also used. Ventilation in hospitals saves lives. Antitoxin for Step/Staph toxic shock syndrome. Doxycycline for staph infections, should be prescribed on discharge from hospitals.

Staphylococcus aureus	Common hospital acquired infection that frequently causes abscess and has a mortality rate estimated at 50%. *S. aureus* produce penicillinase, and penicillin, ampicillin and semisynthetic penicillin antibiotics (including methicillin, nafcillin, oxacilin and dicloxacillin) are inactivated by staphylococcal β-lactamase.	Intravenous methicillin, or an equivalent drug such as nafcillin, 8 to 16 gm daily, if penicillin resistant. Vancomycin, 500 mg intravenously every 6 hours is an effective anti-staphylococcus drug but has significant toxicity, resistance and probably should seldom be used. Antimicrobial treatment should be continued for at least 2 to 3 months, sometimes even longer. Oral doxycycline 100 mg the once a day antibiotic, for the treatment of methicillin resistant *S. aureus* (MRSA)
Branhamella catarrhalis (formerly Neisseria),	Gram-negative cocci. Pathogenic mostly to people with pre-existing lung disease.	Penicillin resistant. Susceptible to erythromycin, tetracycline and doxycycline
Haemophilus influenzae	Aerobic, gram-negative rod frequently causing pneumonia in the elderly, alcoholics, patients with COPD, and those with preceding viral infections.	Ampicillin (Principen) or Amantadine (Symmetrel).
Legionella pneumophila	Typically this organism is transmitted via aerosol secretions. It frequently infects young adults and is uncommon after the age of 50. This organism is responsible for 10% to 50% of pneumonia among college students and military recruits.	The treatment of choice for "walking pneumonia" is erythromycin or tetracycline. Even mild cases should be treated. The drug therapy consists of erythromycin for a minimum of two weeks. Rifampin can be added in refractory cases.
Peptostreptococcus species, *Fusobaterium* species, *Bacteroides malaninogenicus*, *Bacteroides fragilis*, and *Peptococcus* species.	Anaerobic bacterial pneumonia is usually polymicrobial. Anaerobic pneumonia is generally more insidious with a productive cough often with putrid sputum, and systemic manifestations of weight loss and malaise dominate the presentation. Individuals seldom seek help early and necrotizing pneumonia, lung	Drug therapy should consist of either high-dose penicillin or parenterally administered clindamycin. Metronidazole is also used in the treatment of anaerobic lung infection, but this oral medication has not been as effective as clindamycin IV but is safer.

	abscess, empyema and sponataneous bronchopleural fistula frequently occur.	
Klebsiella pneumonia	Gram-negative aerobe that cause significant morbidity and mortality. The mortality ranges from 30% to 60% even when properly diagnosed and treated.	Initial therapy should include kanamycin, 15 mg/kg/day intramuscularly in 2 or 3 divided doses, the total dose being decreased if renal insufficiency is present or appears. Antibiotics susceptibility studies may allow the use of a less toxic antibiotic than either kanamycin or trimethoprim-sulfamethoxazole. (Metronidazole (Flagyl ER) is a safe alternative but clinical trials are needed for the FDA to indicate its use in *Klebsiella*).
Pseudomonas aeruginosa	Gram-negative aerobe causing significant morbidity and mortality. Common in patients with mechanical ventilation, burns, previous chemotherapy, or previous antibiotic therapy. The mortality of these pneumonias ranges from 30% to 60% even when properly diagnosed and treated.	Antipseudomonal penicillin such as azlocillin, piperacillin, mzlocillin, ticarcillin or carbenicillin could be used instead of the third-generation cephalosporin. Parenteral therapy should generally be continued for a minimum of 2 weeks.
Gram-negative aerobes - *Acinetobacter calcoaceticus*, and members of the Enterobacteriaceae family, including *Klebsiella penumoniae*, *Escherichia coli*, Enterobacteriaceae species, *Proteus* species and *Serratia marcescens*.	Gram-negative aerobes that cause significant morbidity and mortality. The mortality of these pneumonias ranges from 30% to 60% even when properly diagnosed and treated.	Bactrim (trimethoprim-sulfamethoxazole) seems to be indicated for the treatment of many of these pathogens however it almost inevitably causes chronic malabsorption of the GI and/or kidneys, vitamin B-12 deficiency, streptococci and candidiasis usually corrected in two hours after antibiotic consumption and for two weeks after completion of the course, with OTC vitamin B-12 supplementation, probiotics and candida clear. Metronidazole (Flagyl ER) seems to be a safe and

		effective alternative however clinical trials are needed for the FDA to adopt specific recommendations (e.g. *E. coli*).
Empiric therapy for the majority of immune-compromised patients with a presumed pulmonary infection	Approximately 75% of immunosuppressed patients with pulmonary complications are infectious. 25% of the pulmonary complications in immune-compromised patients are non-infectious.	Includes antibiotic coverage for both gram-positive and gram-negative organisms (usually a semi-synthetic penicillin or a cephalosporin plus an aminoglycoside. Patients who respond to empiric therapy are treated for up to 3 weeks.
Lung abscess	Circumscribed, suppurative inflammation followed by central tissue necrosis.. Multiple lung abscesses may be a feature of hematogenous dissemination of *Staphylococcus*, *Klebsiella pneumoniae*, or other necrotizing organisms. Multiple abscesses may be caused by septic emboli arising from infected foci or septic phlebitis, especially in association with some coexistent chronic debilitating condition such as alcoholism, cirrhosis, congestive heart failure, or malnutrition. Lung abscesses also commonly occur in the clinical setting of AIDS patients or of immunosuppressive therapy, as in organ transplantation.	Penicillin by mouth and corticosteroids by mouth or nebulizer may be effective in simple lung abscesses. Inpatient treatment of lung abscess, especially the putrid variety, should be 2 to 6 million U crystalline penicillin G intravenously daily; 600,000 U procaine penicillin G intramuscularly every 6 hours for 4 weeks may be sufficient in milder cases. In the presence of serious penicillin hypersensitivity, clindamycin 600 mg 4 times daily, lincomycin 600 mg intramuscularly every 6 hours, or erythromycin 2 gm/day may also be used. Some observers are in favor of adding streptomycin 1 gm intramuscularly daily for at least the first 7 to 10 days, or tetracycline 2 gm daily to 3 to 5 days, then 1 gm daily.

Source: Sanders '11 Table 4; (McClellan & Iseman '89: 65, 66),

Staphylococcus aureus is a gram-positive coccus that appears most often in hospitalized patients who have indwelling catheters, hemodialysis, prosthetic ales, and right-sided endocarditis. This organisms also frequently superinfects influenza patients and a common nosocomial, hospital acquired infection, that is rarely community acquired. Staph can be quite virulent with up to 50% mortality and considerable morbidity despite the appropriate use of antibiotics – doxycycline due to methicillin resistance. Elaboration of exotoxins, namely hyaluronidase, coagulase, and staphylokinase, results in extensie tissue necrosis. Approximately 30% of normal

adults harbor the organism in their nasopharynx, but this incidence is increased in diabetic patients, narcotic addicts, and patients with prolonged hospitalization. Fever, cough and tahpnea are inevitably present; leukocytosis and nonspecific infiltrates on chest radiograph are typical. Complications are bacteremia in 15% to 25% of patients and empyema, requiring drainage with tube thoracostomy. The sighting of *Staphylococcus epidermidis* in blood agar is thought to indicate invasion of the lung parenchyma and of causing pneumonia and/or endocarditis. Most *S. aureus* produce penicillinase, and penicillin, ampicillin and semisynthetic penicillin antibiotics (including methicillin, nafcillin, oxacilin and dicloxacillin) are inactivated by staphylococcal β-lactamase (McClellan & Iseman '89: 65, 66). *S. aureus* is safely and effectively treated with doxycycline 100mg, in those over the age of 8 (it causes permanent yellowing of developing permanent teeth), once a day. Epsom salt baths are indispensable for the treatment of spinal abscesses and cleansing of hospital workers and discharged patients.

Necrotizing bacterial pneumonia resulting in cavitation suggests *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and anaerobes. Cavities frequently occur in fungal and tuberculous infections. A sputum analysis must be performed with Gram stain and culture. If the specimen is acceptable it will have few squamous epithelial cells, the number of polymorphonuclear (PMN) leukocytes must be assessed. Many PMNs imply that an inflammatory process is present, probably an infectious disease. If few PMNs are present, noninflammatory cause of the infiltrate, cardiogenic and noncardiogenic pulmonary edema, should be considered. The presence of bacteria must be determined. A preponderant organism (for example, gram-positive cocci) in the presence of many PMNs and few epithelial cells should be the target of antimicrobial therapy. Atypical pneumonias (especially *Legionalla*, *Mycoplasma* and viruses often reveal many PMNs but few stained bacteria. Percutaneous lung biopsy was first described in 1883 and an accurate diagnosis can be obtained in nearly 90% of patients with this method (McClellan & Iseman '89:62, 63).

In recent years, *Branhamella catarrhalis* (formerly Neisseria), a gram-negative cocci, has been shown to be pathogenic, especially in patients with underlying lung disease. This organism also frequently elaborates β-lactamase, so simple penicillin or ampicillin therapy is inadequate. Isolates are usually susceptible to erythromycin, tetracycline and doxycycline. *Neisseria meningitides* is rarely the cause of adult pneumonia and is treated with penicillin. Another commonly diagnosed community acquired pneumonia is *Haemophilus influenzae* which is aerobic, gram-negative rod frequently causing pneumonia in the elderly, alcoholics, patients with COPD, and those with preceding viral infections. The typical Gram stain finding (pleomorphic coccobacillus) direct therapy to Ampicillin (Principen) or Amantadine (Symmetrel). The majority of other gram-negative aerobes that cause significant morbidity and mortality include *Pseudomonas aeruginosa*, *Acinetobacter calcoaceticus*, and members of the Enterobacteriaceae family, including *Klebsiella penumoniae*, *Escherichia coli*, Enterobacteriaceae species, *Proteus* species and *Serratia marcescens*. Incidence is high in hospitalized patients. If the epidemiology suggests the presence of *Pseudomonas* (patients with mechanical ventilation, burns, previous chemotherapy, or previous antibiotic therapy) an antipseudomonal penicillin such as azlocillin, piperacillin, mzlocillin, ticarcillin or carbenicillin could be used instead of the third-generation cephalosporin. Parenteral therapy should generally be continued for a minimum of 2 weeks. The mortality of these pneumonias ranges from 30% to 60% even when properly diagnosed and treated (McClellan & Iseman '89: 66, 67). Bactrim (trimethoprim-sulfamethoxazole) seems to be indicated for the treatment of many of these pathogens however it almost inevitably causes chronic malabsorption of the GI and/or kidneys, vitamin B-12 deficiency, streptococci and candidiasis usually corrected in two hours after antibiotic consumption and for two weeks after

completion of the course, with OTC vitamin B-12 supplementation, probiotics and candida clear. Metronidazole (Flagyl ER) seems to be a safe and effective alternative however clinical trials are needed for the FDA to adopt specific recommendations (e.g. *E. coli*).

Anaerobic bacterial pneumonia is usually polymicrobial. The most common organisms isolated include *Peptostreptococcus* species, *Fusobaterium* species, *Bacteroides malaninogenicus*, *Bacteroides fragilis*, and *Peptococcus* species. The bacteriology is dependent on whether the infection was community or hospital acquired. In community acquired aspiration pneumonia, anaerobes are the exclusive pathogen in about 60% of patients. The remainder of infections result from coexisting aerobic infection, usually with streptococcal species. However, in hospitalized patients aspiration produced pure anaerobic infection in 17% of patients, aerobic-anaerobic mixture in 47% of patients and aerobic infection (especially gram-negative rods) in 36% of patients. Anaerobic pneumonia is generally more insidious with a productive cough often with putrid sputum, and systemic manifestations of weight loss and malaise dominate the presentation. Individuals seldom seek help early and necrotizing pneumonia, lung abscess, empyema and sponataneous bronchopleural fistula frequently occur. Drug therapy should consist of either high-dose penicillin or parenterally administered clindamycin. Metronidazole is also used in the treatment of anaerobic lung infection, but this medication has not been as effective as clindamycin (McClellan & Iseman '89: 67). *Legionella pneumophila* is a gram-negative organism responsible for sporadic cases of pneumonia, as well as outbreaks in the community. One study from Pennsylvania revealed higher incidence of Legionella than pneumococcal pneumonia over 11 months. The infection can be insidious with malaise, anorexia, and dry cough or quite abrupt with an acutely ill appearance and fever. The Gram stain typically reveals no bacteria, since the agent stains quite poorly. The diagnosis of Legionella has been augmented by improved serologic testing direct fluorescent antibodies and culture techniques. Typically this organism is transmitted via aerosol secretions. It frequently infects young adults and is uncommon after the age of 50. This organism is responsible for 10% to 50% of pneumonia among college students and military recruits. The treatment of choice for "walking pneumonia" is erythromycin or tetracycline. Even mild cases should be treated. The drug therapy consists of erythromycin for a minimum of two weeks. Rifampin can be added in refractory cases.

Many different viruses (influenza, parainfluenza, adenovirus rhinovirus, measles, coxsackievirus, varicella-zoster, herpes simplex, cytomegalovirus, and Epstein-Barr virus) are responsible for adult pneumonias. Most are community acquired. Amantadine (Symmetrel) is effective against influenza A both prophylactically and therapeutically. Response rates of other respiratory viruses to specific antiviral therapies are poor. Actinomyces israelii and Nocardia species are bacterial infections usually associated previous debilitating disease. Tularemia (Francisella tularensis), psittacosis (Chlamydia psittaci), and plague (Yersinia pestis) rarely cause pneumonia in humans. Mycobacterial disease, both tuberculosis and nontruberculosis mycobacterisis, fungal infections with *Aspergillus* species (e.g. *A. niger*), *Cryptococcus neoformans*, *Coccidioides immitis*, *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Candida* species and mucormycosis is capable of causing pneumonia best treated with corticosteroids. Protozoan infections with *Pneumocystis carinii*, *Entamoeba histolytica*, nematodes, cestodes, trematodes, and rickettsiae such as *Coxiella burnettii* are rarely noted for treatment with metronidazole (Flagyl ER). The etiologic agents responsible for pneumonia are diverse and the spectrum is constantly changing. Although improvement have been made in the diagnosis and therapy of pneumonia, little progress has been made in reducing morbidity and mortality (McClellan & Iseman '89: 68, 69).

Despite the development of sophisticated antimicrobial therapy, **respiratory infections** continue to be a major cause of mortality and the role of pneumonia and influenza in mortality statistics may be underestimated. Many cause of pneumonitis, including aspiration of gastric contents, inhalation injuries, interstitial lung disease, hypersensitivity, sarcoidosis, and vasculitis, are not infectious. The spectrum of infectious diseases of the respiratory system has changed dramatically within the last decade, primarily because of an increase in the number of immunosuppressed patients resulting from malignancy or other debilitating diseases, chemotherapy, or HIV infection. The spectrum of pulmonary infections in the immune-competent patient has also changed in the past 10 years. Advances in culturing techniques and serology have improved identification of specific pathogens and have demonstrated a rise in the incidence of atypical pneumonias, especially in community acquired infections. Little progress has been made to diminish the morbidity and mortality from infectious pneumonia over the past quarter century. Improvements in technology and the development of more sophisticated antibiotics have only modest impact on this seemingly treatable disease. Therefore prevention of pneumonia has become a primary concern. The aeorosolization of infectious particles is diminished if good hygiene is maintained. Seasonal increases in the incidence of pneumonias occur because people tend to remain indoors (where aerosolized particles cannot disperse as well as out of doors). In the hospital, rigorous hand-washing and sterilization of equipment is crucial in decreasing the transmission of these infective agents. The patient's nutritional status should be optimized. Medications that may decrease the gag reflex (sedatives) suppress the cough mechanism (narcotics), or reduce the immune status (steroids) should be minimized. In addition, specific vaccines against influenza and pneumococcal infection are available. Most experts recommend annual influenza vaccination of high-risk groups (residents of chronic-care facilities, patients with chronic obstructive pulmonary disease (COPD) and patients with chronic cardiac conditions). Moderate-risk patients, medical professionals, over 65 years old and patients with other chronic debilitating diseases, including diabetes, immunosuppression, renal failure and anemia, should also receive the vaccine. Pneumococcal vaccine is controversial, the major determinant of host resistance against *Streptococcus pneumoniae* infections is the degree of antibody response in the patient's serum after vaccination. Successful treatment of pneumonia requires administration of antibiotics directed against the offending organism. A careful history, a physical examination, and a compilation of suitable laboratory information usually leads to a reasonable choice of antibiotics (McClellan & Iseman '89: 60, 61). Doxycycline is used to treat methicillin resistant staphylococcus aureus (MRSA) and throat infections but causes yellowing of developing teeth in children under age 8, Penicillin, ampicillin or erythromycin, if allergic to penicillin, are the best, often only, choice for upper respiratory infections, sinusitis and meningitis. Metronidazole is the only option for lower respiratory infections of gastrointestinal origin, bone and joint infections, Bactrim causes chronic malabsorption requiring two weeks of probiotic supplementation and doesn't treat the common streptococcus. Metronidazole is under investigation for the treatment of *E. coli* and *Pneumonia auroguinosa*, *Klebsiella pneumonia* and other pathogens for which Bactrim is claimed to be effective, for a cure without ill-effect.

The lung is one of the most common sites of **infection in immune-compromised patients** mostly because the lung is vulnerable to invasion from inhaled, aspirated and blood borne organisms. Virtually all forms of immune-suppression interfere with at least one part of the lungs' normal host defense system. Normally, nasal turbinates filter particulate matter and are a soruce of IgA secretion that facilitates opsonization of bacteria. These features are lost if a patient is intubated or has a tracheostomy. The glottis and vocal cords protect the lungs from aspirating oropharyngeal contents. However, this protection is lost if their function is impaired.

The trachea and bronchi are lined with ciliated epithelium whose mucociliary clearance function can be markedly suppressed by smoking and viral infections. Larger airways are further protected by secretin of IgA, which prevents the adherence of organisms (except for IgA protease-producing organisms such as *Streptococcus pneumoniae* and *Haemophilus influenzae*, and by the process of bronchoconstriction, which prevents large particles from entering into the lung. The alveoli are the next site of lung defense. Alveolar macrophages phagocytize particulate material and provide the basis of cell-mediated immunity when combined with T lymphocytes. These processes are hampered by underlying disease such as pneumoconiosis, malignancy or AIDS; drugs such as steroids and alcohol; and alterations of the local environment by hypoxia or toxic inhalations. B lymphocytes, IgG, and complement provide humoral immunity at the level of the alveolus. Blood-borne neutrophils migrate into the alveoli and phagocytize bacteria unless these functions are hampered by diabetes, alcohol, malignancy or drugs. The alveoli are bathed in surfactant that apparently provides a congenial environment for the other components of the defense system unless the surfactant is diluted (as in pulmonary edema) or its production is diminished (as perhaps in adult respiratory distress syndrome). Thus the description of immune-compromised patient include not only patients with cancer but also patients whose host defense system has been impaired by injury (McClellan & Iseman '89: 71, 73).

The **differential diagnosis of pulmonary disease in immune-compromised patients** is extensive. Approximately 75% of immunosuppressed patients with pulmonary complications are infectious. 25% of the pulmonary complications in immune-compromised patients are non-infectious. Non-infectious pulmonary disease in immuno-compromised patients can be caused by cardiogenic and noncardiogenic pulmonary edema, pulmonary embolism-infarction, drug-induced lung disease, malignancy, primary, metastic or lymphagitic spread, hemorrhage, leukostasis, radiation fibrosis, orxygen toxicity or collagen vascular disease. Pathogens responsible for pulmonary infections in the immunocompromised host are numerous and can be divided into bacterial, viral, fungal, and protozoal. Bacterial causes include Gram-positive organisms *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*. Gram-negative organisms *Escherichia coli*, *Klebsiella*, *Pseudomonas*, *Serratia*, *Listeria*, *Mycobacteria*, *Legionella* and *Nocardia*. Viral causes include Herpes simplex, Cytomegalovirus, Varicella-zoster, Adenovirus, Measles and Influenza. Protozoal causes include Pneumocystis, Toxoplasma and Strongyloides. Fungal causes include *Aspergillus*, *Candida*, *Coccidioides*, *Cryptococcus*, *Histoplasma*, *Blastomyces* and *Phycomycetes* (McClellan & Iseman '89: 73, 74).

Evidence of **hemolytic anemia** might suggest the presence of mycoplasma and lymphocytosis might suggest a viral rather than bacterial infection. **Cytomegalovirus** is the most common infectious agent to cause the combination of abnormal liver function tests and pulmonary disease. A rapid progressing alveolar infiltrate suggests a bacterial pneumonia. **Cavitary lesions** are more common in *Staphylococcus aureus* and gram-negative bacterial and fungal infections. A **slowly developing interstitial infiltrate** suggests a viral, a fungal or a mycobacterial infection rather than a bacterial infection. **Pleural effusions** are more common in bacterial than in fungal infections. Routine sputum Gram stains and cultures may be diagnostic in bacterial infections but are not helpful in fungal, viral or protozoal infections. Blood cultures may be positive in patients with bacteria, fungal or mycobacterial infections. Sputum can be sent for direct fluorescence antibody screen for *Legionella*, for acid-fast smear and culture for tuberculosis, and for either Fiemsa or methenamine silver stain for *Pneumocystis*, especially in patients with AIDS. **Serology** is available for the detection of fungal infection, *Legionella*, *Mycoplasma*, cytomegalovirus, *Chlamydia*, and toxoplasmosis. However, the diagnosis of these

infectious agents often requires the evaluation of both and convalescent titers (obtained after 4 weeks) making them impractical for use in the acute setting. The patient may be treated empirically and observed for 24 to 48 hours. Empiric therapy for the majority of immune-compromised patients with a presumed pulmonary infection includes antibiotic coverage for both gram-positive and gram-negative organisms (usually a semi-synthetic penicillin or a cephalosporin plus an aminoglycoside. Patients who respond to empiric therapy are treated for up to 3 weeks (McClellan & Iseman '89: 74, 75).

Patients who show no sign of improvement or who deteriorate while receiving empiric therapy are generally treated with bronchoscopy. Bronchoscopy can be performed either transnasally or via an endotracheal tube and does not require general anesthesia. Bronchoalveolar lavage was recently studied in non-AIDS patients and found to have a diagnostic accuracy of 83% for opportunistic infections, but only 46% for malignant infiltration and 40% for drug toxicity. Transbronchial biopsies via the flexible fiberoptic bronchoscope in immune-compromised patients has been extensively studied. In several series of patients the diagnostic yield has varied form 5% to 89%. The greatest diagnostic yield is in patients with diffuse rather than localized infiltrates. Transbronchial biopsy is associated with a high incidence of complications, including pneumothorax and hemorrhage. Open-lung biopsy has also been extensively studies and a specific diagnosis can be obtained in 60% to 100% of patients with a reported complication rate up to 19%. Select pieces of tissue are obtained for frozen sections and impression smears (touch preps). This often permits a rapid diagnosis. In one series of 95 patients who had open-lung biopsy, a specific diagnosis was made in 77 and was made rapidly in most patients. Transthoracic needle aspiration and biopsy are associated with a high risk of pneumothorax and hemorrhage and are not widely used. Secretions and tissues should be stained for Pneumocystis (methenamine silver) and Legionella (fluorescent antibody). Both fixed and frozen tissue sections should be reviewed for evidence of malignancy, drug-induced toxicity, infection-related inflammation, and evidence of hemorrhage (Parsons '89: 75, 76).

Acquired immune-deficiency syndrome (AIDS) was first reported to be epidemic in the United States in 1981. By 1991 it has been projected that there were 270,000 cases of AIDS with 179,000 deaths. The disease has been attributed to the human immunodeficiency virus (HIV), which appears to preferentially infect T-helper lymphocytes and monocytes resulting in lymphopenia, defects in cell-mediated immunity, activation of B cells and hypergammaglobulinemia. The presenting manifestations of AIDS involves the lungs in more than 50% of patients. Some series indicate that between 80% and 100% of patients with AIDS will develop pulmonary complications during the course of their illness. Community acquired pneumonia is five to six times greater in AIDS patients than for the general populace. The most common infectious agents are *Streptococcus pneumoniae* and *Haemophilus influenza*, which are associated with defects of B-cell function. *Pneumocystis carinii*, Cytomegalovirus, *Mycobacterium tuberculosis*, *Mycobacterium-avium intracellulare* are other common pulmonary infections in AIDS patients. *Toxoplasma gondii,* herpes simplex, and fungi are also reported in AIDS patients but are less common. Malignancies are Kaposi's sarcoma and Non-Hodgkin's lymphoma. Another cause is Lymphoid-interstitial pneumonitis. These organisms can generally be isolated from routine sputum. The most common opportunistic infection in patients with AIDS is *Pneumocystis carinii*, which accounts for disease in about 50% of patients and up to 85% of patients with pulmonary manifestations. The primary complaints are nonproductive cough and progressive dyspnea with some associated fever and pleuritic chest pain. The illness is longer in AIDS patients than in other immune-compromised groups with pneumocystosis 28 days versus 5 days. Currently, the therapy for pneumocystis pneumonia is 14 to 21 days of either

sufamethoxazole and trimethoprim (Bactrim) or pentamidine. AIDS patients however have even more adverse reactions than the general population (65% of AIDS patients versus 15% non-AIDS patients) so pentamidine is prescribed. Clinical trials are needed to document if Metronidazole (Flagyl ER) is effective against *Pneumocystis carinii*. Before the advent of effective antiretroviral AIDS drugs in 1994 mortality from *P. carinii* infection depends somewhat on the patient's initial presentation. Overall, up to 43% of AIDS patients will die, but in the small subgoupr (10% to 15%) of patients who have respiratory failure the mortality is 90% to 100% (Parsons '89: 79, 80).

Cytomegalovirus (CMV) is a common finding in postmortem analysis of AIDS patients. In general, CMV alone may not be responsible for significant morbidity or mortality but may complicate the course of other infections. Chest radiograph findings of CMV pneumonia are indistinguishable from pneumocystis pneumonia. In fact *P. carinii* and CMV coexist in 21% of patients with pulmonary complications. The diagnosis of CMV pneumonia depends on the demonstration of intra-nuclear or intra-cytoplasmic inclusion bodies in lung tissue. A review of patients with pulmonary complications of AIDS suggests that the mortality form CMV pneumonia alone is 75% and when CMV and *P. carinii* coexist the mortality increases to 86%. *Mycobacterium tuberculosis* is increasingly becoming an infectious agent in the AIDS population, especially in regions where *M. tuberculosis* is endemic such as Florida, New York, New Jersey, and the African continent. *M. tuberculosis* occurs more frequently in patients who are intravenous drug abusers or who are Haitian. Up to 72% of patients have extra-pulmonary tuberculosis, predominantly lymphatic and disseminated disease and the majority of patients manifest pulmonary involvement during the course of their illness. Chest radiographs frequently reveal hilar and/or mediastinal adenopathy with localized or diffuse infiltrates. Unlike *M. tuberculosis* in non-AIDS patients, cavitation is rarely seen. The diagnosis of *M. tuberculosis* depends on the culturing of appropriate material such as urine, sputum, blood, lymph nodes, bone marrow and liver tissue. The therapy for *M. tuberculosis* in patients with AIDS is the standard anti-tuberculosis regimen. Most medical centers initiate therapy with three drugs and continue therapy for at least 9 months. *Mycobacterium-Avium intracellulare* (MAI) infection was recognized as a complication of AIDS shortly after AIDS was recognized as a disease. The reported incidence of infection is as high as 50% in some medical centers. The presenting complaints are usually fever, malaise, and weight loss, with a number of patients complaining of diarrhea and abdominal pain. The diagnosis of the disease requires that the organism be cultured in a normally sterile site and blood cultures are positive in up to 90% of patients with MAI infections. Respiratory secretions have a positive culture in 69% of patients with pulmonary disease. MAI infection is resistant to many of the known antimycobacterial drugs so intensive multidrug regimens are used and AIDS patients respond poorly due to the frequent coincidence of other opportunistic infections (Parsons '89: 78-82).

Kaposi's sarcoma was an extremely rare tumor util the advent of AIDS. Now, Kaposi's sarcoma is a symptom in up to 25% of AIDS patients. The organ involved are usually lymph nodes and skin, although pulmonary involvement s present in up to 20% of patients with metastatic Kaposi's sarcoma. The presenting symptoms include fever, cough, dyspnea and occasionally hemoptysis. The diagnosis of Kaposi's sarcoma requires histologic examination of tissue that is difficult and open-lung biopsy yields a diagnosis in up to 80% of patients. Approximately one half of the definitive diagnoses of pleuropulmonary Kaposi's sarcoma in AIDS patients are made when autopsy is performed. The current therapy for Kaposi's sarcoma is combination chemotherapy. Mean survival rate after the diagnosis of pleuropulmonary Kaposi's sarcoma was only 4 months. **Lymphocytic interstitial pneumonitis** (LIP) is a disorder of

unkown etiology characterized histologically by the infiltration of mature lymphocytes and plasma cells into the lung. Initially, LIP was a problem in the pediatric AIDS population, but recent data indicate that LIP is prevalent in the adult AIDS population as well. Evidence suggests that LIP may represent a premalignant condition, since some patients subsequently develop well-differentiated lymphocytic lymphoma. The diagnosis is made with tissue obtained from tansbronchial biopsies or open-lung biopsy. It is important to establish the correct diagnosis in these patients because a significant number of them respond to steroid therapy (Parsons '89: 82, 83).

A **lung abscess** is a circumscribed, suppurative inflammation followed by central tissue necrosis, indistinguishable in its early stages from any localized pneumonitis. Only after a lung abscess has communicated with a bronchus and started to drain can the characteristic air-fluid level be seen within the area of inflammation. Single lung abscesses usually arise from suppurative inflammation behind a bronchial obstruction or after aspiration. Single lung abscess may also result from superinfecion of a cavitated infarct or from metastasis or amebiasis from the liver, most commonly into the right lower lobe. Multiple lung abscesses may be a feature of hematogenous dissemination of *Staphylococcus*, *Klebsiella pneumoniae*, or other necrotizing organisms. Multiple abscesses may be caused by septic emboli arising from infected foci or septic phlebitis, especially in association with some coexistent chronic debilitating condition such as alcoholism, cirrhosis, congestive heart failure, or malnutrition. Lung abscesses also commonly occur in the clinical setting of AIDS patients or of immunosuppressive therapy, as in organ transplantation. Single abscesses may be putrid or non-putrid. Multiple abscesses are almost always non-putrid. Putrid abscesses are virtually always associated with carious teeth, infected gums and alcoholism, and are usually located in the posterior segments of either the upper or lower lobes. Putrid abscesses are caused by many different organisms, especially anaerobic streptococci, *Bacteroides* and fusospirochetes. During its early acute phase, the pathology of lung abscess does not differ noticeably from that or ordinary pneumonia. As the pneumonia progresses, it fails to heal; ultimately, necrosis involving all elements of lung tissue occurs. As an abscess becomes chronic (present for 6 weeks or more), it may spread to and destroy adjacent tissue or it may empty and the wall lining its cavity may become partially covered with regenerated epithelium. When the abscess ruptures into a bronchus, the patient begins to cough up copious amounts of purulent, often foul-smelling and foul-tasting sputum. When a lung abscess has become chronic, severe debility, pulmonary osteoarthropathy (clubbing) and even secondary amyloidosis may occur. The diagnosis of lung abscess usually presents no difficulty. The differential diagnosis should include primary and metastatic neoplasms, tuberculosis, fungus disease, actinomycosis, nocardiosis, bronchiectasis, pulmonary infarction, pneumonia, aseptic necrosis of a tumor or silcoma, and secondary infection and emphysematous bulla or cyst (Mitchell '89: 101, 102).

Regardless of the organisms originally identified in the sputum. Penicillin by mouth and corticosteroids by mouth or nebulizer may be effective in simple lung abscesses. Inpatient treatment of lung abscess, especially the putrid variety, should be 2 to 6 million U crystalline penicillin G intravenously daily; 600,000 U procaine penicillin G intramuscularly every 6 hours for 4 weeks may be sufficient in milder cases. In the presence of serious penicillin hypersensitivity, clindamycin 600 mg 4 times daily, lincomycin 600 mg intramuscularly every 6 hours, or erythromycin 2 gm/day may also be used. Some observers are in favor of adding streptomycin 1 gm intramuscularly daily for at least the first 7 to 10 days, or tetracycline 2 gm daily to 3 to 5 days, then 1 gm daily. If *Staphylococcus aureus* is found and believed to be a causative agent, intravenous methicillin, or an equivalent drug such as nafcillin, 8 to 16 gm daily,

if penicillin resistant. Vancomycin, 500 mg intravenously every 6 hours is an effective anti-staphylococcus drug but has significant toxicity, resistance and probably should seldom be used. Antimicrobial treatment should be continued for at least 2 to 3 months, sometimes even longer. Oral doxycycline 100 mg the once a day antibiotic, for the treatment of methicillin resistant *S. aureus* (MRSA), seems more ideal. If *Klebsiella* organisms are found and are the causative agent, the initial therapy should include kanamycin, 15 mg/kg/day intramuscularly in 2 or 3 divided doses, the total dose being decreased if renal insufficiency is present or appears. Antibiotics susceptibility studies may allow the use of a less toxic antibiotic than either kanamycin or trimethoprim-sulfamethoxazole. Metronidazole (Flagyl ER) is a safe alternative but clinical trials are needed for the FDA to indicate its use in *Klebsiella*. When *Pseudomonas* is clearly the causative organisms, gentamycin or tobramycin should be used. Penicillin is used for most *Bacteroides* infections that are causally related to lung abscesses, although penicillin-resistant *Bacteroides* have been identified in this setting and may require tetracycline, clindamycin or chloramphenicol (Mitchell '89: 102, 103). Metronidazole (Flagyl ER) is indicated for the treatment of *Bacteroides* spp. (e.g. *B. fragilis*) and is highly effective at curing ulcerative diseases.

Bronchoscopy may be helpful in removing any foreign matter that may be obstructing the bronchus, and apply suction to the orifice of the bronchus leading to the involved area of the lung in hope of initiating or improving drainage of the abscess contents. Lung abscess may often be prevented by following certain practices. Tonsillectomy, tooth extraction, and paranasal sinus operations should be performed under local rather than general anesthesia and under penicillin or other appropriate antibiotic coverage, especially in overtly infected cases. Foreign material should be promptly removed by bronchoscopy; empiric therapy with corticosteroids and penicillin should be instituted. Prompt and appropriate anti-microbial management of acute bacterial pneumonias or any severe infections that could lead to a bacteremia, and the maintenance of good oral hygiene should reduce the risk of lung abscess. The complication of lung abscess include pleural effusion; empyema; blood-stream dissemination, especially to the brain; fatal pulmonary hemorrhage, and, after a period of continued suppuration, the development of localized bronchiectasis, recurrent pneumonia in the surrounding lung and amyloidosis. The prognosis of lung abscess has improved in recent years, but a 15% to 20% mortality occurs in single lung abscess and a 50% mortality occurs with multiple hematogenous abscess (Mitchell '89: 103-105).

III.A.6 Non-tubercular and Tubercular Mycobacterial Disease

March 24 marks the anniversary of the discovery in 1882 by German microbiologist Robert Koch of the bacterium that causes **tuberculosis** (TB) *Mycobacterium tuberculosis*. In 1946, the drug streptomycin became the leading chemotherapy prescribed for pulmonary disease, and then, by the mid 1950s, physicians also began to prescribe isoniazid to treat tubercle bacillus. Large portions of the old Fort Bayard Military Reservation were turned over to the United States Forest Service in 1956. They now are incorporated into the Gila National Forest. By 1965, the need, in the United States, for the high elevation-dry climate tuberculosis facility since 1899, lay several decades in the past, under 24USC§19. For nine months of chemotherapy, the combination of INH and rifampin will result in roughly 95% cure rates. Therapy with INH, rifampin and ethambutol is recommended to avoid the complication of drug resistance. The addition of pyrazinamide to INH and rifampin accelerates the rate of resolution of the disease, allowing reduction of therapy to 6 months' duration. However, side-effects and toxic reactions increase modestly with the addition of pyrazinamide (Iseman '89: 97-100).

Tuberculosis is a chronic infectious disease that involves a protracted or lifelong relationship between the tubercle bacillus, *Mycobacterium tuberculosis*, and the host. Many individuals are infected with this organism yet relatively few develop overt disease, factors include the size of the infecting inoculum, hereditary and acquired immunologic elements. Mycobacterium tuberculosis is an obligate aerobic bacillus. Mycobacteria are non-motile, non-sporulating, rod-shaped organisms that are most notable for their staining properties. Because of the high lipid content of the cell wall, the organisms are relatively resistant to staining with conventional dyes. However, once a dye impregnates the cell wall, the organisms are quite resistant to decolorizing with a potent agent such as acid alcohol. Hence, the organisms are known as acid-fast bacilli. A number of mycobacterial species other than *M. tuberculosis* are known to be pathogenic or saprophytic in humans. A distinguishable feature of *M. tuberculosis* is its ability to elaborate substantial amounts of niacin when growing (niacin positive). Virtually all strains of *M. tuberculosis* are niacin positive, whereas other mycobacteria are not. The nearly exclusive mode of infection with M. tuberculosis is person-to-person spread via aerosolized respiratory secretions. Large particles rapidly fall out of the air, but the smaller droplets remain in the air long enough for evaporation to occur, leaving the "droplet nucleus". Because of their low inertial mass, these small particles (3 to 5 μm) behave like a gas, and when inhaled do not impact on the mucociliary blanket of the conducting airways but are carried out to the distal air spaces where the slowly replicating mycobacteria remain long enough to produce sufficient numbers of organisms to result in infection and disease. There are no known reservoirs of *M. tuberculosis* other than infected humans. The untreated, coughing patient infects others with his or her aerosolized secretions, and fomites such as clothing, bedsheets, or eating utensils of disease patients are not responsible for any measurable number of infections. The disease may rarely be transmitted by means of infected urine or discharges from superficial infected lesions Once the tubercle bacilli reach the air spaces of the previously infected host, they begin to replicate and are soon engulfed but not killed by alveolar macrophages The organisms are carried within the macrophages to regional lymph nodes and then to the bloodstream where hematogenous dissemination typically occurs During this period of replication and dissemination, delayed hypersensitivity and cellularly mediated immunity to various constituents of the mycobacteria develop. With the development of cell-mediated immunity most subjects control their infection. A granulomatous response ensues at the various sites of infection with killing or inhibition of mycobacteria within the macrophages. Thus more than 95% of newly infected individuals "heal" their primary infection. A small number of individuals, including children under 6, fail to limit initial infection and develop progressive primary disease. Approximately 5% of those recently infected will develop overt tuberculosis within 2 years. After the first 2 years following infection the rate of reactivation falls to the range of 0.1% to 1% per year. Some health professionals believe that once an individual has been infected with the tubercle bacillus, virtually all subsequent tubercular disease is caused by endogenous reactivation. However, data based on viral phage-typing of tubercle bacilli suggest that exogenous reinfection may occur, albeit infrequently. The current recommendation is for INH preventive therapy (Iseman '89: 92, 93).

In 1989 ten drugs were used for the treatment of tuberculosis in the United States. The four most important drugs in contemporary chemotherapy are isoniazid (INH), rifampin, pyrazinamide, and ethambutol. Multiple studies confirm that 6 to 9 month short course of multiple drug chemotherapy may be regarded as adequate curative chemotherapy in virtually every patient with drug-susceptible tuberculosis. For nine months of chemotherapy, the combination of INH and rifampin will result in roughly 95% cure rates. Therapy with INH, rifampin and ethambutol is recommended to avoid the complication of drug resistance. The addition of pyrazinamide to

INH and rifampin accelerates the rate of resolution of the disease, allowing reduction of therapy to 6 months' duration. However, side-effects and toxic reactions increase modestly with the addition of pyrazinamide. Side effects from antituberculosis medications are uncommon and usually minor. INH produces disturbances in the liver function of 10% to 20% of patients. Serious hepatitis requiring termination of INH occurs in 1% to 3% of patients. In patients with marginal nutritional status, caution may lead one to include 30 mg of pyridoxine (vitamin B_6) per day. Other uncommon reactions to INH include arthralgias, arthritis, a mild influenza like syndrome and the variable appearance of lupus-like syndrome associated with positive antinuclear antibody reactions. Such reactions are usually reverse on termination of the drug. Rifampin commonly produces a side-effect of red staining of the urine, tears, and other secretions. Hepatitis has been reported in 1% to 3% of patients receiving rifampin. When given erratically, rifampin can induce a pronounced flulike syndrome, thrombocytopenia and acute interstitial nephritis resulting in impaired renal function. Ethambutol is the best tolerated of the tuberculosis medications. The only significant toxic effects of ethambutol is retrobulbar neuritis. When the drug is given at 15 mg/kg ocular disturbances occur rarely. The usual daily dose of pyrazinamide is 30 to 35 mg/kg in split dosages. A common complication of pyrazinamide is elevated levels of uric acid and up to 35% of these patients experience arthralgias and frank gouty arthritis. For the milder manifestations of hyperuricemia low-dose aspirin may reverse this biochemical disturbance and alleviate the symptoms. Noncompliance can lead to the appearance of drug-resistant organisms if the patient takes the medication in suboptimal dosage or in an erratic fashion. Trials strongly support the use of 6 or 9 months' treatment in these patients. Only patients who are significantly immunosuppressed and have disseminated disease now need extended therapy. The only significant route of tuberculosis infection is person to person. One of the responsibilities caring for a patient with pulmonary tuberculosis is to ensure that a **contact investigation** has been performed to determine evidence of recent infection among the patient's home, work, or leisure contacts to administer INH preventive therapy by employing skin tests and other epidemiologic observations. **INH preventive therapy** is the keystone of tuberculosis control during contact investigation. The initial recommendation for INH preventive therapy required 12 months of INH, 300 mg orally per day. European studies however indicate the length of time may be reduced without loss of efficacy. In general if the source patient is being treated for 6 or 9 months for tuberculosis, it is also suitable to treat the patient's contacts with an equal duration of INH preventive therapy (Iseman '89: 97-100).

In 2013, thousands of years after the first human cases of TB were recorded and more than a century after Koch isolated the rod-shaped microbe that causes TB, this disease remains entrenched in many countries around the world. TB bacteria are now thought to infect 1 out of every 3 people worldwide -- more than 2 billion in all. Although most of those individuals do not become sick, the World Health Organization (WHO) estimates that in 2011, approximately 8.7 million people fell ill with TB, and 1.4 million people died from the disease. The overwhelming majority of cases and deaths are among poor and vulnerable people living in low- and middle-income countries. By the 1970s, annual TB cases had fallen sharply in the developed world, beginning two decades earlier after the introduction of effective antibiotics: first streptomycin, then isoniazid, and later rifampin and other medications. Then in the 1980s HIV/AIDS emerged, and TB re-emerged along with it as an AIDS-related opportunistic infection. In the United States, for example, TB cases swelled in New York City in the late 1980s, and the evolution of drug-resistant TB strains increased insidiously. Concerted action by public health officials, at a cost of approximately $1 billion, eventually brought the New York City TB epidemic under control. Subsequently, new international health programs such as the President's Emergency Plan for AIDS Relief and the Global Fund to Fight AIDS, Tuberculosis, and Malaria, helped to reveal

more clearly the health challenges in the developing world. In particular, they showed us the deadly synergy between HIV/AIDS and TB (1 in 4 HIV-related deaths is caused by TB), as well as the increasing problem of TB drug resistance. As a result of aggressive TB control programs, 51 million people with TB were successfully treated and 20 million lives were saved between 1995 and 2011, according to the WHO. New cases of TB have been falling steadily since 2006, and in 2011, they declined by 2.2 percent. the interaction between drugs used to treat TB and those used to treat HIV are complex and makes treating both diseases simultaneously difficult. In addition, active TB enhances HIV replication in the body, and HIV weakens the body's defenses against TB. It is also apparent that the spread of multidrug resistant (MDR) as well as extensively drug resistant (XDR) TB is complicating our efforts to curtail the TB pandemic. The detection of MDR-TB cases is a slow process, and access to appropriate treatment is limited; and at last count, XDR TB has been identified in at least 84 countries (Fauci '13). In the United States tuberculosis patients receive subsidized treatment from their public health department at first world rates which subsidize TB treatment in developing countries.

In December 2010, the WHO endorsed the **GeneXpert TB diagnostic**. This new diagnostic test can detect active TB bacteria in sputum samples and the presence of drug resistance in two hours, much more quickly than the one month or longer required for standard sputum tests. By the end of 2012, according to the WHO, almost 1,000 GeneXpert instruments and nearly 2 million associated testing cartridges had been distributed at a reduced price in 77 countries. In the area of TB treatment, current TB drug regimens are notoriously long in duration and complicated, and some drugs have severe side effects. Moreover, drug development lags behind the emergence of drug resistance. Encouragingly, however, the TB drug "pipeline" has more candidates than ever before and includes several new classes of drugs. Late last year, bedaquiline was the first new drug specifically developed for the treatment of TB that was approved by the Food and Drug Administration in nearly 40 years. It is designed to be used as a part of a combination treatment regimen for patients with MDR TB who do not respond to first-line regimens. On the vaccine front, lack of efficacy was seen in a clinical trial in Africa of a candidate vaccine known as MVA85A given to infants who had already received the licensed TB vaccine, BCG. Although the results were not as hoped, this was the first large-scale test of a new TB vaccine in more than 90 years, proving that such large studies are feasible (Fauci '13).

While tuberculosis may effect any group in modern society, there are certain segments that have disproportionate amount of disease. Elderly patients, Hispanics and nonwhites, and substance abusers have a significantly higher prevalence of tuberculosis. A century ago tuberculosis was epidemic. Elderly patients (50 years of age or older) now constitute nearly half of the newly diagnosed cases of tuberculosis in the United States due to resurgence of latent infections. Individuals infected with HIV are at considerable risk for tuberculosis. The clinical manifestations of tuberculosis are diverse, many patients have chronic constitutional complaints such as fatigue, anorexia, low-grade fever (typically in the afternoon or evening), night sweats and weight loss. The prototypic symptoms associated with pulmonary tuberculosis are productive cough, occasionally hemoptysis, chest pain and dyspnea. Some have a chronic cough. The chest radiograph for an adult with pulmonary tuberculosis is fibronodular infiltration of the posterior or apical segments of the upper lobe, right more commonly than left, with patchy areas of fluffy confluency and irregular areas of cavitation of lucency. The majority of patients control the organisms have been disseminated and never develop overt disease. However some individuals will manifest extra-pulmonary disease commonly including lymphadenitis; pleural disease; genitourinary disease; spinal and other osseous forms of the disease. Miliary, meningeal, pericardial, peritoneal, ocular, otic, laryngeal or cutaneous disorders are seen less

frequently. A normal chest radiograph finding does not allow the exclusion of disseminated tuberculosis when clinical findings prompt suspicion (Iseman '89: 93-95).

The purified protein derivative (PPD) intradermal tuberculin (Mantoux) skin test is regarded as a valuable tool to diagnose tuberculosis and to exclude the disease. Older literature indicates that over 95% of patients with tuberculosis were skin-test positive. Yet new literature indicates that 15% to 25% of newly diagnosed patients with pulmonary tuberculosis have nonsignificant or negative (9 mm or less induration) findings of tuberculin skin tests using PPD 5 Tuberculin Unit (TU) skin tests. Although a positive tuberculin skin test may suggest the presence of mycobacterial infection, a negative result of tuberculin skin test does not exclude tuberculosis. The use of the second strength or 250 TU skin test may detect tubercle bacilli in certain patients who are infected and do not react to the 5 TU skin test. However, the 250 TU may not differentiate from non-tuberculous mycobacteria. The most critical test in the diagnosis of pulmonary tuberculosis is the bacteriologic study of the respiratory secretions. Staining of the sputum using the acid-fast technique (Ziehl-Neelsen or Kinyoun) or the fluorochrome technique (Auramine O) is a quick method of detecting mycobacteria. Sputum smears may range from negative to strongly positive. Patients with cavitary shadows on the radiograph commonly shed large numbers of bacilli and are positive on sputum smear studies. However, patients with fairly extensive noncavitary shadowing may have multiple negative sputum smear results. Mycobacteria, including tubercle bacilli, grow slowly on culture media, becoming visible only after 3 to 6 weeks of incubation. The rapid radiometric culture technique (Bactec) is used in some laboratories to expedite isolation and identification of mycobacteria, although expensive results can be achieved in 7 to 10 days (Iseman '89: 95, 96).

Mycobacteria other than *Mycobacterium tuberculosis* have been found in increasing numbers of cases in the United States over the past several decades. **Non-tuberculous mycobacteria** (NTM), unlike *M. tuberculosis* (TB) are found in the environment. Today there are probably more cases of NTM than TB. Mycobacteria are a group of rod-shaped bacteria that share a number of unusual characteristics, most notably their staining characteristics, their slow replication time in roughly 24 hours in contrast to streptococci, which replicate every 15 to 20 minutes. Used for the past 50 years, the **Ziehl-Neelsen stain method** is the standard technique for impregnating the microbes with red, dye with a blue counterstain under x 100 magnification oil-immersion lens, by laboratory convention, up to 15 minutes per slide must be allocated to designate a smear as "negative". A newer more efficient technique, the **fluorochrome** (FC) method whereby the microbes are impregnated with auramine-rhodamine dyes that fluoresce when excited by specific wavelengths of light. The increased contrast makes it possible to read the slide under x 40 magnification. Since there are occasional false positives an acid-fast smear is used to confirm a positive FC smear. To maximize diagnostic yield of **sputum studies** for mycobacteria, most laboratories in North America mix a digesting proteolytic substance (N-acetyl cysteine) and a decontaminating compound (dilute sodium hydroxide) to the sputum, which is then agitated, allowed to stand, and spun down. Processed sputum can be grown on a variety of media. Two solid media, Oowenstein-Jensen and Middlebrook agar, have been used for decades. Recently liquid medium (Bactec) has been used. This system uses a carbohydrate substrate with tagged carbon (^{14}C). The system is capable of recognizing mycobacterial growth distinguishing *M. tuberculosis* complex from non-tuberculous mycobacteria and performing susceptibility studies with the first line anti-tuberculosis drugs (Iseman '89: 85, 86).

During 1981 to 1983 the prevalence of NTM in the United States was 1.78 cases per 100,000. The most common pathogens were *Mycobacterium avium complex* (MAC) (1.3 cases),

Mycobacterium kansasii (0.29 cases) and *Mycoacterium fortuitum-chelonae* (0.19 cases). The great preponderance of NTM cases were pulmonary. Unlike TB reports of NTM are not mandatory. Unlike M. tuberculosis, for which the only significant reservoir is infected humans, the NTM are widely distributed in nature. MAC is found in dust, soil, water and a variety of animals and fowl and the mode of transmission to pulmonary patients is by inhalation of organisms for the ambient air. MAC causes hot tub lung disease in indoor spas because the mycobacteria is killed by sunlight. Near the ocean these organisms may enter the air via aerosols generated by water breaking on the beaches. Among AIDS patients with disseminated MAC disease, the portal of entry tends to be waterborne organisms in the alimentary canal. Surveys have not discovered natural reservoirs of *M. kansasii* and it is presumed to survive on human to human transmission particularly in younger people. *M. fortuitum* and *M. chelonae* are not only found in the environment but also have produce nosocomial disease associated with contamination of medical and surgical equipment due to airborne infection or aspirated with esophageal contents in intubated patients. The clinical picture of pulmonary disease due to NT is essentially indistinguishable from that of *M. tuberculosis*. The critical question is whether an NTM is an invasive pathogen or merely a saprophyte. Clinicians estimate that 25% of isolates of *M. kansassi* represent colonization and that over 50% of MAC isolates reflect such colonization. NTM are considerably more resistant to drugs than *M. tuberculosis* (Iseman '89: 88, 89).

Various combinations of traditional "anti-TB" drugs are used against most of the NTM. For the usual case of pulmonary disease from *M. avium complex*, an initial regime of isoniazid (INH), rifampin (RIF), and ethambutol (EMB) supplemented by an initial two months of streptomycin (SM) is the standard regimen. If the disease is rapidly progressive or the patient does not respond to initial treatment, the regimen should be intensified according to drug sensitivity studies. Agents most likely to be active include ethionamide and cycloserine. Noteworthy is the lack of activity of pyrazinamide, a powerful agent against *M. tuberculosis*. The usual patient with pulmonary MAC disease receives treatment for 24 months. For the initial treatment of pulmonary disease, a regimen of INH, RIF and EM is given for 15 months. There is commonly partial drug resistance, usually to INH, this does not interfere with the response to this treatment, for which success rates are in the range of 95%. However, acquired resistance associated with ineffective or erratic pretreatment may predict failure to respond, of particular concern is resistance to RIF. Not treatment has proven effective against pulmonary disease caused by *M. fortuitum-chelonae*. Most isolates are susceptible in vitro to cefoxitin and amikacin (or kanamycin). These parenteral agents may result in substantial improvement when given for prolonged periods. The aminoglycoside antibiotic can rarely be used in full dosage beyond 3 to 4 months because of auditory, vestibular or renal toxicity, and most patients relapse. Most strains of *M. chelonae* are very resistant to the oral drugs that have been studied. However, many *M. fortuitum* isolates are susceptible to drugs such as doxycycline, minocycline, erythromycin, sulfamethoxazole, trimethoprim-sulfamethoxazole, or one of the fluoroquinolones such as ciprofloxacin. Hence, for a patient with symptomatic, progressive disease resulting from M. fortuitum, an initial intensive phase of parenteral medication followed by a long-term course of oral antimicrobials offers the best chance of effecting a cure or long-term remission. Agents should be chosen on the basis of *in vitro* studies. An empirical regimen of INH, RIF, EMB and SM may be employed for mycobacteria that are slow growing (Iseman '89: 90, 91)

III.A.7 Fungal Infection

Fungal infections are environmental not contagious. Mold allergies may get worse from spring to late fall, but the first freeze doesn't end the problem with molds as it does with pollen. Molds

are tenacious little fungi that are able to grow at subfreezing temperatures. Even snow, while lowering the outdoor mold count dramatically, doesn't kill mold spores. Only a few molds get the allergen label. In general, *Alternaria* and *Cladosporium* (Hormodendrum) are the allergenic molds most commonly found indoors and outdoors throughout the United States. *Aspergillus*, *Penicillium*, *Helminthosporium*, *Epicoccum*, *Fuarium*, *Mucor*, *Rhizopus*, and *Aureobasidium* (*Pullularia*) are also common allergy triggers (Berger '04: 39, 41, 44). In the normal population three major fungi cause invasive, systemic infection. These are *Coccidioides immitis*, *Histoplasma capsulatum* and *Blastomyces dermatitidis*, each having its own geographic area of distribution and each residing in the soil from whence it becomes airborne and is inhaled into the respiratory tract. A fourth and less frequent systemic mycosis is sporotrichosis, a disease that enters through the skin and lymphatic system and has a wider geographic distribution. The three major fungi are dimorphic, existing in nature in a mycelial form with hyphae that bear spores, which are the infectious agents in humans, and in a yeast form in human tissue after infection is established. Human-to-human transmission is virtually unknown. Amphotericin B continues to be the antifungal of choice in spite of claims that newer agents are effective and less toxic. Small epidemics of mycotic infection can usually be traced to a point source of infected soil that has been disturbed by ever increasing numbers of people impacting the endemic areas (Bindschadler '89: 106). $1 hydrocortisone crème works to eliminate fungal colonization of parts of the anatomy not treated by athlete's foot crème. Corticosteroid nasal sprays and inhalers are highly effective at curing respiratory molds.

A team led by the National Human Genome Research Institute in Bethesda, Maryland, sequenced the DNA of fungi living on the skin at 14 different body areas in 10 healthy adults. Samples were taken from the ear canal, between the eyebrows, the back of the head, behind the ear, the heel, toenails, between the toes, forearm, back, groin, nostrils, chest, palm, and the crook of the elbow. The data reveal that fungal richness varies across the body. The most complex fungal habitat is the heel, home to about 80 types of fungi. The researchers found about 60 types in toenail clippings and 40 types in swabs between the toes. Other favored fungal hotspots include the palm, forearm and inside the elbow. These had moderate levels of fungi, with each location supporting 18 to 32 types. In contrast, the head and the trunk harbored fewer varieties of fungi - just two to 10 each. The bottom line is that the feet are teeming with fungal diversity, so wear flip flops in locker rooms to avoid mixing foot fungi with someone else's fungi. In 20% of volunteers, the researchers observed problems consistent with fungal infections. An imbalance of microbes may provide an opportunity for harmful microbes to flourish and establish disease. Fungi normally co-exist quite happily on the body without causing any harm, except in people with poor immune systems (Findlay et al '13).

Diagnosis and Treatment of Fungal Infections

Fungal Infection	Symptoms	Medication
Coccidioides immitis	Desert fever, valley fever, desert rheumatism, or "the bumps" is endemic to ecologic areas known as lower Sonoran life zone, characterized by an arid to semiarid climate with hot summers, few winter freezes, sparse flora, alkaline soil, and	A total dose of 30 mg/kg of amphotericin is recommended for treatment of progressive or persistent pulmonary disease. Ketoconazole 400 to 800 mg/day are used for non-meningeal infection and 800 to 1200 mg/day for disseminated infections with meningitis.

	low altitudes, such as the southwestern United States and northern Mexico. In some areas, more than 80% of the native population reacts to coccidioidin skin testing.	Miconazole.
Histoplasma capsulatum	The Ohio and Mississippi River valleys are the most heavily contaminated regions in the United States, although distribution of the organism is worldwide. Infection results from the inhalation of spores from an environmental source and leads to several clinical states.	A total dose of 500 to 1000 mg of amphotericin B is used to treat severe primary infections, and 2 to 2.5 gm is used to treat all symptomatic disseminated infection. Ketoconazole 400 to 800 mg/day are used for non-meningeal infection and 800 to 1200 mg/day for disseminated infections with meningitis.
Blastomyces dermatitidis	Endemic disease of he southeastern and south central United States, which also extends up the Mississippi and Ohio River valleys into the north central United States and Canada.	A total dose of 2 to 2.5 gm of amphotericin B over 60 to 90 days is the treatment of choice for severe, life-threatening meningeal disease. 400 to 800 mg of ketoconazole per day for 6 months is effective for less serious situations.
Aspergillus fumigatus, *A. flavus*, *A. niger* and others	Allergic aspergillosis, invasive or disseminated infection or fungus ball (or mycetoma). Fungus ball may develop in the setting of allergic bronchopulmonary or invasive disease and release highly carcinogenic aflotoxin. Common signs and symptoms are repeated attacks of wheezing with fever, evanescent pulmonary infiltrates, bronchial plugging, repeated isolation of *Aspergillus* from sputum, eosinophilia, and positive skin test results to *Aspergillus* antigen.	A total dose of 500 to 1000 mg of amphotericin B is used to treat severe primary infections. Oral sporanox (itraconazole) is reported to be effective. $1 hydrocortisone often works.
Candida (C. albicans)	Thrush, vaginal yeast infection, gastroenteritis, possible cause of squamous cell carcinoma	2 to 3 mg of amphotericin B, sporanox (itracondazole). Micronazole. Ketoconazole 400 to 800 mg/day are used for non-meningeal infection

		and 800 to 1200 mg/day for disseminated infections with meningitis.
Cryptococcus neoformans	Isolated from the excreta of pigeons and other birds.	2 to 3 mg of amphotericin B, miconazole. Ketoconazole 400 to 800 mg/day are used for non-meningeal infection and 800 to 1200 mg/day for disseminated infections with meningitis.
Actinomyces, *Nocardia*, *Streptomyces*, or *Staphylococcus* organisms.		Intravenous penicillin G, 10 to 20 mU daily for 4 to 6 weeks, followed by oral phenoxymethyl penicillin, 2 to 4 gm daily for 6 o 12 months, cures most severe infections; Penicillin hypersensitivity or occasional failures to respond to treatment require alternative antibiotics such as tetracycline or clindamycin.

Source:(Bindschadler '89: 107-117).

Coccidioides immitis, the organism responsible for the disease known as desert fever, valley fever, desert rheumatism, or "the bumps" is endemic to ecologic areas known as lower Sonoran life zone, characterized by an arid to semiarid climate with hot summers, few winter freezes, sparse flora, alkaline soil, and low altitudes, such as the southwestern United States and northern Mexico. In some areas, more than 80% of the native population reacts to coccidioidin skin testing. Of those infected, 60% are clinically asymptomatic; 40% give a history of a flulike illness with cough, fever, pleuritic chest pain, weakness, malaise, myalgia, and arthralgia 1 to 3 weeks after exposure. Subsidence of symptoms over the next 2 to 4 weeks is usual. The chest radiograph during the initial infection reveals small to large scattered areas of infiltrates, often subpleural in location, and hilar adenopathy with or without evidence of pleural involvement. Less than 1% of patients with coccidioidomycosis develop disseminated disease. Mycelial phase antigen, coccidioidin, is the standard reagent for skin testing, but the newer parasitic phase reagent, Spherulin, is just as specific and more sensitive. Skin tests are positive in almost every symptomatic patient by the end of the third week of illness. The inhalation of arthrospores that are highly chemotactic for polymorphonucleocytes (PMN) is followed by an outpouring of those cells with subsequent destruction of arthrospores and the formation of microabscesses. Arthospores that escape destruction begin to form ever enlarging spherules that may contain 10^5 endospores before spontaneous rupture, leading to another cycle of spherule production. Diagnosis can be made by identifying spherules in potassium hydroxide preparations of infectious material, by culturing the fungus from sputum, purulent drainage, or cerebrospinal fluid, or by detecting the organism in histologic section. During the mycelial phase, the organism grows on artificial media, producing highly infectious arthrospores that pose a hazard to laboratory personnel. A total dose of 30 mg/kg of amphotericin is recommended for treatment of progressive or persistent pulmonary disease. Disseminated disease with meningitis required both intrathecal and intravenous therapy for prolonged periods and total doses as high as 10 gm of intravenous amphotericin B. Ketoconazole given orally in doses of 800 to 1200 mg per day

for several months have been shown to be helpful as an adjunct in the treatment of chronic cocci meningitis. Miconazole and transfer factor appear to offer limited help as alternatives or adjuncts to amphotericin B. Surgical removal is necessary for enlarging cavities, that, despite chemotherapy cause recurrent or severe hemoptysis or spread of infection to the pleura. An umbrella of amphotericin B to a total dose of 500 to 1000 mg given before and after surgery is part of the therapeutic approach in these situations (Bindschadler '89: 107, 108).

The dimorphic fungus *Blastomyces dermatitidis* causes blastomycosis, an endemic disease of he southeastern and south central United States, which also extends up the Mississippi and Ohio River valleys into the north central United States and Canada. Men who spend much time outdoors aged 15 to 50 are most likely to become infected. The habitat of B. *dermadititis* is moist soil with an acid pH that has been contaminated with animal excreta. If the conidia of the fungus are inhaled and deposited in the peripheral air spaces of the lower lobes, primary infection can result after a 6 week incubation and may develop pulmonary symptoms. Active infection usually causes a diffuse, patchy lower-love alveolar infiltrate that can be unilateral or bilateral, with hilar adenopathy, usually sparing the pleurae and resolving within 8 to 12 weeks. Systemic symptoms include weight loss, productive cough, hemoptysis, fever, night sweats, and shortness of breath predominate in the chronic stage. Occasionally a mass lesion is mistaken for carcinoma. A careful search of skin for lesions and ulcers should be sought for biopsy and culture. Spheroid cells that are thick walled, 1 or 2 times the size of a red blood cell, with a refractile double-contour and unipolar body are characteristic and usually numerous enough to enable identification. Cultures should be watched for 30 days using Sabouraud's agar at 30°C. Other methods of testing are not reliable. A total dose of 2 to 2.5 gm of amphotericin B over 60 to 90 days is the treatment of choice for severe, life-threatening meningeal disease. 400 to 800 mg of ketoconazole per day for 6 months is effective for less serious situations (Bindschadler '89: 108, 109).

People who inhale the spores of *Histoplasma capsulatum* generally do not develop symptoms. The saprophytic form of the fungus is found in the soil of chicken houses, in caves where bats reside, and in the droppings from starlings and blackbirds. The Ohio and Mississippi River valleys are the most heavily contaminated regions in the United States, although distribution of the organism is worldwide. Infection results from the inhalation of spores from an environmental source and leads to several clinical states. In asymptomatic infection, multiple parenchymal or hilar calcifications may be found in the chest radiograph. Acute symptomatic infection may mimic a viral upper respiratory tract infection with low-grade fever, generalized somatic symptoms, and dry cough that lasts from a few days to a few weeks. Soft, scattered pulmonary infiltrates plus hilar and mediastinal lymphadenopathy are characteristic and usually resolve without residual structural damage. A severe confluent pneumonia that persists for 2 to 3 months or acute respiratory distress syndrome and death may follow inhalation of a large number of organisms from a heavily contaminated source. Progressive destruction of lung tissue and loss of pulmonary function is due to the continuing mycotic infection. Treatment with amphotericin B appears to slow the progression of chronic cavitary disease, but it does not significantly improve lung function. Immune disturbance diseases, such as leukemia, lymphoproliferative syndromes and AIDS predispose patients to histoplasmosis. Adrenal insufficiency is found in half of the instances of disseminated disease. Histoplasmomas are healed primary pulmonary or lymph node foci of infection. Typically they have a fibrotic capsule and a caseous center that contains a calcified nodule. They often increase in size form less than 1 to 4 cm over a 10-year to 25-year period. Distinguishing them from neoplasia may be difficult. The diagnosis of histoplasmosis must be made by isolation of the organism in culture

or histologic specimen. Sputum, blood and urine are reliable. Skin testing with histoplasmin, an antigenic preparation made from a culture filtrate of the mycelia, is useful as an epidemiologic tool but does not have good clinical reliability. A total dose of 500 to 1000 mg of amphotericin B is used to treat severe primary infections, and 2 to 2.5 gm is used to treat all symptomatic disseminated infection. Ketoconazole has been used in the treatment of disseminated histoplasmosis; its role is yet to be fully defined, but it is probably adjunctive to amphotericin B. **Sporotrichosis** is generally a lymphocutaneous disease that results from subcutaneous inoculation with the ubiquitous organism *Sporothrix schenckii* that is found in rose and barberry thorns, splinters of rotten wood, some soils and sphagnum moss. Occasionally the spores are inhaled and cause upper-lobe involvement with nodules, fibrosis and cavitation similar to tuberculosis, cocci and histoplasmosis. The organism is best identified by culture. Iodides are quite effective at treating the cutaneous and lymphatic forms of the infection, amphotericin B is required to treat the pulmonary and disseminated forms. Rarely, even extensive pulmonary disease may resolve spontaneously without any fungal therapy (Bindschadler '89: 109-111).

Aspergillosis is caused by species of the ubiquitous mold *Aspergillus*. Infections caused by *Aspergillus fumigatus*, *A. flavus*, *A. niger* and others result in allergic aspergillosis, invasive or disseminated infection or fungus ball (or mycetoma). Fungus ball may develop in the setting of allergic bronchopulmonary or invasive disease. Bronchopulmonary aspergillosis is frequently a progressive disease with IgE-mediated asthma and IgG-mediated type III parenchymal reactions. Common signs and symptoms are repeated attacks of wheezing with fever, evanescent pulmonary infiltrates, bronchial plugging, repeated isolation of *Aspergillus* from sputum, eosinophilia, and positive skin test results to *Aspergillus* antigen. Serum IgG antibody levels to *Aspergillus* organisms and total serum IgE are elevated. Central saccular bronchiectasis can often be identified in the middle-lung or upper-lung fields in chest radiographs. Patients expectorate brown sputum plugs that contain the organisms. Long-term therapy with oral corticosteroids plus standard antiasthma regiments are often required to control the disease process. Colonization of the tracheobronchial tree with concentric rings of hyphae and surrounding fibrosing granulomatous inflammation or chonic nonspecific inflammatory elements occur in patients with chronic obstructive pulmonary disease. Periodic acid-schiff or silver stains are used to demonstrate *Aspergillus* hyphae in histologic sections. Since symptoms in invasive aspergillosis are usually related to the point of entry and since 90% or more begin in the lungs, fever, chills, shortness of breath, non-productive cough, and pleuritic pain are commonly noted. Hemorrhagic infarction or necrotizing bronchopneumonia are noted. Life-threatening hemoptysis is a major clinical presentation of mycetoma. Other complications include bacterial lung abscess, bronchopleural fistula with fungal empyema and spread of infection to thoracic vertebral bodies. The diagnosis of invasive disease is usually difficult because cultures only transiently yield positive results. *Aspergillus* organisms are a frequent laboratory contaminant and this further complicates the certainty of diagnosis. In immunocompromised situations, aggressive therapy with amphotericin B must be initiated. Systemic therapy with amphotericin B for fungus ball is of no value. Occasionally control of symptoms and reduction in the size of the fungus ball can be achieved by aerosol or insufflation of amphotericin B. Surgical excision is the treatment of choice; the major justification for resection is life-threatening hemorrhage, with a mortality of 5% to 10%. The outcome of surgical therapy usually depends on the degree of underlying lung disease (Bindschadler '89: 112-113). Hydrocortisone crème is often effective.

Candida species commonly colonize the tracheobronchial tree in healthy subjects and are easily identified in sputum smears and cultures. Rarely, primary *Candida* pneumonia occurs in an immunosuppressed host. It cannot be reliably diagnosed by sputum culture and requires lung

biopsy for confirmation. More commonly, *Candida* organisms invade the lung in conjunction with hematogenous dissemination and produce military micro-abscesses. Radiographic findings range from diffuse infiltrations to confluent areas suggestive of pulmonary edema. Allergic bonrchopulmonary disease and fungus balls have also been described rarely. A total dose of 2 to 3 mg of amphotericin B should be used to treat disseminated infection (Bindschadler '89: 113). **Cryptococcosis** is caused by *Cryptococcus neoformans*, a years that can be isolated from the excreta of pigeons and other birds. Although *Cryptococci* organisms in nature are largely unencapsulated, they rapidly form a polysaccharide capsule that protects them from attack by neutrophils and monocytes following their inhalation into the lung. Multiform pulmonary lesions can develop, ranging from an asymptomatic solitary nodule to nonspecific pulmonary infiltrates, and occasionally are associated with pleural effusion, cavitation and calcification. Cryptococcal pneumonia, as well as bronchial colonization, often occurs without subsequent spread to the central nervous system (CNS). Although most cases of pulmonary cryptococcosis resolve without specific therapy, some develop progressive pneumonic spread, whereas others remain clinically and radiographically stable for extended periods. Amphotericin B with or without flucytosine remains the treatment of choice for meningeal cryptococcosis. Modification of the dose of amphotericin B from 2 to 3 grams may be successful when one is dealing only with pulmonary cryptococcosis. Either perioperative flucytosine, ketoconazole, or miconazole may be used to prevent the 5% incidence of cryptococcal meningitis associated with resection of pulmonary lesions (Bindschadler '89: 113, 114).

Actinomycetes are gram-positive organisms that have a filamentous, branching hyphalike appearance that at one time led to their erroneous classification as fungi. Two genera, *Actinomyces* and *Nocardia* of the family *Actinomycetaceae*, cause human disease. *Actinomyces* are microaerophilic or anaerobic; *Nocardia* are aerobic and weakly acid-fast. Most human actinomycoses are caused by *Actinomyces israelii*, with pulmonary involvement resulting from aspiration of infected oral material. Suggestive radiographic findings include extension of pulmonary lesions through the chest wall, destruction of ribs or other adjacent bony structures, infiltrates that cross interlobar fissures, and vertebral erosion from posterior chest structures. Superior vena caval obstruction and tracheoesophageal fistula have been described. Sulfur granules are large aggregate masses of *Actinomyces* organisms that are uncommonly seen today, in part because of the widespread use of antibiotics in earlier stages of infection. Similar conglomerates are seen in other mycoses or with infections due to *Nocardia*, *Streptomyces*, or *Staphylococcus* organisms. Intravenous penicillin G, 10 to 20 mU daily for 4 to 6 weeks, followed by oral phenoxymethyl penicillin, 2 to 4 gm daily for 6 o 12 months, cures most severe infections. Penicillin hypersensitivity or occasional failures to respond to treatment require alternative antibiotics such as tetracycline or clindamycin. **Nocardia** species are soil-born, aerobic, partially acid-fast actinomycetes that enter the body through the respiratory tract. Most inections are opportunistic in patients with a predisposing condition such as lymphoreticular malignancy, long-term high-dose corticosteroid use, pulmonary alveolar proteinosis, bronchiectasis, Cushing's disease, or dysglobulinemia or in transplant recipients. Nocardia is unusual in AIDS. Bronchopneumonia that progresses rapidly to consolidation, multiple wide-spread cavities, and early pleural involvement are radiographic clues to nocardiosis. Dissemination occurs from the lung to the CNS, heart, pericardium, or retroperitoneal or subcutaneous structures. No skin tests work so bronchial brushing, direct percutaneous needle aspiration and bronchoscopy with transbronchial biopsy are used to establish the diagnosis. A sulfonamide, such as sulfisoxazole in a dosage of 6 to 9 gm daily (divided into doses given every 6 hours) to accomplish peak serum levels of 12 to 15 mg/dl is the treatment of choice. Once substantial improvement has been noted, oral therapy with 4 to 6 gm of the same drug may be

used. Treatment schedules often require 2 to 6 months for a cure, especially in patients receiving immunosuppressive therapy. Although trimethoprim-sulfamethoxazole is active against Nocardia organisms in vitro, it is not clear whether this combination is clinically better than a sulfonamide alone. Alternative therapy is 300 mg of minocycline every 12 hours, ampicillin and erythromycin combinations. Empyema requires surgical drainage, but lung abscess usually does not. 60% to 70% of patients with Nocardia organisms infections recover with appropriate treatment (Bindschadler '89: 115, 116).

Amphotericin B, a polyene antibiotic in use since 1958, remains the IV treatment of choice for all serious infections caused by systemic fungi. Unfortunately, it is fungistatic, and not fungicidal, deriving its therapeutic as well as its toxic effects from its affinity for sterols in cell membranes. Its affinity for ergosterol in fungal membranes is 500 times greater than its affinity for the major human cell membrane sterol, cholesterol. Damage to the cell membrane induced by this binding results in the leakage of necessary components and eventually cell death. As an amphoteric substance the antibiotic is highly insoluble and is available only as a colloidal suspension in buffer and deoxycholate. It is not absorbed from the gastrointestinal tract and must be given intravenously. It is prepared in sterile preservative-free water to a concentration of less than 0.1mg/ml, and then administered with a light protective wrapper around the bottle over a 4 to 6 hour period. The use of a butterfly needle for access and the administration of small amount sof added heparin (1,000 units) and hydrocortisone (25 mg) aid in the prevention of phlebitis. In the beginning a 1 mg test dose is given, followed by a daily increase of 5 to 10 mg, until a dose of 1 mg/kg/day is achieved, or toxicity occurs and alters the plan. An alternative is to increase the dose until 0.5/mg/kg/day is reach and then stick to that daily dose. Nephrotoxicity with the development of an active urinary sediment and progressive increase in blood urea nitrogen (BUN) and creatinine usually helps tailor the dose that can be given daily or every other day. It is often necessary to temporarily suspend treatment until the BUN is less than 50 µg/dl and the creatinine less than 3 µg/dl. For most systemic mycotic infections a total dose of 2 to 2.5 gm suffices. Irreversible nephrotoxicity almost always is noted with total doses in excess of 4 gm. Systemic reactions, hypokalemia and hematologic reactions make up tht emost common side effects besides renal dysfunction. Chills, fever, nausea, vomiting and hypotension occur frequently but can usually be managed orally by pretreatment with antipyretics, diphenhydramine, and occasionally by small doses of oral cortisone. Hypokalemia predictably develops with ongoing therapy and requires substantial replacement throughout most courses of amphotericin B. As alternatives or adjuncts to amphotericin B, two imidazole derivatives, ketoconazole and miconazole, have been approved for systemic fungal infection treatment. **Miconazole** is active against *Coccidioides immitis*, Cryptococcus neoformans, and Candida organisms. It must be administered intravenously and has side effects that include nausea and vomiting, phlebitis, hyponatremia and pruritis and should only be used in patients who fail to respond to amphotericin B. **Ketoconazole** is an oral preparation efficient against *Coccidiodes immitis*, *Cryptococcus neoformans*, *Candida* organisms, *Histoplasma capsulatum*, and *Blastomyces dermatitidis*. Absorption depends on an acid environment in the stomach, so it cannot be used in achlorhydria or in conjunction with bicarbonate, antacids, or H_2 blockers. Generally, doses of 400 to 800 mg/day are used for non-meningeal infection and 800 to 1200 mg/day for disseminated infections with meningitis. In 20% of patients, it cause significant nausea and vomiting and, in 1% to 2%, hepatic dysfunction (Bindschadler '89: 116, 117).

III.A.8 Acute respiratory failure, edema, atelectasis and distress

Acute respiratory failure (ARF) occurs in many clinical situations and constitutes a medical emergency requiring prompt and exacting assessment, supportive management and therapy directed at the underlying insult to the respiratory system. ARF may be defined as the sudden inability of the respiratory system and the heart to maintain adequate arterial oxygenation and adequate carbon dioxide elimination. ARF occurs when tissue oxygen transport and carbon dioxide elimination are impaired. Arterial blood gas analysis is most commonly utilized to determine the presence and severity of ARF. Arbitrarily, ARF is defined as the sudden development of an arterial PO_2 of less than 55 mg Hg with or without CO_2 retention. An acute elevation of carbon dioxide tension to more than 50 mm Hg is sometimes called "acute ventilator failure". The differentiation of hypoxemia from hypercapnia or so-called ventilation failure has important therapeutic implications. The pathophysiology of ARF involves impaired lung mechanics, failure of the respiratory muscles (the most vital pump) and respiratory center unresponsiveness. Two common and important clinical states often resulting in ARF are chronic obstructive pulmonary disease (COPD) and primary pulmonary edema resulting in the adult respiratory distress syndrome (ARDS). Disease states leading to respiratory failure are A Impaired ventilation: (1) chronic airflow obstruction: emphysema, chronic bronchitis, chronic asthma and cystic fibrosis; (2) restrictive defects: (a) decreased lung expansion: interstitial fibrosis, pleural effusion, pneumothorax, and fibrothorax; (b) limited thorax expansion: kyphoscoliosis, multiple rib fractures, thoracic surgery and ankylosing spondylitis; (c) decreased diaphragmatic movement: abdominal surgery, ascites, peritonitis, severe obesity, and diaphragmatic paralysis; (3) neuromuscular defects: Guillain-Barre syndrome, myasthenia gravis, multiple sclerosis, muscular dystrophy, botulism, tetanus, brain or spinal injuries, drugs or toxic agents (e.g. curare, acetylcholinesterase inhibitors, aminoglycosides), antibiotics, polio, porphyria; (4) respiratory center damage or depression: narcotics, barbiturates, tranquilizers, anesthetics, cerebral infarction or trauma, uncontrolled high-flow oxygen therapy. B impaired diffusion and gas exchange: (1) pulmonary fibrosis: interstitial fibrosis, sarcoidosis, pneumonoconiosis, (2) pulmonary edema: cardiogenic or non-cardiogenic; (3) adult respiratory distress syndrome; (4) obliterative pulmonary vascular disease: thromboembolism with blood, fat, bone marrow or amniotic fluid; (5) anatomic loss of functioning lung tissue: pneumonectomy, tumor. ventilation-perfusion abnormalities and venous admixture: asthma emphysema, chronic bronchitis, bronchiolitis, atelectasis, pneumonia, thromboembolism, and respiratory distress syndrome (Petty '89: 118, 119).

The **early symptoms of ARF** include dyspnea, cough, tachypnea, tachycardia, increased respiratory muscle activity and falling overall lung and thoracic compliance, irritability and mental impairment, which can be subtle or profound depending on the degree of blood-gas abnormalities and how rapidly they have occurred. Impediments to gas transfer may be termed "shunt factor". In the normal individual a delicate relationship exists between the metabolic production of carbon dioxide and its renewal by alveolar ventilation so that there is a near-normal level of PCO_2 – between 42 +/- 4 mm Hg at sea level (36 +/- 3 mm Hg, Denver altitude). This results in a narrow pH range of 7.35 to 7.45. Arterial puncture is simple and safe. Recent advances in arterial sampling syringes have reduced the pain, hematoma, and artifacts sometimes inherent in older techniques that used large-bore needles. Currently most blood-gas syringes employ lyophilized crystalline lithium heparin. The normal state is a PCO_2 of 40, a bicarbonate of 24 and a pH of 7.40. Acidosis can occur in diabetic ketoacidosis, lactic acidosis or in an uncompensated uremic state. Except in the case of severe respiratory muscle weakness, fatigue, or severe airflow obstruction, acid invasion responds to hyperventilation. Alkalemia is frequently the result of acute hyperventilation, from anxiety, pain or inappropriate mechanical ventilation. PO_2, PCO_2, and pH analysis is accomplished by electrode techniques, direct readout

and printing of these values and a calculated arterial oxygenation saturation are offered and the relationship between oxygen tension and saturation and pH modifications is presented. Oxygen saturation can also be measured with a variety of oximeters that use reflected light at two wavelengths to reflect the reduced and oxygenated hemoglobin expressed as a percentage. Pulse oximetry is rapidly replacing arterial blood-gas analysis when only the state of oxygenation is in question. The continuous monitoring of oxygen consumption and CO_2 production is possible using a mass spectrometer (Petty '89: 121, 125, 134, 135).

When fatigue, exhaustion, cardiac arrest or respiratory arrest occurs, the decision must be made to institute **mechanical ventilator** assistance. The objective of mechanical ventilation are to gain time and to rest the patient so that treatment of acute respiratory failure can occur and the patient can recover respiratory muscle function and general strength and vigor. Mechanical ventilator assistance is well-established. Immediate intubation by the nasal or oral route offers an immediate definite airway. Mechanical ventilation with a high-performance volume ventilator is most commonly used. A short inspiratory and long expiratory time is desired, and tidal volumes of 20 to 12 ml/kg are generally employed at the onset. Careful surveillance is mandatory and all patients mechanically ventilated must receive care in an intensive care unit. During the period of convalescence, it is imperative that patients maintain muscle strength and nutrition. Based on careful prospective study, it is possible to keep an endotracheal tube in place for many days when ventilation is prolonged (more than 3 to 4 days). It is better to perform a tracheostomy for comfort and for ease of feeding. During the first few days when an endotracheal tube is used, feeding can take place through a small nasogastric feeding tube. The patient should be given 2500 calories daily in small aliquots to prevent gastric distention or vomiting. Ensure contains a balanced calorie mixture equivalent to 1 cal/ml. Enteral nutrition is far better than intravenous from the standpoint of being more physiologic and is associated with fewer complications than parenteral nutrition. It is better if patients eat ordinary food. It is easy for patients to eat once a tracheostomy is in place. Approximately 80% of all patients selected or mechanical ventilation with ARF from COPD recover and are discharged from the hospital. Status asthmaticus resulting in mild to moderate respiratory failure is generally managed by non-ventilatory means. In rapidly deteriorating states mechanical ventilation becomes necessary and lifesaving. Usually more aggressive pharmacologic therapy is used including intravenous administration of aminophylline (theophylline) and very high doses of corticosteroids if the precipitating event is not a bacterial infection. Other major forms of ARF are those with self-induced or accidental poisoning and acute neuromuscular paralysis (Petty '89: 143, 144).

Pulmonary congestion and **edema** are characterized by heavy, wet lungs. Fluid accumulates initially in the basal regions of the lower lobes, since hydrostatic pressure is greater in these sites. The alveolar capillaries are engorged and an intra-alveolar granular pink precipitate can be seen. In long-standing cases of pulmonary congestion, such as those seen in mitral stenosis, hemosiderin-laden macrophages are abundant, fibrosis and thickening of the alveolar walls cause the soggy lungs to become firm and brown (brown induration). These changes not only impair normal respiratory function but also predispose to infection. Pulmonary edema can result from **hemodynamic disturbances** (hydrodynamic or cardiogenic pulmonary edema) or from direct increases in capillary permeability, owing to microvascular injury. The most common hemodynamic mechanism of pulmonary edema is that attributable to increased hydrostatic pressure, as occurs in left-sided congestive heart failure. Accumulation of fluid in this setting can be accounted for by Starling's law of capillary interstitial fluid exchange. Hemodynamic edema can also be cause by pulmonary vein obstruction, decreased oncotic pressure from hypoalbuminemia, nephrotic syndrome, liver disease, protein-losing enteropathies or lymphatic

obstruction. **Injury to the capillaries of the alveolar septa** does not usually elevate pulmonary capillary hydrostatic pressure, and hemodynamic factors play a secondary role. The edema results from primary injury to the vascular endothelium or damage to the alveolar epithelial cells (with secondary microvascular injury). This results in leakage of fluids and proteins first into the interstitial space and, in more severe cases, into the alveoli. When the edema remains localized, as it does in most forms of pneumonia, it is overshadowed by the manifestations of infection. Microvascular injury can be caused by infectious agents, viruses, Mycoplasma, and others; inhaled gases, oxygen, sulfur dioxide, cyanates and smoke; liquid aspiration of gastric contents or near-drowning; drugs and chemical chemotherapeutic agents such as bleomycin and others, other medications such as amphotericin B, colchicine, gold, heroin, kerosene and paraquat, shock trauma and sepsis, radiation, acute pancreatitis, extracorporeal circulation, massive fat, air or amniotic fluid embolism, uremia, heat, diabetic ketoacidosis, thrombotic thrombocyutopenic purpura (TTP), disseminated intravascular coagulation (DIC), high altitude and neurogenic origin. Edema due to microvascular injury can be caused by infectious agents, viruses, Mycoplasma, and others, inhaled gases.

Atelectasis is the collapse of all of a lung caused by obstruction of the bronchus (the main air passage through the lung) or the bronchiole (smaller air passages). After collapsing the lung loses its elasticity and cannot take in air, consequently, the blood passing through it can no longer absorb oxygen or dispose of carbon dioxide. In an adult, atelectasis is usually not life-threatening, since unaffected parts of the lung (or, if the whole lung has collapse, the other lung) expand to compensate for the loss of function in the collapse area. However, when a lung collapses in a newborn baby – as the result of mucus blocking the bronchus – the baby's life is at risk. Lung collapse can be caused by perforation in the pleura from **pneumothorax**. The bronchus is usually obstructed by one of four mechanisms. First secretions of mucus in the bronchus or bronchioles may accumulate and cause blockage. This can happen after an abdominal or chest operation that has made the dispersal of mucus by coughing difficult due to pain; as a possible complication of general anesthesia; in a baby at birth; in asthma; or in certain infections, such as pertussis (whooping cough) in children or chronic bronchitis in adults. Second, an accidentally inhaled foreign body, such as a peanut, may stick in the bronchus; this is more common in children than in adults. Third, a benign or malignant tumor in the lung may press on the bronchus. Fourth, enlarged lymph glands (which occur in tuberculosis, other lung infections ,and some forms of cancer) may exert pressure on the airway. The main symptom is breathing difficulty. There may also be a cough and/or chest pain, depending on the underlying cause. The condition is diagnosed by chest X ray. Treatment is directed to deal with the cause of the blockage. If the cause is an accumulation of mucus, chest clapping, deep breathing, coughing and postural drainage will be used. Once the obstruction has been removed, the collapsed lung usually reinflates gradually, although some areas of it may be permanently damaged or scarred (Clayman '89: 140).

Mucolytic agents are often used in some medical centers with physical therapy techniques and intermittent positive-pressure breathing (IPPB) to aid the removal of mucous secretions. Acetylcysteine is the only mucolytic drug available in America, but it may cause irritation and bronchospasm. This can be avoided by the concomitant administration of a bronchodilating aerosol. Most experts prefer a non-pharmacologic method that uses water as a bland aerosol with careful hydration of the patient, as well as physical therapy techniques. Pharmacologic agents including methylxanthines and beta-agonists, are effective in improving airflow in some states of acute respiratory failure such as exacerbation of COPD and status asthmaticus. Bronchodilators are effective because of their role in combating muscular bronchospasm and

probably through their effect on improving mucociliary clearance. Stimulation of mucociliary clearance is an action of both beta agonists and methylxanthines. Intravenous administration of aminophylline (theophylline), widely used in asthma, is also used in patients with COPD because bronchospasm may be present. The standard loading dose is of 5 to 6 mg/kg is probably appropriate for patients with COPD. Theophylline also strengthens failing respiratory muscles and is a respiratory stimulant. Beta agonists are effective by the systemic route, but they are not commonly administered subcutaneously or orally in seriously ill patients. Inhaled beta agonist solutions are rapidly effective in responsive patients and offer the greatest degree of bronchodilation. Albuterol (Proventil or Ventolin), bitolterol (Tornalate), isetharine (Bronkometer), metaproterenol (Allupent or Metaprel) and terbutaline (Brethaire) are used widely today in metered dose inhalers. Occasionally atropine is also used as an inhaled bronchodilator. Ipratropiuim bromide is also a patent bronchodilator in patients with COPD. Corticosteroids improve airflow compared with placebo in a study using methylprednisolone sodium succinate 0.5 mg/kg every 6 hours. In doses of 100 to 200 mg of prednisone or prednisolone daily seem appropriate in most patients. In most cases of COPD with acute respiratory failure, a combination of steroids, inhaled beta agonists and intravenous methylxanthines is effective in improving airflow. In a study in which corticosteroids were used in COPD exacerbations revealed that 43 of 44 patients survived with or without corticosteroids, attesting to the overall effectiveness of oxygen, physical therapy and pharmacologic agents (Petty '89: 139-141).

Acute exacerbations of bronchitis with purulence are commonly caused by *Haemophilus influenza*, *Streptococcus pneumoniae*, and *Branhamella catarrhalis and* occasionally *Mycoplasma pneumoniae*, Legionnaire's bacillus species and other less common organisms. Usually an acute virus infection is the initiating event with the bacterial invasion occurring secondarily. Antibiotics should be given promptly. Ampicillin has generally been the drug of choice in patients able to take penicillin and derivative. Doxycycline, tetracycline, trimethoprim with sulfa, and chloramphenicol are alternative choices for patients allergic to penicillin. Erythromycin is the drug of choice for *Legionella pneumophila*. Rifampin is an alternative. These antimicrobials are administered for 5 to 7 days or more until purulence is reduced by the examination of expectorated sputum and the patient has reduced fever and leukocytosis.
Pulmonary thromboembolism is perplexing when it complicates the course of hospitalized patients. Diagnosing this complication is extremely difficult because of ventilation and ventilation-perfusion abnormalities inherent to the problem of COPD. Congestive left-heart failure may complicate the mechanical derangements of advance COPD and right heart failure may be associated with significant salt and water retention and edema formation that complicate pulmonary mechanics. Spontaneous or traumatic pneumothorax may occur in advanced COPD worsening pulmonary mechanics. 10% to 15% small anterior or axillary chest tube placement with underwater seal or suction is required and if the duration of air leak is long, continuous chest tube drainage is necessary. During this time patients tend to be immobilized and fail to clear secretions because of pain. Analgesic dugs may help the patient cough and mobilize secretions. Patients should be active and when the patient walks in halls and corridors, the chest tube bottle should be on a portable stand or a one-way Heimlich valve that allows the egress of air (Petty '89: 141-143).

Pulmonary edema at high altitudes (of clinical concern above 8000 feet) occurs with physical exertion in un-acclimitized individuals either during an initial exposure to altitude or after return to high altitude by long-term residents who have descended to sea level for at least 10 to 14 days. There is risk of pulmonary hypertension, and extra-pulmonary irritation of the left atrial and

superior vena cava areas following the appearance of high-altitude pulmonary edema, and rather prompt improvement with oxygen enrichment suggest that hypoxic vasoconstriction plays a prominent role in the genesis of this syndrome that so often leads to **adult respiratory distress syndrome** (ARDS). When diffuse, alveolar edema is an important contributor to the serious and often fatal condition - adult respiratory distress syndrome (ARDS) (Schoen '94: 676, 677).

ARDS is a group of disorders in which edema and atelectasis cause the lung to become stiff, interfere with oxygenation of the mixed venous blood and result in progressively severe hypoxemia and circulatory deterioration. Experimental permeability edema produced with intravenous endotoxin on procoagulant and fibrinolytic activity tend to render the endothelial cell more thrombogenic and may contribute to the intravascular coagulation and fibrin deposition noted within days of onset of gram-negative sepsis. If the patient survives 2 to 3 weeks profound remodeling of the pulmonary vasculature may be encountered while pulmonary arterial pressure is often normal, these various structural changes form the basis of pulmonary hypertension reported late in the course of the syndrome. The development of ARDS is a late and often irreversible manifestation of endotherlial injury. The use of corticosteroids is controversial and evidence improved survival is lacking. **Supportive measures** include osmotically active substances, either low molecular weight (urea and mannitol) or macromolecules s uch as albumin or dextran, are used to increased the return of lung water to the vascular compartment. Diuretics also may be used to promote renal elimination of the fluid load thus generated. Hypoxemia is dealt with by **oxygen supplementation and assisted ventilation**. While the response to such treatment can be gratifying, especially with early diagnosis and prompt admission to the intensive care unit, mortality remains quite substantial. Airway narrowing produced by chronic inflammation, loss of ciliary function and retained bronchial secretions markedly reduces alveolar ventilation in a large portion of the lung (Enson '89: 1145, 1145).

Hypoxemia can be effectively corrected by using controlled oxygen enrichment of the inspired air. This can be accomplished either by double nasal cannula or by so-called Venturi masks that adjust the inspired fraction of oxygen. Both devices correct hypoxemia without the development of hyperoxia, and both may be used successfully without significant CO_2 retention. Nasal cannula are preferred for patient comfort, ability to eat and talk and for keeping the oxygen device in place over the Venturi mask. The nasopharynx effectively entrains the oxygen flow from the nasal prongs and the nasal prongs have an additional advantage in hypoventilation. Care must be exercised with the use of Venturi masks. The mask should bring the PO_2 to the desired level of 55 to 65 mm Hg and offers an oxygen saturation of 88% to 92%. Correction of hypoxemia is fundamental to patient care and results in improved oxygen availability to tissues and the consequences of hypoxemia on circulation, for example reactive pulmonary hypertension and impaired cardiac output (Petty '89: 136-138).

The mortality rate among the 150,000 adult respiratory distress syndrome (ARDS) cases seen yearly in the United States is still about 60% despite improvements in supportive respiratory therapy, 90% of deaths occur within 2 weeks of the onset of illness (Petty '89: 257). ARDS and its many synonyms (including adult respiratory failure, shock lung, diffuse alveolar damage (DAD), acute alveolar injury, and traumatic wet lungs) are descriptive terms for a syndrome caused by diffuse alveolar capillary damage and characterized clinically by the rapid onset of severe life-threatening respiratory insufficiency, cyanosis, and severe arterial hypoxemia that is refractory to oxygen therapy, and that frequently progresses to the extra-pulmonary multi-system organ failure. In most patients there is evidence of severe pulmonary edema with chest radiographs showing a diffuse alveolar infiltration. Although hyaline membranes are a

characteristic histologic feature of both ARDS and the respiratory distress syndrome of newborns the pathogenetic mechanisms are distinct. ARDS is a well-recognized complication of numerous and diverse conditions, including both direct injuries to the lungs and systemic disorders. Direct lung injuries causing ARDS include diffuse pulmonary and other viral infections, oxygen toxicity, inhalation of toxins and other irritants, and aspiration of gastric contents. Systemic conditions causing ARDS include septic shock, shock associated with trauma, hemorrhagic pancreatitis, burns, complicated abdominal surgery, narcotic reactions to organic solvents, hemodialysis, and cardiac surgery involved extracorporeal pumps or combination (Schoen '94: 679).

Upper airway obstruction must be differentiated from respiratory distress caused by pulmonary, neurologic, cardiovascular and esophageal disorders. Upper airway obstruction in adults tends to be inflammatory or neoplastic, whereas in children it tends to be inflammatory or congenital. While the narrowest part of the adult airway is the glottis, in children it is the subglottis. Newborns are obligate nasal breathers because they have a high riding larynx. Any nasal obstruction can produce cyclical cyanosis. The baby cries once the cyanosis becomes uncomfortable and is able to breath through the mouth. The character of noisy breathing in relation to the respiratory cycle helps localize the site of obstruction. Treatment centers on relief of the airway obstruction. If airway support is indicated, the safety of intubation versus tracheotomy must be determined. If complete airway obstruction occurs and intubation is not possible, emergency cricothyrotomy may be the simplest way of achieving an airway. This procedure can be performed through a small horizontal or vertical incision made directly through the skin, subcutaneous tissues and cricothyroid membrane, preferably with a single stab. Care is taken not to enter the esophagus or the posterior wall of the trachea. An endotracheal tube, tracheostomy tube, or other instrument is inserted a-traumatically. Bleeding is controlled with digital compression of the vessels. The patient should then be transported to the operating room for more definitive treatment. Cricothyrotomy should not be attempted on young children, because the cricothyroid space is too small to accommodate a tube large enough for ventilation. (Wynn & Goldsmith '04: 257, 260, 261).

The basic abnormality in ARDS is loss of integrity of the lung's air-blood interface, leading to increased alveolar capillary permeability. Neutrophils release proteases that damage the structure component of the lung. Neutrophils also generate and release a family of toxic oxygen radicals that alter membrane lipids, damage cells, inactivate proteins, destroy connective tissue, and potentiate proteases released by neutrophils. Platelet microemboli and plugs of fibrin are found within the lungs of patients who have ARDS. Arachidonic acid metabolites act on capillary smooth muscle to increase pulmonary vascular resistance and permeability. Other inflammatory mediators important to ARDS include macrophage factors, endothelial factors, platelet-activating factors, fibrin degradation products, kallikreins, histamine and serotonin. There is an alteration or decreased production of surfactant in ARDS because of lung injury. Alveolar units collapse. With injury the lungs leak and are difficult to inflate. Other alterations in function include right-to-left shunts. Wide-spread alveolar and interstitial edema can be found within the first 24 hours of symptoms. During the next 24 to 48 hours thickening of the alveolar walls, resulting from capillary congestion and alveolar hemorrhage occurs. Fibrin, platelet microemboli, and aggregates of leukocytes may be found in the capillaries (Petty '89: 259-262).

The first sign of ARDS is increased respiratory rate. The next is falling oxygenation with increasing oxygen requirements. 100% oxygenation may be required to maintain adequate arterial oxygenation. Compliance is the relationship between inflation pressure and volume

delivered. Thus if the tidal volume is 800 ml and the delivery pressure at the end of inspiration is 40 ml water, the compliance is 20 ml/cm. Normal total compliance is 75 to 100 ml/cm inflation pressure or more. Tachypnea and progressive refractory hypoxemia with falling compliance, emerging leukopenia emerge. A white blood cell count falling below 4,000 has a high predicable value for ARDS. After a patient has developed ARDS, a combination of low pH, low bicarbonate level, rising blood urea nitrogen levels, and less than 10% band forms constitute a poor prognosis. Patient age and organ system dysfunction influence the outcome for recovery. ARDS may rapidly emerge into a state of multiple organ system failure with 2 deaths out of 88 patients within 6 months after hospital discharge. Common complications associated with ARDS recovery are (1) respiratory complications: pulmonary emboli, pulmonary barotrauma (pneumothorax, pneumomediastinum, subcutaneous emphysema), oxygen toxicity and pulmonary fibrosis; (2) infection: nosocomial pneumonia, catheter-related infection or sepsis (bacteremia); (3) gastrointestinal complication: stress ulceration and hemorrhage, ileus, and pneumoperitoneum; (4) renal insufficiency; (5) cardiac complications: decreased cardiac output and arrhythmias; (6) hematologic complications: anemia, thrombocytopenia and disseminated intravascular coagulation and (7) the consequences of endotracheal intubation: laryngeal ulceration, tracheal ulceration, tracheal malacia and tracheal stenosis. Careful review of all the drugs the patient is getting will help minimize renal and other complications. Early nutritional support prevent bacterial infections and allows lung regeneration. Currently survival among individuals who developed ARDS is approximately only 40%, within 6 months of hospital discharge. An established method for managing ARDS patients by supportive means will save approximately 40% (Petty '89: 268, 270).

With the first sign of respiratory distress, the chest radiograph finding is most frequently normal and remains normal for the first 12 to 24 hours after the initial insult. The first abnormality found in the early stage of ARDS is patchy, diffuse, symmetric, bilateral, interstitial and alveolar infiltrates. The patchy zones of alveolar infiltrates rapidly coalesce to a massive air space. A second type of chest radiograph is the "galloping pneumonia type" full blown, diffuse, bilateral infiltrates, gradually developing over the next 48 hours. The injured lung has an immense ability to regenerate following acute lung injury. Many complications may occur during the course of ventilator management. Barotrauma may lead to pneumothorax, pneumomediastinum, extra-thoracic gas dissection, interstitial pulmonary air accumulation and fibrosis. Although it is possible to interfere with the various inflammatory mediators by the use of corticosteroids, arachidonic acid metabolite blockers, anti-proteases, antioxidants or combinations of these agents, it is not known whether apply these pharmacologic agents can effectively prevent or treat ARDS. The principles of ARDS management include: the establishment of a definitive airway (usually the endotracheal tube), the use of a volume ventilator employing large tidal volumes, approximately 10 to 12 ml/kg and the use of positive end-expiratory pressure (PEEP). Most patients improve with PEEP levels between 8 cm and 12 cm H_2O. Ventilator support must continue until the patient can achieve adequate ventilation and gas transfer without artificial means. In general this is when PEEP is no longer required and the inspired oxygen fraction is less than 40%. Generally patients can be weaned from mechanical ventilation when their resting minute ventilation is 10 liters or less, the respiratory rate is 20 or less, and the forced vital capacity measured by a simple hand spirometer is 1 liter or more. The correction of anemia with packed red blood cells helps maximize oxygen carrying capacity and tissue oxygen delivery (Petty '89: 262, 263, 265-267).

III.A.9 Chronic obstructive pulmonary disease (COPD)

Chronic obstructive pulmonary disease (COPD) and chronic obstructive lung disease (COLD) are terms that the medical profession uses to describe chronic bronchitis, asthmatic bronchitis, and emphysema. They share a common trait: persistent difficulty in getting the air to flow out of the lung normally. COPD (chronic obstructive pulmonary disease) is primarily a smoker's disease, which clusters in families and worsens with mold and viruses. The mild anti-smoking allergen, bacteria or virus certainly needs to be identified and eliminated from the *methicillin resistant Staphylococcus aureus* (MRSA) Epsom salt bathing public. Doctors have learned about the underlying processes which damage the airways and alveoli and have developed powerful therapeutic approaches, and can improve the lives of patients diagnosed with COPD, even in advanced stages. Oxygen studies have resulted in improved survival and life quality. Today most people with COPD live into their seventies or eighties, a normal life span. The National Lung Health Education Program (NLHEP) aims to identify patients in incipient stages of disease, who are mostly smokers beginning to lose airflow. A simple device, known as a spirometer, measures both airflow and volume. This device should be present in all primary care physicians' offices. Early identification can lead to smoking cessation, which is the most important therapeutic intervention. Eighty-two percent of those who die of COPD are smokers, and smokers are ten times more likely than non-smokers to die of the illness. Although many of the lung changes of COPD are permanent, improvement in symptoms and signs of disease often begins by stopping smoking. Industrial pollutants may also be a factor in some cases of emphysema. Prolonged exposure to cadmium or certain airborne fibers favors the later development of lung disease. Emphysema can also be caused by an inherited problem which affects how your body reacts to lung damage. Those who inherit a low level of a chemical called alpha-1 antitrypsin the lungs are easily damaged. Emphysema can develop over the years and the lungs overreact to cigarette smoke and to infections. The prominent features of chronic obstructive pulmonary disease are cough, unusual amounts of sputum, and shortness of breath, with constant fatigue. Next to coronary heart disease, COPD accounts for more severe disability and untimely deaths than any other health-related problem in the United States. According to the American Lung Association, 15.4 million Americans are affected with COPD. People who smoke and develop COPD are more likely to develop cancer than those who smoke and do not develop COPD (Tucker, Carter & Nicotra '01: Xvii, xviii, 3, 4). The onset of chronic lung disease is diagnosed after six months of uncured viral, bacterial infection or fungal allergy of the lung. Antibiotics treat pneumonia. Corticosteroids treat respiratory virus and mold infections.

The lungs pull air in, transferring the oxygen to the blood, where it is pumped by the heart to the rest of the body to provide oxygen and sending the blood back to the lungs where the carbon dioxide is pushed out by the lungs. Lung tissue does not regenerate, so loss of lung function is permanent. Other parts of the body can be trained to compensate for this loss, as least to some degree, but lungs cannot be restored to their original condition after significant damage from emphysema, chronic bronchitis and severe asthma. In COPD, the loss of oxygen is gradual, occurring over a period of years, unless there is a major illness (Tucker et al '01: 29, 38). **Chronic obstructive pulmonary disease** (COPD) is a clinical syndrome of dyspnea on exertion with objective evidence of reduced airflow not explained by specific or infiltrative lung or heart disease. Productive cough is often present. Reduced airflow is detected on physical examination by diminution in the sounds of air movement, especially on expiration, throughout both lungs. Reduced airflow may be measured by the standard ventilation tests (MVV, FEV_1, REV_1/FVC, and FEF_{25-75}) or by measuring increased R_{aw} (in the body plethysmograph). **Synonyms** include chronic obstructive pulmonary emphysema, chronic obstructive lung disease, chronic airways obstruction, diffuse obstructive pulmonary syndrome, emphysema, chronic bronchitis, and others. **Emphysema** is defined morphologically as a state of the lungs in which the air spaces

distal to the terminal bronchioles are abnormally increased in size and undergo destructive changes in their walls. **Chronic bronchitis** is characterized by excessive mucus secretion in the bronchial tree with chronic or recurrent productive cough on most days for a minimum of 3 months a year for not less than 2 successive years. The diagnosis can be made only after excluding the presence of specific diseases of the lungs or bronchi, such as tuberculosis, abscess, tumor, bronchiectasis, and others that may cause identical symptoms. COPD is almost always a mixture of emphysema and chronic bronchitis, and occasionally has elements of bronchiolitis and asthma. In normal lungs most of the normal resistance to airflow lies in airways more than 2 mm in diameter because the total cross-sectional diameter of the smaller ones is much greater than those larger than 2 mm in diameter. Therefore, involvement of the small airways must be extensive before MVV, FEV_1, FEV_1/FVC, and FEF_{25-75} will be abnormal (Mitchell & Petty '89: 146, 147).

COPD is more common in men than in women and in smokers than in nonsmokers. It is also more common in urban than in rural dwellers and socioeconomically disadvantaged than in economically privileged persons. Cigarette smoking is the most important known risk factor in the pathogenesis of COPD, whether it is manifested by emphysema, chronic bronchitis or both. Although autopsy studies reveal that all smokers have emphysema, the extent and severity is often insufficient to produce the clinical picture. The causes of emphysema have been elucidated in recent years. It is presumed that most nonsmokers who develop emphysema may have a genetic deficiency of α_1-antitrypsin. Proteases can be released by disintegrating inflammatory cells, or inhalation of papain or other proteases, thus causing alveolar wall dissolution or "tenderizing", normally inhibited by α_1-antitrypsin, resulting in emphysema. Cigarette smoke contains numerous irritants that stimulate mucus production, impair and ultimately destroy ciliary function and induce cough. Persons who regularly smoke cigarettes are also more susceptible to recurrent deep respiratory infections, which contribute the development of COPD. Cigarette smoke contains high concentrations of carbon monoxide, which can aggravate the hypoxemia that is a frequent problem late in the course of the disease. Urban air pollution plays a role in COPD similar to that of cigarette smoke but to a lesser degree. Severe chronic cough may cause further damage to already partially damaged bronchial, bronchiolar and alveolar walls. The **mechanisms of airways obstruction** are (1) inflammatory swelling of the bronchial and bronchiolar walls, causing them to narrow, (2) the presence of excessive and viscid muscles obstructing airflow, especially in the bronchioles, (3) atrophy of airway walls, presumably a complication of previous inflammation, together with loss of the normal supporting elastic structure and elastic recoil, and (4) bronchioles no longer patent because of previous obliterative inflammation. Loss of elastic recoil is a major factor in airflow limitation (obstruction) (Mitchell & Petty '89: 147-149).

People with COPD are usually middle-aged or older, and have often been or still are smokers. These folks may develop the same disease other people do as they age and may need surgery. But because of abnormalities with breathing which are always present with COPD, any surgery is a problem. If the disease is mild, it may not increase the risk of surgery much, if at all. If disease is severe and the person is not likely to survive long just because of the severity of the lung problems, then surgery is probably not an option. To decide how bad the lung situation is, lung function is measured. Categorizing lung function as mildly, moderately or severely abnormal is generally based on the FEV_1 test, the amount of air exhaled in the first second of blowing. The worse the abnormality in lung function, the higher the surgical risk. Maximal voluntary ventilation is measured by what the person can actually breathe with a major effort. This is determined in the laboratory by how much air can move in and out by really

hyperventilating, breathing hard and fast for several seconds, at maximal effort. Some surgeons prefer to have the person exercise while they watch. If lung function measurements indicate that the person has moderate or severe disease, then arterial blood gases are drawn so the lungs' ability to get rid of carbon dioxide can be evaluated. Getting rid of carbon dioxide is a measure not only of lung function but also of the brain's activity in signaling the lung muscles to take a breath. Arterial blood gases are also measured for oxygen in the blood, an important number to guide the anesthesiologist in the operating room (Tucker et al '01: 198).

In some patients COPD originates from **repeated chest infections in childhood**. However, about two-thirds of cases begin in individuals aged 30 to 50 with chronic productive cough and repeated "colds" or deep chest infections. Approximately 15% of patients have a history of episodic, non-effort-dependent, wheezing dyspnea (presumably bronchial asthma) generally during childhood, before the onset of effort-dependent dyspnea. Some 20% of patients insist that dyspnea on exertion was their first symptom, but when closely questioned, most reveal that chronic cough started at the same time or soon after. Another 5% of patients deny the presence of chronic cough. Sudden episodes of dyspnea and coughing are often labeled pneumonia but may be episodes of acute bronchiolar inflammation, which may become chronic or result in irreversible obliteration of many bronchioles or extensive microscopic thromboembolism. The course of COPD is commonly punctuated by exacerbations, usually caused by infections or by the inhalation of noxious fumes and by trauma, but sometime apparently unrelated to any identifiable event. When an exacerbation was complicated by right-side heart failure, the outlook was poor before the use of continuous low-flow oxygen. The **causes of death in COPD**, in order of frequency are respiratory failure, congestive heart failure secondary to cor pulmonale, pneumonia, sepsis, bronchitis, pulmonary thromboembolism perforation or hemorrhage of a peptic ulcer, and spontaneous pneumothorax. The **differential diagnosis of COPD** should include other causes of congestive heart failure, other causes of erythremia, and the various specific causes of chronic cough and expectoration such as tuberculosis, functional dyspepsia, bronchiectasis and fungal disease. Progressive weight loss is a poor prognostic sign (Mitchell & Petty '89: 149, 154, 155).

Chronic obstructive pulmonary disease (COPD) and chronic obstructive lung disease (COLD) are terms that the medical profession uses for chronic bronchitis, asthmatic bronchitis, and emphysema. They share a common trait: persistent difficulty in getting the air to flow out of the lung normally. Once these chronic diseases or processes start, one can never be normal again. One may have just one disease, or two , or all three. Other obstructive lung diseases belong in this group but are quite different in their cause and somewhat different in their treatment, they are – asthma, bronchiectasis, and inherited emphysema. **Asthma**, as it occurs in most lifetime non-smokers, is quite different in that most people with it have normal breathing most of the time. **Bronchiectasis**, although it is a chronic process, is caused by genetic problems such as cystic fibrosis or severe childhood infection. **Inherited emphysema** is caused by the destruction of alveolar sacs by enzymes in the absence of alpha-1 antitrypsin. A new alpha-1 antitrypsin drug costs exceed $50,000 a year (Tucker et al '01: 49, 53).

Emphysema has been classified as centrilobular (CLE) or centriacinar involving initially the respiratory bronchioles, panlobular (PLE) or panacinar involving the entire acinus, paraseptal and irregular or "scar" emphysema". As CLE progresses, it becomes increasingly difficult to distinguish it from PLE and it may be labeled mixed or endstage. CLE is predominantly a disease of bronchitis patients who smoke cigarettes, whereas PLE, the type associated with α_1-antitrypsin deficiency (zz type), is also often found in bonrchitic patietns who smoke cigarettes.

The airway tissues, especially the cartilaginous tissues, have often become atrophic, resulting in flabbiness and premature collapse on expiration. Physiologically, advanced emphysema is most commonly identifiable by loss of elastic recoil, increased total lung capacity, and impaired oxygen diffusion. **Chronic bronchitis** is characterized morphologically by hypertrophy and hyperplasia of the mucous glands lining the bronchi, chronic leukocytic and lymphocytic infiltration of the bronchial walls, increase in mucus-secreting goblet cells, loss of cilia, and squamous metaplasia. These changes often extend to the non-cartilage-bearing bronchioles some of which may be almost or totally occluded by inflammation, exudate, or dried mucus plugs (as in bronchiolitis and asthma) (Mitchell & Petty '89: 147).

Pulmonary diagnostic chart of chronic diseases

Disease	Cough	Wheeze	Mucus	Dyspnea	Description and cause
Emphysema	Yes			Yes	Destruction or enlargement of alveolar sacs. Often caused by smoking. Causes dyspnea (shortness of breath) and may cause coughing
Chronic bronchitis	Yes	often	Yes	yes	Long-term, excessive production of mucus by the trachea and bronchial tubes. Often caused by smoking
Asthmatic bronchitis		Yes	Yes	Yes, during attack	Bronchitis associated with wheezing and rapid change in ability to breathe, similar to asthma. Treatment for asthmatic bronchitis may be different than threating either asthma or bronchitis alone.
Acute bronchitis	Yes	often	Yes	yes	The mucous membranes of the bronchial tubes are inflamed by infection, allergy, air-borne materials, cold air.
Asthma	yes	yes		Yes, during attack	Extreme allergic reaction resulting in constriction of the bronchial airway. Often the patient is normal between attacks.
Inherited emphysema:	yes			yes	Emphysema. The destruction of alveolar sacs by enzymes in the

alpha-1 anti-trypsin deficiency					absence of alph-1 antitrypsin. An inherited deficiency, causing emphysema.
Bronchiectasis	yes		Large amounts		Chronic dilation of bronchial tubes with secondary infection in lower part of lung. Usually caused by a prior infection.

Source: Tucker et al '01: Table 1; COPD and other pulmonary diseases 50

Chronic bronchitis is diagnosed when there is a history of excessive mucus production (also called sputum or phlegm) with cough on most days for three of more months, and recurring yearly for at least two years. Most people with chronic bronchitis cough much more than this, and bring up a lot of mucus almost every day, especially on getting up in the morning. The most common cause of chronic bronchitis is long exposure to the damaging substances in cigarette smoke for more than 20 years. Less common is long exposure to air pollution, and breathing in dust for a long time. These substances cause the lining of the bronchial tubes to become irritated or inflamed. Then the mucus glands in the airways produce more and thicker sputum. The delicate cilia, the tiny hair-like structures in the bronchial tubes responsible for the upward movement of mucus, become damaged, can no longer work in cooperation, and are not effective in clearing mucus out of the lungs. Excess mucus stays longer in the bronchial tubes and makes the airways,. Which are normally sterile and free of bacteria, more susceptible to infection. Chronic bronchitis begins slowly as sputum production increases, due to more cells making mucus, and enlargement of the mucus glands. A morning cough may develop. In winter, or anytime you have a cold or an upper respiratory infection, longer periods of sputum production may occur. This process continues until mucus secretion is continuous. At some point, the airways swell, making them narrower and causing the bronchial tube muscles to spasm. With the narrowing of the bronchial tubes, muscle spasm, and partial filling of the tubes with mucus, it becomes harder to breathe. Then wheezing may begin, leading to a diagnosis of **asthmatic bronchitis**. As the disease gets worse other problems may occur. Oxygen level in the blood may fall as the airway becomes plugged by phlegm. If the low oxygen level is not corrected, it can lead to problems with thinking. Also as a result of low oxygen level, increased strain is placed on your heart, so that it doesn't pump as well as it should. Medically, this is heart failure. When this occurs, the feet and possibly the abdomen swell. Extra oxygen may bring relief, but eventually, even with extra oxygen, the lungs fail to keep up with the need to breathe and you die. With chronic bronchitis, especially with asthmatic bronchitis, allergy symptoms such as: runny nose, sinus problems, postnasal drip and wheezing, may present after exposure to house dust, molds, certain blooming or seeding plants, or animals such as cats (Tucker et al '01: 50, 51).

Pulmonary emphysema is quite different from chronic bronchitis, although both types of lung damage often co-exist. Emphysema is destruction of the structure of the lung. In bronchitis, the bronchial tubes are still there, even though they are not normal. In emphysema, large numbers of alveolar sacs are destroyed in parts of the lung. The remaining alveolar sacs become enlarged, and do not function normally. They no longer have the normal number of capillaries next to them, essential for transfer of oxygen from the air in the alveoli to the blood. So even though you keep breathing in and out of these damaged areas, oxygen is unable to transfer efficiently to the blood. So even though you keep breathing in and out these damaged areas, oxygen is unable

to transfer efficiently to the blood. Alveolar destruction also results in the loss of the elastic nature of the lung. Normally, the lung is able to be blown up, then shrink and expel air easily, because of the elastic qualities of the alveolar sacs. As these are destroyed, the lung can no longer expel air easily. Besides this, the elastic alveolar sacs also help to hold the tiniest bronchial tubes open by pulling on them. When the alveolar sacs are destroyed, the airways begin to collapse. These changes are irreversible, they never go away. The lung never grows new alveolar sacs. Certain chemicals in cigarette smoke attract alveolar macrophage cells to the lung. These cells release damaging enzymes, which destroy lung tissue. More than 90% of people with emphysema in various studies were heavy smokers, typically consuming more than one pack of cigarettes per day for many years. One pack per day equals twenty cigarettes per day. For one year this is called a one pack-year consumption history. Most people with emphysema due to cigarette smoking have at least a 20 pack-year history before symptoms become bad enough to seek medical assistance. Occupational exposure to cadmium and possibly other substances present in some industries can also result in emphysema (Tucker et al '01: 52, 53).

The normal airway is formed by the outer wall, muscle and mucous membrane, with a large open air passage. In bronchitis, the mucous membrane is swollen, the muscle is inflamed, and excessive secretions all combine to reduce the size of the air passage. In asthma, the muscle goes into spasm, the mucous membrane is swollen, and excessive secretions all combine to narrow the airway. In emphysema, the muscle is inflamed, the airway is flabby and compressed, but the airway passage is still open. Exacerbations of COPD occur after an upper respiratory infection or a bout of sinusitis. The exacerbation may occur because of a change, particularly a decrease, in the amount or type of medicine you take. Some medicines even cause bronchospasm and should be avoided. A common example is the group of heart and blood pressure medications called beta blockers. Such beta blockers are very different from the beta agonists used for the treatment COPD. The exacerbation may follow exposure to an allergic substance or an irritating dust, or to secondhand cigarette smoke. Exacerbations are usually due either to increased irritation or inflammation of the bronchial tubes, or to increase narrowing causing wheezing (Tucker et al '01: 53, 55).

In the **diagnosis of COPD** the following tests are ordered (1) chest x-ray, (2) breathing tests, (3) arterial blood gas, (4) electrocardiogram and (5) exercise testing with oximetry to check oxygen level. The most useful test is **spirometry**, which is done by filling the lungs with air, then blowing out as hard and as fast as possible. Testing is repeated after 20 to 45 minutes to test the effectiveness of medication. The most important measurement made during the spirometry, and the one which most doctors mean when they say you have “60% of lung function” or “half lung function” is the amount of air which one can forcibly blow out in one second. This is called FEV_1. FEV_1 is the number which is best at predicting how a person with COP will do. It helps your doctor decide how much risk there is for a surgical procedure and when to start watching for low oxygen level in your blood. It can also tell your doctor whether you are likely to die from your lung disease, or from something else. FEV_1 less than normal but greater than 60% of the expected value for age, race, sex, and size, indicates mild disease. If the FEV_1 is between 40 and 60% of expected, disease is moderate. For an FEV_1 less than 40% of expected, disease is severe. FEV_1 should be measured before and after using a bronchodilator inhaler, in order to get a true picture of best value. Another measure of lung function is the fastest rate at which you can get air out, or peak flow rate. Although this test is helpful in asthma, it is not as useful in COPD. Normal expected values for oxygen saturation very depending on altitude, but should be at least 90%. Values less than 90% indicate low oxygen in arterial blood. People desaturate (lose blood

oxygen) during activity and it is appropriate to compensate by increasing oxygen flow. **Arterial blood gas levels** are important cues to the severity of and need for treatment of abnormality in the lungs. This test has to be done on arterial blood coming out of the heart before it circulates to tissues. This test can be painful as the artery is right beside a nerve in the wrist. A local anesthetic such as lidocaine is very helpful (Tucker et al '01: 57, 58, 59).

People with COPD may also have **sleep apnea**, a common condition in which there are repeated pauses in breathing during sleep, breathing may stop more many seconds. Sleep apnea results in daytime sleepiness, sometimes so severe that people fall asleep while driving or talking. Obstructive sleep apnea is caused by airflow blockage in the upper back of the throat, often caused by the relaxation of the upper airway or by the tongue. Symptoms may include loud snoring, repeated pauses in breathing lasting longer than 10 seconds, and periodic gasps when the person awakens partially and resumed breathing. Snoring and hypopnea (a reduction in airflow) can also affect sleep quality. Central apnea is the failure of the brain to signal the lungs that it is time to take a breath. Mixed apnea consists of both a decrease in the effort to breath and airway obstruction. In less severe cases the person may be unaware that sleep disturbances have occurred, yet will waken un-refreshed. Whatever treatment is chosen for sleep apnea, success needs to be confirmed by an overnight study. Weight loss in is a practical prescription made easier if apnea is first controlled with CPAP positive airway pressure (PAP). A custom mouthpiece (oral device or dental appliance) can be worn at night to treat mild problems with restricted airflow during sleep, and in some individuals this method has been helpful treating sleep apnea. Supplemental oxygen is often used to treat falls in oxygen level at night. Surgery is often considered as a treatment for apnea. Surgical removal of excess tissue from the back of the throat is rarely successful and carries only modest long-term results. The use of laser surgery, nor radio-frequency energy, has not proven successful. Some people may receive full or partial relief when structure in the nose are corrected to eliminate restriction in airflow, e.g. a deviated septum. If losing weight and trying CPAP or bi-level airway pressure have been conclusively shown to be ineffective, there is a surgical solution called tracheostomy. It is a surgical opening in the trachea, through the neck. This opening in the neck bypasses the upper airway obstruction in the throat or back of the mouth. Supplemental oxygen can also be provided through a tracheostomy. The tracheostomy can be closed off during daily activities permitting normal speech and eating, although caution must be used to avoid letting in water (Tucker et al '01: 116, 117).

Patients with COPD often breathe in a rapid, inefficient fashion. They tend to hyper-inflate the chest with their accessory muscles and try to force air in with their abdominal muscles. The patient needs to relax the abdomen and lower chest encouraging the abdomen to protrude on inspiration, thus allowing maximum descent of the diaphragm. Exhalation against pursed kips, as in whistling, also promotes more complete emptying of the lungs and improved gas transport across the alveolar membrane. Many patients gain immense relief employing this careful breathing pattern during exercise; some patients even learn to follow this pattern while at rest and during sleep. General muscular reconditioning is also important. Patients with severe COPD become progressively unfit, do fewer tasks, and therefore find themselves in a downhill spiral of dyspnea, muscular impairment, progressive disability and weight loss. Patients with marked hypoxemia, often associated with cor pulmonale, benefit from long-term use of oxygen. The knowledge that oxygen can reverse pulmonary hypertension is fundamental to the management of cor pulmonale; oxygen may also improve myocardial function in patients with severe hypoxemia. However, the most important effects of oxygen are improved brain function, improved exercise tolerance, and overall improved quality of life in patients with advanced

COPD and sustained server hypoxemia. Not all patients with advanced COPD require oxygen. A PaO_2 under 55 mm Hg is generally a sign that oxygen may be necessary. However, it is important to identify the cause of hypoxemia and to treat it appropriately and specifically before embarking on long-term home oxygen with its attendant cost and inconveniences. If sustained hypoxemia is present despite therapy directed at underlying causes, evidence points to improved survival with oxygen. Home oxygen tanks used with a long (50-foot) tubing allow mobility in the home and various portable devices allow oxygen to be used outside the home. Liquid portable oxygen devices remain very popular and provide up to 9 hours of oxygen at a 2 L flow (weight is approximately 4 kg). Lighter weight devices that provide up to 5 hour supply are now available. The latest oxygen delivery system is a home oxygen concentrator that concentrates oxygen from the air (Mitchell & Petty '89: 158, 159).

People who have diseases such as diabetes, or who use medicines such as steroids on a long term basis, may have a greater chance of developing lung infections. These diseases and medications may damage the immune system which provides the defenders and makes the antibodies. Damage makes it more likely that the invader will initiate a full scale invasion and overwhelm the defending cells. Smoking damages protective systems. Cigarette smoke is made up of many chemicals, some of which attract the cells designed to repel invaders. When these cells arrive in the lung, even though there is no invader, they may release their packets of enzymes, which are destructive not only to invaders, but to the body's own tissue. Over years of smoking, millions of these defender cells come to the lung and eventually they may damage or destroy large parts of the lung by releasing too much enzyme, and releasing enzymes inappropriately. In one type of emphysema that is inherited, the lung's ability to turn off enzymes is severely limited because the protein which normally does this is in short supply – alpha-1 antitrypsin deficiency emphysema. This is a cause of emphysema unrelated to smoking (Tucker et al '01: 39, 41).

Shortness of breath or **dyspnea** is the most-reported complaint for people with COPD. Dyspnea is insidious in its onset, usually occurring only after significant lung injury. If occurs first when COPD has only damaged a small amount of the lung, as difficulty breathing during exertion. However, as the disease advances, eventually, dyspnea may be present during the simplest of efforts and at rest. Sudden worsening so dyspnea may be experienced with acute bouts of infection, or with bronchospasm. The healthy network of capillaries (tiny blood vessels) envelops each air sac (alveolus). The interior wall provide a large area of surface contact between the blood vessels and the air chambers. With emphysema, a typical alveolar sac shows the loss of the inner walls. The remaining structure has very little flexibility, there are no inner networks of blood vessels, and the remaining blood vessels provide a much smaller surface area for exchange between blood and air. Oxygen can't get into the blood and the carbon dioxide can't get out. A number of measures can help reduce shortness of breath: Some people breathe with only the upper part of their chest, and don't use the diaphragm. This means that air doesn't get down into the lower lobes of the lungs where most of the gas exchange takes place. Control the speed of breathing, when taking short shallow pants, inhale and exhale so fast that new oxygenated air doesn't get to the lower lobes of the lungs. Due to physical or psychological tension, the shoulders are held very tight. The abdominal muscles might also tighten up making it harder to breathe. Relax these muscles by breathing deeply and evenly in a more relaxed fashion (Tucker et al '01: 41, 42, 45).

Patients with cough, expectoration, and relatively mild expiratory airflow obstruction can be effectively managed simply by the cessation of smoking, the careful use of antibiotics during each specific chest infection, and possibly the use of a bronchodilating aerosol with a metered-

dose device each morning, or corticosteroid. Patient with an FEV_1 over 2 L who follow these simple measures seem to have a nearly normal prognosis, if COPD can be reversed. Moderately advanced cases require more aggressive daily therapy, with vigorous bronchial hygiene and physical reconditioning. It is likely the prognosis of patients with an FEV1 of 1 to 1 1/1 L can be improved, although patients who have this degree of disease tend to progress slowly and a normal life expectancy is unlikely. Nonetheless, systematic care improves the quality of life for these patients. Severely afflicted, home-bound patients often require home oxygen to improve the quality of life. If the disease is caught early or is partly reversible, the prognosis is generally favorable. Even with greater degrees of impairment, patients can lie outside the hospital and are often able to work. Certainly, the solution to the COPD problem is early identification and management. This important strategy is based on office spirometry and education on the protection of the lungs from smoking and air pollution. Identification of genetic background factors help determine patients at highest risk (Mitchell & Petty '89: 159, 160).

After the avoidance of smoking and irritants, probably the most important principle of COPD management is daily bronchial hygiene to clear mucus usually by daily inhalation of bronchodilating aerosols such as isoetharine, isoproterenol, albuterol, or metaproterenol. The dosage of bronchodilating aerosol varies greatly among patients. In the metered-dose device, 1 or 2 puffs (350 µg isoetharine/puff) every 4 to 6 hours is usually sufficient. Patients should continue to inhale their bronchodilator to the point of relief but not to the point of toxicity. Symptoms of toxicity include palpitation, nervousness, and lightheadedness. After the inhalation of bronchodilating aerosols, patients with retained secretions often benefit from the inhalation of moisture. Following this, expulsive coughing and postural drainage over pillows in bed help remove the retained secretions. Antibiotics are among the most important drugs for patients with COPD. The three most common bacterial organisms are *Streptococcus pneumoniae*, *Haemophilus influenza* and *Branhamella catarrhalis*. The most useful antibiotics are doxycycline, ampicillin and metronidazole. Common regimens are doxycycline 100 mg once a day for ten days, ampicillin 500mg one twice a day for five days, or metronidazole one twice a day for seven days. Generally, antibiotics can be started at the first sign of a deep chest infection, with the appearance of purulent sputum, increasing cough and fever. Patients are often given a supply of antibiotics to use on their own when infection develops. Although corticosteroid drugs are very useful in asthma and reversible bronchitis their use remains controversial in COPD. Any patient not doing well with a complete bronchial hygiene regimen should receive a clinical trial of corticosteroid drugs. Generally, 40 mg prednisone is given daily for approximately 1 week, then the dosage is reduced to around 10 mg every other day. It the patients experiences marked improvement, the steroids should be continued. The dreaded side-effects, including peptic ulcer, osteoporosis and cataract formation are quite uncommon on low dosages, particularly on alternate-day steroid therapy. Inhaled beclomethasone may be useful in steroid responsive patients as a maintenance drug with little risk of side effects. Flurisolide and triamcinolone acetonide are also effective steroids available by the inhaled route. Both digitalis (or Hawthorn) and diuretics may be useful in heart failure associated with cor pulmonale. The role of digitalis in cor pulmonale has been controversial in the past, but these cardiac glycosides are generally accepted as being useful for atrial tachycardia and associated left-sided heart failure. Short-acting digitalis preparations such as digoxin are preferable. Generally, the thiazide diuretic are preferable when edema formation is not controlled by salt restriction. Oral bronchodilators theophylline and theophylline salts (methylxanthines) are commonly used if tolerated by the gastrointestinal tract and if there is a reversible bronchospastic component. A common dosage is 400 mg twice a day. Once a day theophylline dosing aids compliance. Oral beta agonists are generally reserved for patients who won't or can't use an inhaled agent.

Influenza virus vaccine sis recommended for COPD patients each fall. Pneumonia vaccine should be given once a lifetime (Mitchell & Petty '89: 155 – 158)..

Disorders of ventilation while awake may result from abnormalities in the respiratory control center, interruption of afferent input to the respiratory control center from chemical and mechanical sensors, or abnormalities in the innervation of respiratory muscles, the muscles, the lungs, or the chest wall. Abnormalities frequently result in hypoventilation. Diseases of or injuries to the brainstem may alter respiratory control center activity. The **Arnold-Chiari malformation** may damage the control center or affect the modulating input from the carotid body. Infections or inflammatory diseases such as encephalitis and bulbar poliomyelitis may involve the medulla and cause dysfunction of the respiratory control center. Cerebrovascular accidents and local trauma can significantly alter respiratory control center function. The best-known defect of the respiratory control center is primary alveolar hypoventilation, also known as **Ondine's curse**. Affected patients typically have chronic hypoxemia and hypercapnia and a normal alveolar-arterial oxygen gradient. These patients can usually hyperventilate voluntarily to correct arterial blood gas imbalance. Patients who have primary alveolar hypoventilation frequently demonstrate significant cognitive dysfunction. Ventilation is usually depressed further during sleep when many patients develop frank apneas. Loss of input from central and peripheral sensors is another cause of ventilator disorders. Infections or inflammatory disorders (encephalitis and bulbar poliomyelitis) may involve the medulla, possibly causing dysfunction of the central chemoreceptors that can be affected by cerebrovascular accidents or local trauma. The recurrent pattern is increasing tidal volumes followed by decreasing tidal volume that decrease to a frank apnea, a ventilator pattern known **Cheyne-Stokes respiration**. Damage to the phrenic nerve from trauma, tumors, or inflammatory disease may impair transmission of these impulses to the diaprag. Generalized neuromuscular disorders sucha s the Guillain-Barre syndrome, poliomyelitis, myasthenia gravia, or myotonic dystrophy may cause severe hypoventilation. Mechanical disorders of the lungs and chest wall can also result in abnormal ventilation. The increase in elastic recoil associated with interstitial lung diseases frequently triggers rapid shallow breathing (Ballard '89: 243, 244).

The use of respiratory stimulants in patients who have disorders of ventilator control generally has been disappointing. **Progesterone** is an agent that stimulates ventilation. Increased blood progesterone levels in the last trimester of pregnancy and in the latter portion of the menstrual cycle reduce PaCO2 by increasing minute ventilation. The effects of progesterone usually occur within 48 hours of initial administration with maximal effects observed within the first 7 days. The agent acts centrally and may stimulate ventilator responses to hypoxemia, hpercapnia and exercise. Progesterone has been used to successfully treat primarily alveolar hypoventilation and a subgroup of people with sleep apnea. **Theophylline** is a stimulant of the central nervous system, derived from green and black tea, that increases ventilation and hypoxic ventilatory responses while decreasing PaCO2 in healthy patients. This agent, green or black tea, may stimulate ventilator responses by increasing the metabolic rate or by stimulating central and peripheral chemoreceptors directly. Although theophylline is known primarily for its bronchodilator and respiratory muscle effects, it is not a powerful respiratory stimulant although it has been used to treat recurrent apnea in premature infants. **Doxapram** produces an increase in resting ventilation manifested by an increase in tidal volume, as well as a slight increase in respiratory rate. Doxapram is used primarily in patients who are hypoventilating postoperatively because of general anesthesia and patient show have mild central nervous system depression caused by drug overdoses. **Carbonic anhydrase inhibitors** such as acetazolamide are not strictly defined a respiratory stimulants. They produce a mild metabolic acidosis that stimulates

ventilation. Bicarbonate transport across the blood-brain barrier may be affected also. Carbonic anhydrase inhibitors are useful in the therapy for patients who have primary alveolar hypoventilation and in selected patients who have primary central sleep apnea. They also improve mean arterial oxygen saturation while reducing central apneas observed at high altitudes during sleep (Ballard '89: 243-245).

Estimates of the incidence of **sleep apnea** are 1% to 2% of the population in the United States. There are six types of disordered breathing that can occur in patients during sleep. These are upper airway obstruction (UAO), central apnea (CA), mixed apneas (MA), primary alveolar hypoventilation (PAH), hypopnea, and ventilation-to-perfusion V/Q mismatching. A UAO is defined as a cessation of air movement for at least 10 seconds with continued respiratory effort. A CA is defined as cessation of airflow for at least 10 seconds with nor respiratory effort being made (neural output to the respiratory muscles has stopped). In MA airflow has ceased for at least 10 seconds and within that interval a lack of respiratory effort is followed by attempts to breathe. PAH leads to an elevated $PaCO_2$.and a decrease in PaO_2. Hypopneas are progressively smaller tidal volumes that are usually followed by hyperpnea (increased volume and frequency). Increased $PaCO_2$ may or may not accompany this type of respiratory pattern and the hypoxemia that develops is out of proportion to the hypercapnia. The V/Q mismatching occurs when lower airway problems develop during sleep. This produces hypoxemia and, if severe enough, hypercapnia. Up to 75% of asthmatic patietns have nocturnal exacerbations of their asthma, which may or may not symptomatic. The nocturnal bronchospasm may lead to V/Q mismatching hypoxemia during sleep. Known causes of upper airway obstruction and mixed apneas are adeno-tonsillar hypertrophy, usually benign but may be cause by lymphoma, intra-thoracic goiter, temporo-mandibular joint disease, hypothyroidism (particularly males), micrognathia, acromegaly, myotonic dystrophy, Shy-Drager syndrome, cushingoid habitus and obesity. Clinical features of sleep apnea and hypoventilation are daytime hypersomnolence, loud snoring, restless sleep, morning headaches, potentially lethal cardiac arrhythmias during sleep, erythrocytosis, systemic hypertension, pulmonary hypertension, cor pulmonale, heart failure, personality changes, decreased intellectual capacity, recent weight gain (not always obese) enuresis and sexual impotence. Patients with COPD often complain about disturbed sleep. Approximately 70% of all respiratory arrests and deaths occur between 12 AM and 6 AM in this patient population. Although 80% of these patients are obese 20% are not overweight (Martin '89: 247-252).

A screening test determines whether hypoxemia develops during the night. This test is performed by ear oximetry that continuously measures and records the oxygen saturation level. A 5% to 10% or more fall from baseline oxygen saturation develops, the cause of hypoxemia should be determined. If no oxygen desaturation is found, either the test is negative or the patient may havfe slept poorly and did not reach rapid-eye-movement (REM) sleep. The phase of sleep before REM is when the most severe abnormal breathing and hypoxemia occurs. Protriptyline is a tricyclic antidepressant that improves or terminates UAO and MA in about 20% of this population. The dosage is 5 to 30 mg orally at bedtime. Oxygen via nasal prongs at 2 to 3 liters/min helps about 40% of these patients, a drawback is the high cost, from $200 to $400 a month. Although the patient has appropriate weight loss, apenas may persist in some individuals. **Progesterone** acts as a respiratory stimulant and mainly helps those individual who hae daytime hypercapnia and severe hypoxemia. Nasal CPAP is a new technique that provides a "pneumatic splint" to maintain patency of the oropharynx. This technique is the best medical intervention, with success in about 70% of patients. **Uvulopalatopharyngoplasty** is a surgical intervention with about 40% success. If previous therapies fail, tracheostomy is recommended.

For CA and PAH patients respiratory stimulation is the initial therapeutic choice. A **carbonic anhydrase inhibitor** such as dicklorphenamide 50 mg p.o. b.i.d. or acetazolamide 250 mg p.o. qid is highly effective. Progesterone 20 to 40 mg orally t.i.d. can also be used. If needed, supplemental low-flow nasal oxygen can alleviate hypoxemia and occasionally apnea. Weight loss can be important. Nocturnal oxygen is the mainstay for COPD patients with hypopnea (Martin '89: 252-255).

Some of the **COPD medications** currently available in the United States are bronchodilators, quick-acting beta-agonist bronchodilators, anti-cholinergic bronchodilators, corticosteroids, non-steroid anti-inflammatory inhalers, anti-inflammatory pills, nasal inhalers, theophylline, expectorants, mucolytics, antibiotics, antifungals, antivirals, diuretics and vaccines for influenza and pneumococcus. **Bronchodilators** open up or dilate the bronchial tubes for easy passage of air. They relax the muscle around the bronchial tubes so that it will not be in spasm. When the muscle spasm relaxes, the inside of the bronchial tube is wider making it easier to breathe and cough mucus. Bronchodilators are inhaled from a puffer device or a nebulizer. They are usually liquid, but some powder and pill preparations are available. They are marketed at metaproterenol (Alupent, Metaprel), albuterol (Proventil, Ventolin, Rotahaler), terbutaline (Brethaire), pirbuterol (Maxair), bitolterol (Tornalate), isoetharine (Bronkometer), ipratropium bromide (medium) (Atrovent), ipratropium and albuterol (quick onset, medium length) (Combivent), salmeterol (long)(Serevent), **Quick-acting beta-agonist bronchodilators** stimulate an area of the cell called the beta receptor. These agents usually start working within a couple of minutes. As they usually don't last very long, they can be used every few hours if needed. Medication available before such as epinephrine (Primatene) or adrenaline and isoproterenol lasted a much shorter length of time and were much more likely to cause side effects. Side effects of commonly-used, inhaled beta-2 agonists include anxiety and occasional rapid heart rate or dizziness. For most, these side effects are mild and tend to disappear shortly after use of the medication (Tucker et al '01: 69-77, 69, 70). A large observational study has found no difference in the increased risk for cardiovascular disease between the two main classes of drugs used in the first-line treatment of chronic obstructive pulmonary disease (COPD). LABAs (long-acting inhaled beta-agonists) and LAMAs (long-acting muscarinic antagonists) have a variety of beneficial effects in COPD patients, but evidence has been building that these agents may produce a small but significant increase in cardiovascular risk.

Salmterol and formoterol are very long-acting, lasting about 12 hours. Salmeterol is available in the U.S. packaged as Serevent, a spray inhaler. Formoterol will be available soon as a powder inhaler. Both medications may cause either shakiness or tremor, or increase anxiety. With regular use, they are very effective for long-lasting relief of shortness of breath. They need to be used regularly every 12 hours, but as they do not work right away, you need to keep quick acting medication on hand. Serevent (salmeterol) is available only as an inhaler, although nebulizer medication is planned. Another important bronchodilator, is **inhaled ipratropium bromide** (Atrovent). It may slow progression of the COPD, so it is recommended by many pulmonary physicians. This medication does not work quite as quickly as the beta-2 agonists, taking about 30 minutes, but its effects last longer. Ipratropium is available as an inhaler or as a liquid for nebulizer. The most common side effect of ipratropium is spasmodic cough, which is usually relieved by stopping the medication. If a high dose of ipratropium or atropine is used it may cause difficulty in urinating, particularly in men. Ipratropium or atropine is used it may cause difficulty in urinating, particularly in men. Ipratropium may be mixed with albuterol or one of the other quick-acting bronchodilators in a nebulizer. A new inhaler, Combivent, combining

ipratropium with albuterol is also available for more convenient dosing (Tucker et al '01: 69, 70, 71).

Corticosteroids are different from anabolic steroids used by athletes to promote muscle growth and strength. Medical use of steroids, when taken as prescribed, does not damage the liver and does not produce heart disease which is seen as a result of high anabolic-steroid used in athletes, but may cause osteoporosis, or bone loss. Corticosteroids are powerful medications, effective in the treatment of acute episodes of worsening shortness of breath, sometimes when nothing else seems to work. Some studies have shown that using inhaled steroids prevents progression of COPD. Some of the newer, stronger inhaled steroids may cause the body to stop normal production of steroids, so that when stopping to take them, or in case of a severe illness, it is possible to suffer from steroid shortage. Common corticosteroid inhalers used in 1999 were triamcinolone 100 micrograms (Azmacort), beclomethasone 42 micrograms (Vanceril, Beclovent), beclomethasone 84 micrograms (Vanceril DS), flunisolone 250 micrograms / puff (Aerobid M), fluticasone 220, 110, 04 44 micrograms (Flovent) and budesonide 200 mcg (powder)(Pulmicort Turbohaler). Overall, inhaled steroids are safe because they are administered in small doses. For example a small pill of a common steroid, prednisone (Deltasone and other names) delivers 5,000 microgram or 5 milligrams. One puff of a common inhaled corticosteroid, beclomethasone (Vanceril DS), gives 84 micrograms per puff, but less into the lung where it is absorbed. Using a fairly standard regimen of beclomethasone of four pugs daily gives a total dose of 336 micrograms. It would take over 60 puffs daily to equal one prednisone tablet. Inhaled steroids do not correct a severe exacerbation of wheezing COPD. Corticosteroid pills or injections treat increased shortness of breath, increased cough or other acute exacerbations and symptoms of lung disease. In general due to side-effects, doctors try to have you on steroids for the shortest possible time, a large dose initially, rapidly cut down as you improve over several days. Treatment is usually complete within one to two weeks. Steroids have strong anti-inflammatory properties and will stop bronchospasm (wheezing) reduce swelling of the air tubes and cut down on the production of mucus. Whether an injected steroid or pills are used depends on how ill you are, whether intestinal difficulties are present, how high a dose you need, and how long the medication is to continue. Most doctors avoid chronic or long-term use of steroids, because of their side effects. Positive side-effects of oral or injected steroids are improved sense of well-being, improved appetite, fluid retention, weight gain, rounding of the face, changes in mood, increased blood pressure. Negative side-effects are development of diabetes, weight gain, osteoporosis (thinning go of the bones), cataracts, myopathy (muscle weakness) (Tucker et al '01: 82, 72, 73).

There are steroid and non-steroid nasal inhalers. Steroidal nasal inhalers are fluticasone (Flonase), triamcinolone (Nasalcort), beclomethasone (Beconase AQ, Beconase, Vancenase AQ, Vancenase), and flunisolide (Nasalide, Nasarel). Non-steroidal nasal inhalers are cromolyn (Nasalcrom) and ipratropium (Atrovent) are used preventively and should not be used for rapid onset episodes. Nasal inhalers are used to treat and prevent chronic nasal stuffiness and drainage and thus prevent chronic sinusitis. A common problem that occurs with COPD is chronic rhinitis or sinusitis, inflammation of the nose, causing nasal or post-nasal drip, nasal stuffiness, hoarseness, and blocked nasal passages. If rhinitis is severe, it may cause the sinuses to become inflamed or infected. If rhinitis is severe, it may cause the sinuses to become inflamed or infected. The reasons for these problems are related to allergies and also to direct irritation. Unfortunately, the nasal problems can last a long time after the direct irritation has cleared up, becoming perennial rhinitis. Treatment is important, as nasal drip and blocking may worsen lung problems. Non-steroid anti-inflammatory inhalers, cromolyn (Intal and nedocromil (Tilade) are

used preventatively. **Anti-inflammatory pills**, zafirlukast (accolade) twice daily and montelukast (Singulair) once daily may be useful in COPD. They prevent inflammation which may cause damage to the bronchial tubes and may prevent acute attacks of bronchitis and wheezing if used regularly (Tucker et al '01: 73, 74).

Theophylline has been used in treatment of lung disease for many years. Its major purpose in COPD is to reduce bronchospasm, which relieves shortness of breath. It may also help the diaphragm to work more effectively, preventing fatigue with increased activity. It has about as many ill effects as good. Because of its side-effects, it is used less frequently than inhaled medications. Theophylline is most frequently administered s sustained-release pills or capsules. In acute illness, it may be given intravenously. As theophylline takes time to build up in the blood stream to a therapeutic level, adjustment may be necessary, with blood testing to monitor your blood levels. Some people cannot tolerate theophylline. A major side effect is anxiety, which may lead to tremulousness and insomnia, even in therapeutic doses and with normal blood levels (Tucker et al '01: 75). **Expectorants and mucolytics** such as guafenesin (Humibid, Tussi-ortganidin) or the herb mullein help liquefy secretions and allow one to cough up mucus more easily. One of the best expectorants is water. Drinking an adequate amount of water, about one quart per day, will make clearing phlegm easier, which may lead to improved breathing (Tucker et al '01: 75).

Antibiotics are used to treat infections caused by bacteria. Doctors suspect bacterial infection when a person is coughing up increased amounts of sputum, often discolored yellow or green, and particularly with a low-grade temperature. Antibiotics are not helpful in treating viral infections, which may also produce sputum discoloration. There are many types of antibiotics for different infection-causing bacteria. Sometimes a specimen of phlegm is collected to see what type of bacteria are present, so that the correct antibiotic can be prescribed. Infection may clear without antibiotic treatment. Some people have an allergic reaction to penicillin. Antibiotic resistance is becoming an increasing problem worldwide. This means that some antibiotics will not kill the target bacteria, even when they are given in appropriate dosages for the correct amount of time. This has made many doctors reluctant to treat people with antibiotics just because the sputum is discolored, without other evidence of infection. Antibiotic prescription in the future will be more cautious, for fear of increasing antibiotic resistance.
Antifungal medications are used occasionally in people with COPD, especially if high doses of inhaled or oral steroids are prescribed. Thrush is treated with a gargle or pills containing an antifungal agent. Less commonly, a fungal infection may reach the lungs, particularly with high doses of steroids for a long time. Severe fungal infection in the lungs is diagnosed by bronchoscopy or surgery and requires extended treatment. People who have weak immune systems, for example after a lung transplant, may need continuous antifungal treatment.76
Antiviral treatment is available to treat influenza (the flu) although prevention by yearly vaccination is the best course. Antiviral medicine can shorten illness and reduce severity, but to be effective, medication must start as soon as possible after the first symptoms. At times, medication is started after an exposure to the flue but before symptoms are evident. New medications to treat a cold are coming to market, such as nasal sprays to shorten the time a cold lasts and decrease the symptoms (Tucker et al '01: 75, 76).

Diuretics are commonly referred to as water pills, because they help to eliminate excess water from the body, reducing swelling and lowering high blood pressure. In people with severe COPD, low oxygen level may lead to weakening of the heart, swelling of the ankles, and swelling of other parts of the body, including the abdomen. This may result in increasing

shortness of breath. Treatment includes correcting the low oxygen level and giving diuretics to reduce swelling. Diuretics should be taken in the morning, to avoid waking up at night to urinate. They may be taken as pills once a day, or given intravenously. Diuretics are more effective if taken with meals, when the largest load of salt and water is presented to the body. Some diuretics may also eliminate large amounts of potassium, so it is common for a potassium supplement to be ordered or for the doctor to suggest an increase of the intake of certain food high in potassium. Bananas, lima beans, split peas, sweet potatoes, fresh spinach, dates, raisins, dried fruits, orange juice, salmon, bacon and beef are excellent sources. Signs of low potassium include muscle weakness and cramps (Tucker et al '091: 76, 77).

Almost all elderly people and people with chronic disease such as COPD are highly encouraged to get yearly influenza vaccine or **flu shots**. Most years these shots are effective, but effectiveness depends on the vaccine development process. Most viruses which produce epidemics in North America and Europe have previously done so in Asia (Beijing Flu, Taiwan Flu). The Centers for Disease Control in Atlanta develops vaccine for the United States to protect from whatever viruses were in Asia six months earlier. But sometimes new viruses occur in the U.S. without first showing up in Asia, and sometimes the viruses change. Therefore, there is no guarantee, even with vaccination, that the flu can be avoided. However, one will probably have a milder case if you've had the shot. The pneumonia vaccine, **Pneumovax**, was developed to prevent pneumonias caused by the pneumococcus bacteria, which can cause severe, even fatal pneumonia. After receiving Pneumovax, the body is able to make antibodies against the pneumococcus bacteria. These antibodies, in people with COPD, appear to remain at high levels for five to ten years or longer, so injections at about ten-year intervals are usually recommended. This vaccine can cause increased soreness and swelling at the injection site if given too soon after the last injection, because of the high antibody levels still present in your body (Tucker et al '01: 77).

Supplemental oxygen is prescribed for people with chronic bronchitis or emphysema, it may be prescribed for sleep, during exercise, or 24 hours a day. Present medical knowledge supports continuous use of supplemental oxygen for people with a low oxygen value at rest in their usual state of health. Oxygen flow rates may be adjusted for periods of increased activity and sleep. 85 Abnormal values have been arrived at by consensus among medical experts and are used for reimbursement by Medicare. The amount of oxygen in the blood is measured as the oxygen partial pressure. **Normal value** depends on the altitude, but at sea level in an older person the blood oxygen value is typically above 80 millimeters of mercury. In a person with COPD, an oxygen pressure below 55 is abnormal enough that extra oxygen is usually prescribed. The amount of oxygen which is bound to hemoglobin, the red pigment in the blood, is called the oxygen saturation or saturation. A normal level is above 96%. Saturation values at or below 87% are abnormal and enough extra oxygen is prescribed to get the saturation level above 90%. **Arterial blood gas** or oximetry testing is most commonly done during a daytime office visit. If the test demonstrates low oxygen level, supplemental oxygen will be started or increased, and your oxygen level will be rechecked to confirm your oxygen needs, or that adjustments are needed (Tucker et al '01: 86, 87).

The warning label on **oxygen storage devices** states: Stay at least eight (8) feet away from an open flame while using oxygen. Do not use oxygen while cooking with an open flame such as gas appliances, or gas or charcoal-fired barbecue. Never smoke while using oxygen nor around someone using oxygen. Put on a sign on the door of every room where oxygen is in use: Oxygen in use, No Smoking. Never use petroleum-based face creams or ointments, such as Vaseline.

Use only water-based creams, lotions and cosmetics. Never use a hair dryer or electric razor when using supplemental oxygen. Store oxygen equipment at least five (5) feet from open flames, space heater, large windows, or any heat source. Do not store a concentrator in a small enclosed space. Never allow the supply tube to be exposed to sharp edges, a heat source, or flame. There are two main categories of oxygen storage systems (1) stationary or base systems, and (2) portable systems. Stationary, or **base systems** provide oxygen in a fixed location and may be: (1) Liquid oxygen containers with gas condensed into liquid by extreme cold, (2) Concentrators with an electric motor to take nitrogen out of the air, concentrating oxygen to between 94% and 98% and (3) H.S, or M60 cylinders: large tanks containing oxygen under high pressure usually used as a backup and rarely as a base system for daily use. Oxygen concentrators are often used in the home and are probably the most economic source of supplemental oxygen. An oxygen concentrator passes room air through a powder to separate oxygen form nitrogen. The oxygen is concentrated and delivered while the nitrogen is periodically released back into the air. Concentrators are fairly small, weighing about 50-70 pounds, and need an electrical source. A backup oxygen supply system must be available during electrical failure. Some new oxygen concentrators, such as the CHAD Therapeutics, Oxylite™ can fill small cylinders at home, providing oxygen portability for more active people. The portable B/M6 unit weight about five pounds, holds 164 liters of oxygen, and can provide eight to ten hours of use with a conserving device, at two liters per minute. This conservation device administers oxygen during the first third of inspiration. Oxygen flow can be significantly reduced by using an **oxygen-conserving device** to reduce flow while maintaining the same level of oxygen delivery. Depending on the device, the flow of oxygen stops momentarily, while you exhale, during part of your inhalation, or both. Oxygen-conserving devices can lengthen use of a tank by up to eight times (Tucker et al '01: 88, 97).

The **nasal cannula** is the most common form of oxygen delivery. They are inexpensive, relatively comfortable, provide a great deal of flexibility, and allow you to pursue daily activities. You can talk, eat and cough while wearing them. A nasal cannula has two small prongs in the nose attached to a tube coming from an oxygen source. Two to six liters of oxygen per minute can be administered, but consistent use of more than three liters per minute may dry the lining of the nose and lead to sinusitis. Bubbling the oxygen through a humidifier before delivery at the nose moistens the gas. At low oxygen glow rates of one or two liters per minute, or with a conserving cannula, it may not be necessary to moisten the gas. A nasal cannula may produce some irritation around the ears. Face masks, called the Venti-mask, for oxygen delivery are not often used outside a hospital. **Transtracheal oxygen delivery** is efficient, cosmetically more acceptable for some people, promotes continuous use of oxygen, and reduces breathlessness during eating. For example, a person needing two liters per minute with a regular cannula may need only one liter per minute with a transtracheal catheter. This lengthens the amount of time for one E cylinder from five hours to ten. The system requires a surgical procedure. There are standard methods for inserting a catheter (small tube) through the skin at the front of the neck into the windpipe to enable the direct delivery of oxygen into the trachea. A needs is inserted through the cricothyroid membrane. Then a catheter is introduced through the needle and remains in place after the needle is withdrawn. The oxygen source is connected to the small tube. In order to prevent infection, the catheter needs attention and cleaning on a daily basis (Tucker et al '01: 96, 97, 100).

Medicare in the US will only pay a standard rental to the supply company regardless of the type of system. US Medicare currently covers some of the cost of oxygen for those who need it continuously, but not only for use during exercise and not only for portable systems. Liquid

oxygen systems need more service from home/health care providers, and are not fully reimbursed. With 25% cuts to reimbursement for oxygen implemented in January of 1998, many health care companies are attempting to remove liquid oxygen from some people. By law, however, the oxygen provider cannot change the method of oxygen delivery prescribed by the doctor. Another 5% cut in US Medicare reimbursements took place in January, 1999, totaling 30% reduction in oxygen reimbursements and coverage by Medicare. Companies that provide oxygen equipment and service claim that they cannot withstand 25 and 30% cuts in their income. A person on Medicare may buy a system outright, but it is expensive and requires upkeep (Tucker et al '01: 101, 102).

III.A.10 Pneumonitis, bronchiectasis and pneumoconiosis

Hypersensitivity pneumonitis or extrinsic allergic alveolitis, is often associated with specific professions. In these instances, animal, vegetable or bacterial enzyme material may induce the disease. For example, inhalation of *Thermoactinomyces vulgaris* or fungal spores of *Microsporum faeni*, which can contaminate hay, moldy sugar cane, or mushroom compost, have been causally related to farmer's (thresher's) lung, bagassosis, and mushroom-worker's lung. In a similar way, *Cryptostroma corticale* has been associated with maple bark disease of woodworkers, *Penicillium caseii* to cheeseworker's disease, *Aspergillus clavatus* and *A. fumigatus* to brewer's lung disease. A regimen of environmental control and hyposensitization is normally prescribed for pollinosis. Currently, three basic drugs have preempted ephedrine for use in the control of asthmatic attacks: epinephrine (adrenalin) and its congeners administered by aerosol, the methylxanthines administered intravenously for acute attacks and orally for chronic asthma, and the steroids (cortisone), corticosteroids, for severe and intractable states, in combination with other drugs mentioned (Elvin-Lewis '77: 76, 77). The Occupational Safety and Health Administration estimates that 11 million workers are exposed to some **200 substances** associated with occupational asthma, and about 15 percent of "disabling" cases of asthma are related to the workplace. The Americans with Disabilities Act (ADA) covers asthma and requires employers to take reasonable measures to accommodate employees with special health issues and disabilities (Berger '04: 228, 229). In 1985 as a direct result of the AIDS epidemic, health authorities implemented the use of universal health precautions to protect against transmission of HIV and hepatitis C. All health care and emergency workers began wearing protective gear, including surgical gloves, which are typically made from natural rubber, or latex. Today, it's estimated that more than 5.6 million American health care workers use more than 7 billion pairs of gloves each year. That has resulted in a significant increase in late allergies, with an estimated 1 to 6 percent of the general population affected, and 5 to 10 percent of health care workers (Berger & Gordon '04: 260).

Work Related Causes of Pneumonitis and Asthma

Farm workers	Organic phosphorus insecticides
Bakers, farmers, flour mill workers, and grain elevator workers	Flour and grain dust
Silk-processing workers, research laboratory workers, and insect-raising facility workers	Insects
Prawn, snow-crab and fish processors	Seafood and other marine organisms

Laboratory workers and animal handlers	Animal dander
Detergent producers, food industry workers, and blood-processing lab workers	Various enzymes
Carpet manufacturing workers, pharmaceutical industry workers, latex glove manufacturing workers, and health care workers	Latex and gums
Plastic, rubber or foam manufacturing workers; spray painters; foam insulation installers	Diisocyanates such as toluene, diphenylmethane, and hexamethylene
Solderers and electronics industry workers	Abietic acid, soldering fluxes
Woodworkers, foresters and artisans	Plicatic acid in Western red cedar wood dust
Refinery workers	Metals such as chromium, platinum and nickel
Textile workers	Dyes
Plastic and epoxy resin workers	Anhydrides, such as trimetillitic and phthalic anhydride
Adhesive handlers	Acrylates
Health care workers	Glutaraldehyde and formaldehyde
Pharmaceutical industry workers	Certain pharmaceuticals
Toluene 2, 2-diisocyanate	Polyurethane synthesis

Source: Berger '04: 64, Bethel '89: 163

The **chronic form of hypersensitivity pneumonitis** may be extremely difficult to diagnose. Cough and dyspnea develop insidiously and are not directly related to specific episodes of antigenic challenge. Physical examination may show hyperexpansion, diminished breath sounds, hyper-resonance and rhonchi of COPD or the "Velcro" sounding rales of diffuse interstitial fibrosis. The chest radiograph usually demonstrates hyper-expansion with a generalized increase in interstitial markings, but may be easily mistaken for the picture of simple COPD. Pulmonary function testing in individuals with chronic forms of hypersensitivity pneumonitis is variable, with degrees of both restrictive and obstructive diseases. Lung volumes are usually diminished, although ratio of residual volume to total lung capacity may be elevated. The diffusion capacity for carbon monoxide (DLCO) is depressed). Lung biopsy of patients who have more acute forms of hypersensitivity pneumonitis demonstrate marked interstitial infiltration consisting of plasma cells, lymphocytes, and clumps of epithelial cells with scattered granulomas. Many foamy macrophages are seen within alveoli and terminal airways, and a terminal bronchiolitis may be present. In the chronic form of the disease there is nonspecific peribronchial fibrosis with some degree of centrilobular emphysema.

A suspected **diagnosis of hypersensitivity pneumonitis** may be confirmed by three immunologic procedures (1) an inhalation challenge with suspected antigens, however, it is rarely necessary and should be performed only by personnel familiar with the disease and capable of treating the potential severe pulmonary reactions that may ensue, (2) agar gel precipitation tests may be performed because more than 70% of patient sera contains precipitating antibodies. Generally, standard Ouchterlony double diffusion test is sufficient and (3) skin testing with the suspected antigen may elicit either a type III (Arthur) response or a dual response consisting of a type I response followed by the Arthus reaction in several hours. Delayed hypersensitivity skin reactions are not seen in these patients. In patients whose diagnosis remains uncertain an open lung biopsy is recommended. The only effective treatment hypersensitivity pneumonitis is complete avoidance of the offending antigen. Corticosteroids may dramatically abort the acute attack, with improvement seen as early as 1 or 2 hours following their administration. Treatment of the chronic forms of the disease is less successful and patients whose lungs hae progressed to a state of centrilobular emphysema with interstitial fibrosis, even if further antigenic exposure is avoided, rarely improve even with corticosteroid therapy (Dreisin '89: 232-236).

The term **bronchiectasis** means simply dilation of the bronchi, but in general usage it also implies the infectious destruction of bronchial walls. Saccular bronchiectasis is the classic advanced form characterized by irregular dilations and narrowings. The term cystic is used when dilatations are especially large and numerous. Tubular bronchiectasis is simply the absence of normal bronchial tapering and is usually a manifestation of severe chronic bronchitis rather than of true bronchial wall destruction. The term **pseudobronchiectasis** is applied to cylindric bronchial widening, which may complicate a pneumonitis but disappears after a few months. **Dry bronchiectasis** is true saccular bronchiectasis but without cough or expectoration, it is located especially in the upper lobes where good dependent drainage is available. A proximal form of bronchiectasis (with normal distal airways) complicates aspergillus mucus plugging. Most bronchiectasis is acquired and includes repeated or prolonged episodes of pneumonitis, especially those complicating pertussis or influenza during childhood, and gastroesophageal reflux and recurrent sinusitis. Bronchial obstruction caused by neoplasm or the inhalation of a foreign body may also result in bronchiectasis. When the bronchiectatic process involves most or all of the bronchial tree, whether in one or both lungs, it is belieed to be genetic or developmental in origin. Cystic fibrosis, Kartagener's syndrome (bronchiectasis with dextrocardia and paranasal sinusitis) various cartilaginous defects and ciliary defects, and agammaglobulinemia are examples of inherited or development diseases associated with bronchiectasis. Most cases of bornchiectasis are accompanied by severe chronic bronchitis, which is really the other extreme of a wide clinical spectrum of bronchial disease. Advanced bronchiectasis is often accompanied by anastomoses between the bronchial and pulmonary vessels, causing right-to-left shunts, with resulting hypoxemia, pulmonary hypertension, and cor pulmonale. The frequency of bronchiectasis has waned considerably in recent years because of measles and pertussis vaccinations and early widespread use of antibiotics for respiratory infections (Mitchell '89: 238, 239).

The principal clinical feature of **bronchiectasis** is a chronic cough, usually production of large amounts of muco-purulent, often foul-smelling sputum. In advanced cases the sputum settles out into three layers: cloudy mucus on top, clear saliva in the middle, and cloudy purulent material on the bottom. It is frequently associated with chronic paranasal sinusitis. Frequent broncho-pulmonary infections as the disease advances, chronic malnutrition, sinusitis, clubbing, cor pulmonale, and right-sided heart failure are characteristic features of advanced untreated disease.

The diagnosis of bronchiectasis can often be made from the history alone. Bronchoscopy findings often reveal a velvety deep red mucosa and pus welling up from the areas of involvement in the bronchiectasis. Gram stains of sputum often show a variety of organisms, especially the fusospirochetal organisms. Cultures also reveal a variety of nonspecific organisms including the common mouth flora, *Pseudomonas aeruginosa*, anaerobic streptococci, and many others. Microscopic examination of the sputum may reveal necrotic elastic tissue, muscle fibers, and epithelial debris. The most important feature of the treatment of bronchiectasis is regular, daily, vigorous bronchial hygiene, with postural drainage, generally continued for the rest of the patient's life. Antimicrobial therapy for periods of 7 to 10 days may be helpful in the management of acute exacerbations of bronchiectasis. Prolonged and especially multiple antimicrobial drug therapy tends to eliminate the drug-susceptible organisms, allowing drug-resistant organisms to multiply in the irreversibly ulcerated bronchi. Local treatment of an accompanying purulent sinusitis with penicillin or erythromycin is also important. Resection of bronchiectactic segments or lobes depends on the unequivocal demonstration of irreversible involvement of localized areas plus freedom from involvement of both lungs and should be postponed until all efforts at medical management have failed and the results of planned surgery are highly successful. Except for the congenital forms of the disease, bronchiectasis should be regarded as preventable. A child who inhales a foreign body should have it removed immediately by bronchoscopy or surgery if necessary. Vigorous antimicrobial and other appropriate treatment for all forms of pneumonia greatly reduces the frequency of complicating bronchiectasis. Timely vaccination against measles, pertussis, and other childhood diseases commonly complicated by pneumonia is also a preventive measure. Complications include chronic bronchitis, pneumonia with or without atelectasis, cor pulmonale, metastatic brain abscesses, emphysema, and amyloidosis. The prognosis of severe untreated bronchiectasis is poor, generally no more than 10 to 15 year of survival, death is generally a result of pneumonia, empyema, right-sided heart failure, or exsanguinating hemorrhage. The outlook has been greatly improved by the appropriate use of antimicrobial therapy during periods of exacerbation (Mitchell '89: 239-241).

Pneumoconiosis is any change in the lung caused by inhaled dusts. Various occupations in which pulmonary lesions have been reported include: (1) **aluminum pneumoconiosis** in ammunition and fireworks makers; (2) **asbestosis** in asbestos weavers, brake and clutch manufacturers, filter and floor tile makers, insulator, lagger, miller, miner, roofer, shipbuilder and steam fitter**;** (3) **baritosis (barium)** barite miller and miner, ceramics worker, fluorescent lamp maker, glassmaker and metallurgist; (4) coal workers' pneumoconiosis in coal miner, motorman, roof bolter, tipple worker and trimmer; (5) **kaolinosis (clay)** in brick maker, ceramics worker, china maker, miner and potter; (6) **siderosis (iron)** in ship breaker and welder; (7) **silicosis** in abrasives worker, bentonite mill worker, brick maker, ceramics worker, coal miner, missile worker, neon sign maker, nuclear energy worker, phosphor maker, propellant manufacturer, steel foundry worker, toxicologist and X-ray tube maker; (8) **beryllium disease** in alloy maker, bronze maker, ceramics worker, demolition person, electronic tube maker, extraction worker, flame cutter, foundryman, grinder, metalworker, metallizer, polisher, scarfer, diatomite worker, enameler, filter maker, miner or miller, motorman, paint maker, polisher, quarry man, sandblaster, shotblaster, stonecutter, stone driller, well driller; and (9) **talcosis** in ceramics worker, cosmetics worker, miner or miller, papermaker, plastics worker, and rubber worker.

Examples of currently acceptable **threshold limits of dust per cc** if respirated per cubic foot are for (1) crystalline silica (0.1 mg); (2) amorphous silica: silica gel (5.0), diatomoaceous earth

(10.0); (3) asbestos: amosite (0.5 fibers/cc), chrysotile (0.5), crocidolite (0.2), other (2.0); (4) talc (2.0); (5) Portland cement (10.0) and (6) coal dust (2.0). The **particle size** is important because particles of more than 5 µm seldom penetrate to the alveoli. When they become submicronic (that is, less than 0.5 µm) in size, on the other hand, some may enter the lungs and pass right out again like a gas. In short, particles larger than 5µm are most likely to be deposited in the nasopharynx; those from 0.5 to 5µm are most likely to be deposited in the nonciliated pulmonary surfaces – alveolar walls – and are labeled "respirable" **Occupational dust disease** examples are crudely graded as follows: (1) **inert pneumoconiosis**, a. iron: siderosis, b. tin: stannosis, c. barium: baritosis, d. cement, e. fiberglass, f. man-made material fiber (MMMF) may be harmful; (2) **active pneumoconiosis caused by silica** or silica content (that is, fibrosis and other diseases that are pathology producing: a. silica, b. certain silicates, including kaolin, c. diatomaceous earth, d. asbestos, e. bauxite and f. talc; (3) **active pneumoconiosis caused by dusts other than silica**: a. aluminum and aluminum oxide, b. coal, c. graphite, d. nickel carbonyl, e, tungsten carbid, f. beryllium, g. cadmium and h. cerium (Mitchell '89: 334-335, 337). A variety of offending agents and their environmental sources have been identified since the inhalation of organic dusts was first implicated in the production of pulmonary diseases in 1713. The antigenic material is a fungal spore in the majority of clinically recognized instances, although heterologous serum proteins and bacterial enzymes have also been implicated. The source of exposure is usually related to a specific occupation or hobby. Most particles responsible for the production of hypersensitivity pneumonitis are extremely small, facilitating deposition within alveoli and terminal airways.

Antigens that can produce hypersensitivity pneumonitis

Disease	**Source of antigen**	**Precipitins**
Air-conditione and humidifier lung	Fungi in air conditioners and humidifiers	Thermohilic actinomyces
Aspergillosis	Ubiquitous	*Aspergillus fumigates*, *A. flavus*, *A. niger*, *A nidulans*
Bagassosis (surgarcane worker)	Moldy bagasse	*Thermoactinomyces vulgaris*
Bird fancier's lung	Pigeon, parrot, hen droppings	Serum protein and droppings
Byssinosis	Cotton, flax, hemp workers	Unkown
Farmer's lung	Moldy hay	*Micropolyspora faeni*, *T. vulgaris*
Malt worker's lung	Moldy barley, malt dust	*A. clavatus*, *A fumigatus*
Maple-bark pneumonitis	Moldy maple bark	*Cryptostroma corticale*
Mushroom worker's lung	Mushroom compost	*M. faeni*, *T. vulgaris*
"New Guinea" lung	Moldy thatch dust	Thatch of huts
Pituitary snuff-taker's lung	Heterologous pituitary powder	Heterologous antigen of pituitary snuff
Sisal worker's lung	Unknown	Unknown
Sequoiosis	Moldy redwood sawdust	Graphium *Aureo basidium pullulans*
Suberosis	Moldy oak bark, cork dust	Unknown
Wheat weevil disease	Infested wheat flour	*Sitophilus granarius*

Source: Dreisin '89: 231 Table 20-2

Farmer's lung is a form of hypersensitivity pneumonitis elicited by the inhalation of the spores of a group of fungi known as the thermatophilic antinomycetes, particularly *Micropolyspora faeni*. These fungi are known as thermatophilic because they grow best at elevated temperatures, between 40° and 60° C. These temperatures are readily achieved by the growth of bacteria and fungi in the moldy vegetable matter found in barns and silos. An exposed farmer may retain as many as 750,000 spores per minute, within the tracheobronchial tree because of the enclosed spaces in which such fungi grow and the small size of their spores (less than 4 μm). Two types of clinical responses may occur. The classic form of farmer's lung disease occurs in patients intermittently exposed to high concentrations of fungal spores. After working in a contaminated silo, an affected person usually remains asymptomatic for 4 to 6 hours. However, symptoms develop that are both respiratory and systemic. These consist of a persistent nonproductive cough, dyspnea, malaise, anorexia, chills, and fever from 104° to 106° F. Chest pain is absent and hemoptysis is rare. The symptoms generally subside in 12 to 48 hours, but frequently become so severe hospitalization is required. Examination may reveal fever and cyanosis, as well as fine crepitant rales heart throughout the chest. Patients frequently return to the site of exposure wearing protective facial masks. Such measures are ineffective because of the small size of the spores, and the typical patient experiences many episodes of the disease during the period progressive weight loss is common and generalized fatigue may be incapacitating (Dreisin '89: 232).

In determining whether an individual has a symptom or disability producing occupational disease, a complete **work history** is essential. It is not enough to know that the patient was a foundry worker; the physician must also learn whether the individual operated a shake-out section or an iron torch in the casting-cleaing department of the foundry. Such a distinction is significant because the person who operates a shake-out section is often exposed to high concentrations of finely divided dusts containing fibrogenic free silica; the iron torch operator, on the other hand, is usually exposed only to high concentrations of benign iron oxide fumes. Welding details are also important, some metals are known to cause disease, cadmium, for instance, may produce a chemical pneumonitis. Dangerous exposure to ozone or to silica may result from welding. Gas-shielded arc welding can produce excessive con entrations of ozone, a chemical highly damaging to the lungs. Some welding fumes contain silica, but iron oxide fumes are essentially harmless (Mitchell '89: 336-337).

Silicosis was first suspected by Hippocrates. Agricola described the fatal effects of silica dust in 1556. About 3,000 new cases per year are diagnosed in the United States, an incidence of one in a million of the general population. The disease occurs particularly in persons engaged in underground mining foundry work and sandblasting. The duration of exposure needed to produce silicosis varies from as little as 18 months to as long as 30 years, depending on the intensity of the exposure. The disease process, once started, continues to worsen for at least 1 to 2 years after exposure ends. Collagen formation and hyalinization produce silicotic nodules measuring 2 to 5 mm. Microscopically these nodules show as fibrous whorls, are avascular and laminated, and contain silica particles that can be seen with lateral illumination. As the process progresses, the nodules coalesce and when large enough, may undergo aseptic necrosis, that is, cavitate. They tend to be distributed in the peribronhial and perivascular spaces that have perilymphatic drainage. Bronchiolar smooth musle atrophy is frequently seen. Simple silicosis is essentially a change ono the chest radiograph consisting of nodulation with no single nodule greater than 9 mm in diameter. Complicated silicosis is the advanced stage of the disease and is characterized by the presence of lumpy desntities that are associated with parenchumal fibrosis – cough, expectoration, repeated chest inections, nonpleuritic chest pain, wheezing, dyspnea on

exertion, ventilator restriction and airways obstruction may be present. In time the small nodules are replaced by large conglomerate masses 1 cm or larger, and the condition is labeled progressive massive fibrosis (PMF). Respiratory insufficiency, pulmonary hypertension, cor pulmonale, congestive right heart failure and death may result. Superimposed tuberculosis and the non-tuberculous mycobacterioses greatly accelerates the onset of disability and death in silicosis. Silica and silicon dioxide react synergistically with mycobacteria; not only is their growth accelerated on culture media, but host immunity to them is reduced. Fully developed silico-tuberculosis is difficult to treat. Patients with silicosis who react to tuberculin (that is, 10 mm induration or more to intermediate-strength PPD-T) should be given INH as preventive therapy for 2 years after careful exclusion of the presence of active tuberculosis, especially by sputum microbiology. The treatment of advanced, disabling silicosis is not very effective, it consists mostly in relieving the hypoxemia with oxygen-enriched air (Mitchell '89: 337-340).

Asbestos is a mixture of hydrous silicates of magnesium, sodium and iron in various proportions and in fibrous form. There are two major types: the amphiboles (crocidolite, amosite, anthophyllite) and chrysotile. Crocidolite fibers (long, thin and straight in comparison with the others, which are larger and serpentine) are more prone to cause harm; the reason is that they are less easily damaged by lung tissue. Asbestos has many industrial uses, including the manufacture of clutch facings, brake linings, auto undercoating, roofing, insulation and fire-resistant textiles. Asbestosis is a pulmonary fibrosis cause by the inhalation of asbestos dusts. It was first reported in the medical literature in 1901 but was not generally recognized until the 1940s and 1950s. Most cases occur in those who are occupationally exposed when loading and unloading sacks of asbestos, handling asbestos aging and textile materials and applying and removing asbestos insulation. Concomitant smoking tends to shorten the latency interval between exposure and onset. The risk of asbestosis is related to the degree – intensity, nature and duration – of exposure. The onset is usually delayed from 20 to 40 years after exposure but may occur earlier if the exposure has been intense. Most people who are exposed do not exhibit any indication of asbestosis during a normal life span. Asbestosis is a form of restrictive or interstitial lung disease or fibrosis that begins in the lower lungs and involves the visceral pleura. The advent of disease consists of an alveolitis, a reaction to asbestos fibers that are engulfed by macrophages and deposited in the alveolar walls, principally around the respiratory bronchioles. These alveoli fill with macrophages first by deposition of fibrin and subsequently by collagen formation. As the fibrosis spreads and inevitably contracts, airways and airspaces tend to enlarged and create the appearance of honeycombing. Dyspnea occurs as the disease progresses. Life expectancy in proven asbestosis is 70% of normal at five years and 50% of normal at 10 years, with almost all deaths resulting from complicating lung cancer. Once it has started, asbestosis frequently shows some progression even though exposure has ended. A pseudotumor caused by fibrosis-induced infolding of partially atelectatic lung tissue may occur. The differential diagnosis of asbestosis is with COPD, emphysema, chronic bronchitis, idiopathic pulmonary fibrosis (cryptogenic fibrosing alveolitis), various forms of organizing pneumonia, scleroderma, rheumatoid lung, bronchiectasis and other pneumoconiosis. Asbestos is not amenable to treatment.

Pleural **mesothelioma** has been recognized for years as a very rare tumor that was associated with asbestos in 1960. By 1965 the fact that 60% to 90% of subjects with pleural mesothelioma had had some asbestos exposure became recognized, the disease usually appears 30 to 40 years after exposure. Some 1200 cases of pleural mesothelioma are reported in the United States annually. It is three times more common in men than women. Some dose-response relationship is evident. The disease usually begins with chest pain (often non-pleuristic), followed by

dyspnea on exertion and then progressive constitutional symptoms. The course may vary but is often quite short and almost invariably fatal within 2 years of onset. Radiation and chemotherapy are without benefit. Peritoneal, gastrointestinal and laryngeal cancers also have some statistical relationship with asbestos exposure. The greatest hazard resulting from asbestos exposure is the **increased risk of bronchogenic cancer**. The risk is almost totally confined to those who are also exposed to cigarette smoke. Smokers who have not been exposed to asbestos have approximately a 12-fold greater risk of developing bronchogenic cancer than do non-asbestos-exposed nonsmokers. Those who have been exposed to both have a 50-fold to 90-fold increase. It is estimated that between 2% and 2.5% of the 150,000 lung cancer cases now occurring annually in the United States may be asbestos-related (Mitchell '89: 340-344).

Talc (soapstone) is a hydrated magnesium silicate widely mined and milled for use as a dusting powder and as a constituent of paints, ceramics, asphalt, roofing materials, insecticides and cosmetics. Whether talc per se (free of fibers) can cause disease is not known. The disease of talc workers is attributable to tremolite fibers and possibly chrysotile and anthophyllite (asbestiform) as well. Exposure may produce massive fluffy densities, especially in the midlungs, without significant symptoms, there is a distinct risk, however, of disabling or fatal progressive fibrosis. Inhaled in high concentrations, talc may produce an acute broncho-constriction that may be fatal to children. Corticosteroids may cause symptomatic relief in severe cases. **Coal workers' pneumoconiosis** (CWP) is defined as the accumulation of coal dust in the lungs and the reaction of the tissues to its presence. It should not be confused with black lung which is a legal or lay term meaning any chronic respiratory disease as a coal miner. The reason for making this distinction is that black lung compensation benefits are given to surface coal miners, as well as underground coal miners, with (or without) respiratory disability after 25 or 30 years of exposure – without the necessity of confirmation of CWP by chest radiograph. Silica is present in some coal dusts (especially anthracite and higher grades of coal) and the radiographic of silicosis and CWP are indistinguishable. The initial pulmonary reaction to coal dust is the **coal macule**, which ranges in size from 1 to 5 mm. Coal macules are located in the secondary lobule especially in the upper lobes. They are found in black pigment deposits around respiratory bronchioles, often with a zone of air space (focal emphysema) surrounding them. **Coal nodules** are almost always seen in a background of coal macules. They tend to start in the same location, are larger – up to 20 mm before they coalesce – are palpable on the cut surface of lung and contain variable amount sof reticulin and collagen. When more than 13% (some say 18%) of the lung ash at autopsy proves to be silica, the case is diagnosed as silicosis. CWP was described in Great Britain in the 1830s, after 1400 years of coal mining. In the past it took 15 to 20 years of exposure to acquire the disease. Today the risk after even 35 years of exposure is minimal, except in small, poorly monitored and ventilated mines. The ILO '80 Classification System divides each lung into three zones. The fine nodulations are classified as predominantly rounded or irregular and rated as 1, 2 or 3 according to the profusion or numbers of the shadows. The process progresses from simple to complicated when any opacity measures at least 1 cm (category A), when one or more apacities combined measure more than 5 cm but less than one third of one lung (category B) and when one or more large apacities added together have a diameter exceeding one third of one lung (category C). Death caused by CWP is usually related to the development of restriction (fibrosis) usually with some degree of airways obstruction, hypoxemia, pulmonary hypertension and cor pulmonale. Tuberculosis and mycobacteriosis are rare complications. Treatment of CWP is essentially nonexistent. Prevention depends on dust monitoring and control, adequate ventilation of the mines, wet-drilling, effective and tolerable masks, annual chest radiographic examinations and termination of employment of those with category 2 or more advanced CWP (Mitchell '89: 345-347).

There are several other pneumoconiosis known to involve silica. **Shaver's disease** was caused by the inhalation of fumes containing aluminum oxide and silica produced by fusing bauxite powder in iron pots at over 2000° C. It occurred almost exclusively in a small region near Niagara Falls in Canada. The course of the disease was rapid with sever dyspnea, spontaneous pneumothoraces, severe respiratory insufficiency and death. Diatomite, or **diatomaceous earth** contains amorphous silicon dioxide and is mined in several parts of the world, especially in coastal California. It is used to manufacture abrasive polish, insulation and cleaning materials. In the calcined or flux-calcined form it can produce a severely disabling pneumoconiosis because of contamination with free crystalline silica. **Caplan's syndrome** was first described in Welsh coal miners with rheumatoid arthritis. It consists of large "cannonball" infiltrates in both upper lungs, generally with no or mild pulmonary symptoms. The nodules are morphologically similar to rheumatoid nodules. These lesions have more recently been found in hard rock miners and even in a few non-miners with the rheumatoid diathesis in many other parts of the world (Mitchel '89: 347). **Beryllium** has become and important and useful metal because of its lightness and tensile strength. It has been used, for example, in the phosphors used in fluorescent lighting tubes, in the cement used to manufacture false teeth bridgework, in the solid fuels for space flight and in ceramics and various alloys. Because of the hazards, it is currently used mostly in nuclear physics to reduce the speed of fission reactions and for windows in radiograph tubes. The raw ore is not hazardous until it has been processed into the pure metal or one of its salts. Inhalation of purified beryllium may cause an acute rhinitis, tracheobronchitis or pneumonitis, usually after a brief but heavy exposure. The interval between exposure and onset may vary up to several weeks Although some 80% of people afflicted recover completely, the resulting pneumonia or edema-like processes produce severe hypoxemia; the patient requires supplementary oxygen and, at times, mechanical ventilation. Mortality is around 10%; some 10% of patients progress to the chronic form. Beryllium granulomas may occur in the skin. Chronic beryllium granulomatosis is a systemic disease that produces granulomas throughout the body, especially the lungs It has occurred as late as 15 years after initial exposure. The morphology is almost indistinguishable from miliary sarcoidosis, except that the lesions and many involved and uninvolved organs contain a significant amount of beryllium. Response to corticosteroids is often dramatic, but temporarily, beneficial (Mitchell '89: 347, 348).

Arc welder's siderosis probably should not be classified as a disease, since symptoms, abnormal sins and disability do not occur, and autopsy shows no tissue changes. The chest radiograph shows a fine military stippling caused by the deposition of iron pigment. When the welding process includes minerals other than iron (for instance silicon dioxide, silicates and aluminum) it becomes hazardous. Acute welder's lung is apparently a pneumonitis occurring in response to high concentrations of ozone, usually caused by the presence of aluminum. **Tungsten carbide** or hard metal workers are exposed to a very fine powder and may develop interstitial fibrosis or airways obstruction possibly because of cobalt content. **Nickel carbonyl**, emitted during nickel processing and used as a catalyst in petroleum, plastic, rubber, and nickel plating industries, may cause acute pneumonitis and bronchiolitis, it is also associated with an increased risk of lung cancer. **Uranium miners** are unavoidably exposed to silica. In addition, especially if they are cigarette smokers, they have a high risk of lung cancer – significantly higher than cigarette smoking alone would cause. It has gradually become evident that virtually all lung diseases related to the inhalation of dusts of all varieties are made worse by and sometimes even confined to those people who also have been regular cigarette smokers. All physicians should be on the watch for occupational or environmental causes of chest symptoms and radiographic changes. It

is also possible that such exposures may precipitate pulmonary collagenoses such as lupus erythamatosis and scleroderma .(Mitchell '89: 348, 349).

Air pollution from the burning of coal has been recognized as an unpleasant nuisance for at least 400 years. At least 10 acute air pollution disasters have been recognized and well documented in various parts of the world, including the United States. These have all ben related to sulfur dioxide and particulates from coal combustion. The 1952 disaster in London was responsible for over 4000 deaths. The various ways in which urban, industrial or community air pollutants may cause adverse effects include (1) metal, paint and rubber corrosion; (2) crop damage; (3) weather alteration; (4) visibility impairment; (5) bad odors; (6) disease aggravation – heart and lungs; (7) disease cause – eye, lungs and heart; and (8) greenhouse effect from the stimulation of plant growth from excess carbon dioxide and the resultant warming effect on the immediate environment. **Major sources of pollution** include: (1) production, processing and use of petroleum products; (2) chemicals, metal processing, ceramics from factories; (3) backyard, industrial and community incineration; (4) combustion of coal and wood; (5) chemical solvents and (6) certain agricultural practices. Urban air pollution constituents are typically divided into primary emission, reaction products and materials of natural origin. (1) **Primary emissions** of: sulfur oxides, nitrogen oxides, carbon monoxide, carbon dioxide, hydrocarbons, organic solvents, fluorides, insecticides, lead and radioactive dusts; (2) **reaction products**: oxidants: ozone and other free radicals, preoxyacetyl nitrates (PAN), fly ash, formaldehyde, benzo(a)pyrene and numerous other polycyclic aromatic hydrocarbons; and (3) **materials of natural origin**: allergens, soil dust, radioactive isotopes, asbestos fibers and rubber particles from tires. Air pollutants are capable of causing bronchial irritation, excess mucus secretion, cough, increased resistance to airflow, paralyze cilia temporarily, lower resistance to respiratory infections, aggravate chronic lung (and heart) disease by interference with oxygen transport (CO) or induce carcinogenesis (Mitchell '89: 351, 352). Air pollution clearly aggravates and may play a partial causative role in chronic bronchitis, emphysema, and COPD. These diseases are more common in men than in women and in cigarette smokers than in nonsmokers. Polluted air is inhaled through the nose and is thus partially filtered, but it is inhaled constantly. Cigarette smoke is inhaled directly through the mouth without being filtered by the nose but the inhalation is intermittent. Persons with COPD having acute exacerbations have shown significant improvement in airflow when removed from Los Angeles air to rooms ventilated with thoroughly filtered clean air. Ozone has been shown to impair oxygen diffusion into the lungs of humans. **Tokyo-Yokohama asthma** was a severe wheezing bronchitis clearly related to heavy industrial air pollution; it was confined almost exclusively to cigarette smokers (Mitchel '89: 353).

Carbon monoxide has a hemoglobin affinity 245 times that of oxygen; even small concentrations tend to block oxygen transport especially to the brain and heart. Driving through commuter traffic in downtown Los Angeles can produce a blood level high enough to cause symptoms even in a nonsmoker; commuters who smoke get even higher concentrations. Carbon monoxide may also be involved in angina attacks and the pathogenesis of atherosclerosis but is primarily hypoxic. Urban air pollution – carbon monoxide and oxidants in particular – can aggravate preexisting chronic lung and heart diseases and, in combination with cigarette smoke, can play a causative role in chronic bronchitis and emphysema. Urban air pollution is also offensive to the eye, nose, and spirit. **PAN** is a free radical formed by the interaction of sunlight, hydrocarbons and nitrogen oxides from automobile exhausts. It is the substance known to inhibit enzyme activity in plants, causing the death of plants and trees along highways in southern

California. In minute quantities undetectable by humans, it has been shown experimentally to impair exercise performance in health people (Mitchell '89; 353, 354).

III.A.11 Pneumothorax, pleural, interstitial, systemic and rheumatic disease

Pneumothorax is the presence of air between the visceral and parietal pleura. Air can enter the pleural space either from the lung (spontaneously) or directly through the chest wall. Normally, the pleural space is free of air because of the low partial pressures of gases in venous blood, which creates a driving pressure of gas from the pleural space to blood. Traumatic pneumothorax is a result of blunt or penetrating chest trauma. Iatrogenic pneumothorax occurs as a consequence of a diagnostic or therapeutic procedure such as thora-centesis, pleural biopsy or central line placement. The approximate incidence of primary spontaneous pneumothorax ranges from 2.5 to 18/100,000 population and from 0.01% to 0.17% of all hospital admissions. Spontaneous pneumothorax is a major problem in young adults with cystic fibrosis. In persons over 40, spontaneous pneumothorax is most commonly due to COPD. Spontaneous pneumothorax can occur in bronchial asthma in status asthamiticus. *Staphylococcus aureus* pneumonia is probably the most common infectious cause of spontaneous pneumothorax. Primary spontaneous pneumothorax occurs when a strategically located subpleural bleb rupture into the pleural space. These blebs probably form following the passage of air from a ruptured alveolus via the interstitial space into the fibrous layer beneath the visceral pleura. Depending on the quantity of air in the pleural space several days are required for complete reabsorption of a pneumothorax. Chest pain (<90%) and dyspnea (80%) are the most common presenting symptoms. A nonproductive cough is present in about 10% of patients. Pneumothorax occurs with strenuous activity, including coughing or sneezing, in 80% of patients. The diagnosis of pneumothorax can only be confirmed by identifying the visceral pleural line on chest radiograph. Bed rest and the use of supplemental oxygen, is appropriate in a previously healthy individual who had a small pneumothorax without severe dyspnea and no indication that the pneumothorax is getting worse. Without operative intervention, resolution of pneumothorax requires 3 to 4 weeks, since intrapleural air is absorbed at a rate of approximately 1.25% of the hemithorax volume per day (Sahn '89: 291-294).

Systematic analysis of the pleural fluid provides a definitive diagnosis in approximately 20% of cases and a presumptive diagnosis in about 50% of cases. Diagnosis that can be established definitively by **thoracentesis** include malignancy, empyema, tuberculosis, fungal infection, lupus pleuritis, esophageal rupture, urinothorax and chylothorax. The daily rate of normal pleural liquid formation is probably less than 20 ml for a 70 kg man and consists of fluid with a protein concentration of 1 to 1.5 g/100 ml and a small number of mononuclear cells. Only a few ml (less than 10) of pleural fluid is present in the normal pleural space. Abnormal amounts of fluid may accumulate when one or more of the following occurs (1) increase in hydrostatic pressure, as in congestive failure, (2) increase in oncotic pressure, as in severe hypo-albuminemia, (3) increase in capillary permeability, as in inflammatory and neoplastic effusions, (4) increase in intra-pleural negative pressure, as in major atelectasis, (5) decrease in lymphatic drainage, as in malignancy and/or (6) movement of fluid from the peritoneal space, as in cirrhosis with ascites. The symptoms that cause a patient to see a physician are seldom cause by the effusion but by the underlying disease process. However, a large effusion may cause exertional dyspnea in a patient with underlying lung disease. When a pleural effusion occurs, the lung is separated from the chest wall by a layer of fluid that interferes with sound transmission. Sounds are altered if a bronchial obstruction or consolidation of the underlying tissue exists. Occasionally more than 300 ml of fluid is situated between the bottom of the lung and the

diaphragm. When the diagnosis of a pleural effusion is established radiographically and ocalized by physical examination, a diagnostic thoracentesis should be performed unless the clinical diagnosis is secure. When thoracentesis is performed, color, odor and character of the fluid should be noted. Some of the following tests should be performed: red cell count, white ell count with differential, analysis for protein and glucose lacti-dehydrogenase (LDH), amylase, pH, Wright, Gram and acid-fast bacilli (AFB) stains, aerobic, anaerobic, mycobacterial and fungal cultures and cytology (Sahn '89: 284- 286).

In the **differential diagnosis** of pleural effusion, it is helpful to classify the fluid as either a transudate or an exudate. If any one of the three following criteria is present the fluid is usually an exudate (1) a pleural fluid-to-serum total protein ratio of more than 0.5, (2) a pleural fluid LDH of more than two-thirds the normal upper limit of the serum, or (3) a pleural fluid-to-serum LDH ratio of more than 0.6. **Transnudate causes** of pleural effusion are congestive heart failure, cirrhosis ofhte liver, nephrotic syndrome, atelectasis, hypo-albuminemia, peritoneal dialysis, constrictive pericarditis, malignancy (under 10%) or urinothorax. **Exudate causes** of pleural effusion are bacterial pneumonia, pulmonary embolism, malignancy, viral disease, connective tissue disease, tuberculosis, fungal disease (blastomycosis), parasitic disease (amebiasis), rickettsial disease (Q fever), gastrointestinal disease (pancreatitis, subphrenic abscess, esophageal rupture, drugs reaction (nitrofurantoin, methysergide), asbestos pleural effusion, Meigs' syndrome, post-cardiac injury syndrome, trapped lung, lymphatic abnormalities (yellow nail syndrome), uremic pleurisy, radiation therapy, chylothorax, and/or sarcoidosis. Transnudate fluids and some exudates are **clear and straw colored**. A white, milky color suggests chylothorax, a reddish tinge indicates blood, a brown color may suggest rupture of an amebic liver abscess into the pleural space, and a black discoloration suggests aspergillus infection. Elevated **white cell counts** and increased amounts of lipids make pleural fluid turbid. Pus aspirated fro the pleural space confirms the diagnosis of **empyema**. Anaerobic empyemas have a foul odor. A bloody, vicious fluid suggests a malignant mesothelioma. If the fluid's leukocyte count is greater than 1000/µl, it is probably exudative. An **erythrocyte count** of 5000 to 10,000/µl is needed to make the pleural fluid hemorrhagic. If fluid is bloody without trauma a malignancy is likely. A low pleural fluid **glucose** (less than 60 mg/100 ml or pleural fluid/serum ratio (PF/S) of less than 0.5) narrows the differential diagnosis of the exudate to (1) rheumatoid pleurisy, (2) empyema, (3) carcinoma, (4) tuberculosis or (5) lupus pleuritis. A low pleural fluid **pH** (less than 7.30) has been found only in empyema, esophageal rupture, rheumatoid pleurisy, tuberculosis, malignancy and lupus pleuritis. If the pleural fluid pH in a parapneumonic effusion is more than 7.30, the fluid will almost always resolve spontaneously with antibiotic therapy without sequelae. However, it the pleural fluid pH is less than 7.10, the patient will most likely have a complicated course requiring a surgical procedure to drained immediately from the pleural space with a chest tube.

An elevated pleural fluid **amylase**, usually twice the serum amylase, suggests one of four possibilities, (1) acute pancreatitis, (2) pancreatic pseudocyst, (3) esophageal rupture, or (4) primary or metastatic carcinoma of the lung. Chylous effusions (caused by severing or obstructing the thoracic duct with drainage into pleural space) contain chylomicrons and a high triglyceride concentration (more than 110 mg/100 ml). On the other hand, chyliform effusions (long-standing, loculated effusions seen occasionally in tuberculosis, malignancy, trapped lung, or rheumatoid disease) contain a high cholesterol concentration and low levels of triglycerides (less than 50 mg/100 ml). In cases of malignant disease of the pleura, cytologic tests are positive in 65% to 70% of patients. AFB, Gram, Wright stains, pleural biopsy and therapeutic thoracentesis, should be performed. Nasal oxygen should be given during and for several hours

following therapeutic thoracentesis, since transient and sometimes substantial falls in PaO_2 may occur despite relief of dyspnea. The incidence of pleural effusion associated with pneumonia depends on the cause of pneumonitis. *Streptococcus pneumoniae* causes parapneumonic effusion in 40% to 60% of patients and especially in patients with positive blood cultures and prolonged symptoms before antibiotic therapy. *Staphylococcus aureus* pneumonias are frequently complicated by effusion (70% in infants, 40% in adults). *Streptococcus pyogenes* pneumonias are not common but are frequently (55% to 95% of the time) associated with large pleural effusions. The gram-negative aerobic pneumonias (*Klebsiella*, *Escherichia coli*, and *Pseudomonas* species) are associated with a high incidence of parapneumonic effusion (Sahn '89: 288-291).

Congenital malformations may exist in the mediastinum and include cysts and vascular malformations such as a right-sided aortic arch. Vascular disease that may occur as mediastinal abnormalities include aneurysms and non-aneurysmal dilatation of vessels secondary to increased pressure, as is commonly observed in pulmonary artery enlargement secondary to pulmonary hypertension. Both primary and metastatic malignancies as well as many benign tumors, are common in the mediastinum. Mediastinal infections may result from hematogenous dissemination of bacterial or viral pericarditis, secondary to eiterh esophageal rupture (Boerhaave's syndrome) or surgical intervention; and from lymphatic spread from the lungs of tuberculosis, histoplasmosis and coccidioidomycosis). **Noninfectious inflammatory diseases** involving the mediastinum include collagen vascular diseases such as systemic lupus erythematous and rheumatoid arthritis, which commonly cause pericarditis. Fibrosing mediastinitis may follow granulomatous lung infections and the use of the drug methysergide, however, most cases are idiopathic. Severe chest trauma can injure the mediastinum. Air in the mediastinum (pneumomediastinum) may occur after trauma, as a complication of pneumoperitoneum, in association with infection, or as a result of dissection of air from ruptured alveoli into the mediastinal spaces during severe asthma attacks. The majority of mediastinal masses are asymptomatic and show up on routine chest radiographs. When symptoms are present, they are frequently related to compression of normal mediastinal structures. Superior vena cava syndrome is caused by compression of the superior vena cava with obstruction to venous return from the head and neck –dilating the superficial veins of the head, arms and upper thorax and suffusing the conjunctivae. Compression of the recurrent laryngeal nerve may cause hoarseness, compression of the sympathetic ganglia by upper mediastinal tumors may cause Horner's syndrome; and compression of one of the phrenic nerves may cause hemidiaphragmatic paralysis (Rodell '89: 296-298).

Anterior mediastinal masses are usually malignant. In younger patients they are likely to be lymphomas – most often Hodgkin's disease (ages 32 – 65), and less commonly germ cell tumors such as teratomas, seminomas, embryonal cell carcinomas, and choriocarcinomas. Of the germ cell tumors, teratomas are the most common and may be benign or malignant. In older patients, anterior mediastinal masses are commonly either benign or malignant thymomas. These tumors may be associated with myasthenia gravis, which is found in up to 50% of cases. Uncommon tumors that occasionally occur as anterior masses include lipomas, lipsarcomas, fibromas, fibrosarcomas, and parathyroid tumors. Benign **middle mediastinal masses** may be congenital cysts (such as bronchogenic or pericardial cysts), infectious lymph node enlargement when combined with hilar node enlargement, or vascular enlargement such as aneurysms of the aortic arch or main pulmonary artery. In patients who are obese or on corticosteroid therapy, mediastunal or pericardial fat may present as a mediastinal mass. Hiatal hernias are commonly smooth, round masses visible behind the heart on the posterio-anterior chest radiograph. The

middle mediastinum is the most common compartment to be affected by malignancy, with Hodgkin's and non-Hodgkin's lymphoma occurring most frequently. Metastases to the middle mediastinal nodes presenting as a mediastinal mass are common, both from primary tumors of the lung (in which case ipsilateral hilar node enlargement is usually seen) and from other systemic neoplasms, which may metastasize directly to mediastinal nodes without involving the hilum. Nonpulmonnary tumors that commonly metastasize to the mediastinum include testicular and ovarian cancers and upper gastrointestinal and renal cell carcinomas. **Posterior mediastinal masses** may be aneurysms of the descending aorta, diffuse esophageal dilatation (achalasia) or focal diverticulae, gastroenteric cysts, thoracic duct cysts, and meningomyeloceles. Neoplasms in the posterior compartment usually derive form neural tissue, the bone and connective tissue of the vertebral column, or the esophagus. Tumors of neural origin are more common in children, but neurofibromas and occasionally other neural tumors are sometimes seen in adults. Bone tumors do not commonly present as posterior mediastinal masses, however, all types can affect the thoracic spine. Leiomyomas of the esophagus may present as asymptomatic posterior mediastinal masses, however, carcinoma of the esophagus usually becomes symptomatic before it becomes visible on plain chest radiograph (Rodell '89: 298, 299).

Interstitial lung diseases (ILD) are a heterogeneous group of lung disorders characterized by the insidious onset of exertional dyspnea, radiographically by interstitial infiltrates on the chest film, physiologically by a restrictive ventilator defect, and pathologically by alveolar wall inflammation resulting in fibrosis. Interstitial lung disease can be separated into five major groups: the pneumoconiosis, drug-induced diseases, the collagen vascular disease, various primary diseases with associated ILD, and an idiopathic pulmonary fibrosis (IPF). Commonly used drugs that can cause idiopathic pulmonary fibrosis are nitrofurantoin, gold, bleomycin, cyclophosphamide, methotrexate, busulfan, nitrosoureas, and amiodarone. Primary pulmonary disorders associated with diffuse interstitial infiltrates are sarcoidosis (third stage), pulmonary histiocytosis X, hypersensitivity pneumonitis, lymphangiomyomatosis, lymphangitic carcinomatosis, neurofibromatosis, tuberous sclerosis, amyloidosis, adult respiratory distress syndrome, lipoidosis (Gaucher's disease Niemann-Pick disease). Synonyms for idiopathic pulmonary fibrosis are Hamman-Rich syndrome, acute interstitial fibrosis of the lung, interstitial fibrosis, cryptogenic fibrosing alveolitis, honeycomb lung and interstitial pneumonitis. Histiopathic classifications of IPF include desquamative interstitial pneumonia (DIP), usual interstitial pneumonia (UIP), lymphocytic interstitial pneumonia (LIP), bronchiolitis obliterans and diffuse alveolar damage (BIP) (seen with DIP, UIP and LIP), and giant cells interstitial pneumonia (GIP) rare. IPF was originally reported by Haman and Rich in 1935. They reported that some patients rapidly developed cor pulmonale, died within 6 months after onset of dyspnea. Postmortem examination revealed alveolar wall fibrosis and the secondary vascular changes of pulmonary hypertension. Case reports of Hamman-Rich syndrome immediately followed. The mean survival is 4 years, although many patients live 10 years after the onset of IPF. After initial pulmonary testing corticosteroid therapy is initiated with prednisone, 1.5 mg/kg/day, not to exceed 100 mg. Optimally, this dose is maintained from 8 to 12 weeks. Afterwards prednisone is reduced to 0.25 mg/kg/day for one year. If pulmonary function has not improved an additional immunosuppressive drug (cyclophosphamide or azathioprine) is added (Schwarz '89: 179-186).

III.A.12 Systemic rheumatic disease

Rheumatoid arthritis is characterized by a chronic course of exacerbations and remissions of joint disease. Approximately 15% of patients have progressive, disabling arthritis. The pleuro-pulmonary complications associated with rheumatoid arthritis are (1) pleurisy with or without

effusion, (2) idiopathic pulmonary fibrosis, (3) necrobiotic nodule (non-pneumoconiotic intrapulmonary rheumatoid nodules) with or without cavities, (4) Caplan's syndrome (rheumatoid pneumoconiosis), (5) pulmonary vascular lesions and hypertension secondary to rheumatoid pulmonary vasculitis (6) bronchiolitis obliterans with and without organizing pneumonia, (7) apical fibrobulous disease, (8) thoracic cage immobility and (9) respiratory tract infections, especially typical and atypical tuberculosis. In addition, cricoarytenoid arthritis may cause severe laryngeal stridor and upper airway obstruction. Pleurisy with or without effusion is the most frequent thoracic complication of rheumatoid arthritis. Empyemas, both sterile and septic, sometimes with large accumulations of pus, may be found with no apparent predisposing condition other than rheumatoid arthritis. Occasionally necrosis and cavitation of a necrobiotic pleural nodule results in a broncho-pleural fistula and pyopneumothorax. The pleural fluid has a yellow-green color and is an exudate. A low pleural fluid glucose (less than 30 mg/100ml) is characteristic of rheumatoid arthritis (70% to 80% of cases) and is secondary to the impaired transport of glucose by the clinically inflamed pleural surfaces. High concentrations of total lipids and cholesterol, giving the fluid a milky or apalescent appearance, have been described, especially in long-standing effusions. Idiopathic pulmonary fibrosis occurs with increased frequency in patients with rheumatoid arthritis, especially in men, and in pulmonary function tests, up to 40% of rheumatoid arthritis patients are shown to have restrictive ventilator impairment, reduced diffusing capacity and varying degrees of resting hypoxemia that worsen with exercise. 50% of patients have subcutaneous nodules. Cough and dyspnea are often present. Finger clubbing is quite common. The chest radiograph shows diffuse interstitial infiltrates most marked in the lung bases. Honeycomb often occurs. Pleural disease accompanies the interstitial lung disease in one fifth of the patients. Cardiomegaly and pulmonary hypertension may be associated with appearance of cor pulmonale. Bronchiolitis obliterans with organized pneumonia may be a prominent component of the interstitial lung disease of rheumatoid arthritis. Corticosteroid therapy is the treatment of choice for severe disease. Rapidly progressive fatal lung disease (Hamman-Rich syndrome) occurs in a significant proportion of patients with rheumatoid arthritis (King '89: 187-191).

Caplan's syndrome was originally described in coal miners as multiple pulmonary nodules with rheumatoid arthritis. A similar syndrome has been reported in sandblasters, asbestos workers, potters, boiler scalers, aluminum powder workers and brass and iron workers – that is, in persons exposed to silica, not just coal mine dust, who also have rheumatoid arthritis. Rheumatoid pneumoconiosis is characterized by rounded densities, usually located in the lung periphery, that may evolve rapidly and can undergo cavitation and occasionally calcification. The rheumatoid pneumoconiotic nodule consists of layers of partially necrotic collagen and dust and occasionally contains foci of tuberculosis. The pulmonary disease may precede or coincide with the onset of arthritis. Cricoarytenoid arthritis is estimated to be present in 26% of adults with rheumatoid arthritis. Ear pain, dysphagia, the sensation of a foreign body in the throat, dyspnea on exertion and inspiratory stridor are suggestive symptoms. It is been demonstrated that respiratory infection causes 15% to 20% of death in rheumatoid arthritis patients, exceeding the rate of controls. Because of the widespread use of gold in the treatment of rheumatoid arthritis, gold has recently been suggested to be a cause of pulmonary fibrosis (King '89: 191, 192

Systemic lupus erythematosis (SLE) is a disorder characterized by dysfunction of multiple organ systems, including: a non-erosive arthropathy, a variety of mucocutaneous lesions (butterfly rash, photosensitivity, Raynaud's phenomenon, discoid lesions, alopecia, erythematous maculopapular eruptions and mucosal ulceration), renal disease manifested as glomerulonephritis and interstitial nephritis, pleuritis, pericarditis and a spectrum of neuro-psychiatric abnormalities.

Most characteristic is the demonstration of antibodies reactive nuclear and cytoplasmic antigens. The lungs and pleurae are involve more frequently in SLE than in other connective tissue diseases, incidence varies from 38% to 89%. The pleuro-pulmonary manifestations of SLE are (1) pleurisy with or without effusion, (2) atelectasis, (3) acute lupus pneumonitis, (4) diffuse interstitial disease, (5) uremic pulmonary edema, (6) diaphragmatic dysfunction with loss of lung volume, (7) pulmonary vascular disease, (8) pulmonary hemorrhage, (9) bronchiolitis obliterans, (10) upper airway dysfunction, epiglottitis, laryngitis, and cricoarytenoid arthritis, and (11) infections. The predominance of SLE in females is striking. In those patients surviving the acute illness, the chest radiograph clears completely in 50% of patients and the remaining patients develop chronic interstitial pneumonitis with hypocapnia, hypoxemia, restrictive pulmonary defect and impaired diffusing capacity. Corticosteroids are the best treatment for unwitting poison oak or ivy exposure suspected of causing SLE.

Progressive systemic sclerosis (PSS) (Scleroderma) is a multi-system disease characterized by tissue atrophy and sclerosis. The disease occurs most often in women between 30 and 50 years of age. Although skin manifestations are prominent, it is the visceral involvement – renal, cardiovascular or pulmonary – that determines survival. The esophagus is the organ most frequently involved. Morphologic studies have demonstrated pleural and pulmonary involvement in 82% to 90% of patients with PSS. Pulmonary function is almost invariably abnormal. Diffuse interstitial fibrosis is found in nearly all patients at postmortem. Recurrent aspiration pneumonia may result from disturbances of esophageal motility and food retention. Pleuritis is found in 30% of patients. PSS has been shown to be associated with an increased risk of broncho-alveolar cell carcinoma or adenocarcinoma (King '89: 192-197).

Polymyositis is a diffuse inflammatory and degenerative disorder of striated muscles that causes symmetric weakness and atrophy, principally of the limb girdles, neck and pharynx. When an erythematous skin rash accompanies the weakness and pain, the disorder is termed dermatomyositis. The disease is twice as frequent in women as in men and occurs commonly at two ages, before 10 years and between 40 and 50 years. Polyarthritis or polyarthralgia occurs in 35%. Cardiac problems are found in 30% of patients. Hypergammaglobulinemia is frequently present, 20% have rheumatoid factor and 50% to 60% of patients have antibodies to a defined extractable nuclear antigen (PM-1 antibody). The pulmonary manifestations of polymyositis and dermatomyositis are (1) idiopathic pulmonary fibrosis), (2) aspiration pneumonia caused by pharyngeal and esophageal pathology, (3) hypostatic pneumonia secondary to chest wall involvement and hypoventilation, (4) drug-induced hypersensitivity pneumonitis (for example methotrexate) and (5) bronchiolitis obliterans. Pulmonary hypertension , spontaneous pneumothorax, and pleural disease have been rarely reported. 5% to 10% of patients develop interstitial pneumonitis. In approximately 40% pulmonary disease precedes the skin and muscle manifestation by 1 to 24 months. 14% develop aspiration pneumonia. Respiratory failure secondary to generalized respiratory muscle dysfunction occurs in less than 10% of cases. Mild respiratory impairment is common. **Corticosteroids** have caused remissions with stabilization or improvement in the symptomatic, radiographic, and physiologic abnormalities in 40% of patients who are treated with methotrexate (King '89: 197-199).

Sjögren's syndrome is an autoimmune exocrinopathy that occurs as an idiopathic symptom complex (for instance, keratoconjunctivitis sicca, xerostomia [oral dryness] and recurrent swelling of the parotid gland) or in association with rheumatoid arthritis (50% of patients), sLE, systemic vasculitis, dermatomyositis, and scleroderma. Sjögren's syndrome shows a remarkable predominance in females (90%). The disease appears to result from an aggressive T and B

lymphocytes invasion. Patients manifest hypergammaglobulinemia and non-organ specific autoantibodies such as rheumatoid factor (75% to 100% of patients), antinuclear antibodies (66% of patients, antithyroid antibodies, and antibodies to other tissue cells. The pleuropulmonary manifestations of Sjögren's syndrome are (1) pleurisy (with or without effusion), pleural thickening and adhesions, (2) interstitial fibrosis indistinguishable from that found in other connective tissue diseases, seen in approximately 15% of patients, (3) desiccation of the tracheo-bronchial tree secondary to lymphocytic infiltration of the mucous glands, resulting in mucous gland atrophy and plugging of the respiratory tract by inspissated secretions followed by atelectasis and secondary infections, and (4) lymphoid interstitial lung disease is relatively uncommon, a highly differentiated reticulum cell sarcoma or unclassifiable malignant lymphoma is the most common malignant complication, (5) pulmonary vasculitis and primary pulmonary hypertension and (6) chronic obstructive pulmonary disease presumably secondary to small airways disease, resulting from mononuclear cell infiltration of the airway walls. Treatment is not clearly defined but corticosteroids and cytotoxic therapy has had limited success (King '89: 199).

In 1972 it was suggested that features of systemic lupus erythematosus, progressive systemic sclerosis, Sjögren's syndrome and polymyositis constituted a distinctly different rheumatologic syndrome, which they labeled **mixed connective tissue disease** (MCTD). The presence of antibodies to ribonucleorotein (RNP) is generally considered a sine quo non of the diagnosis of MCTD. Pulmonary hypertension is a potentially fatal complication of MCTD. Esophageal dysmotility is present in approximately 80% of patients with MCTD and aspiration pneumonitis often occurs. Recurrent pleurisy and interstitial lung disease occur. Dyspnea, pleuritic pain, rales, increased P2, and cough are the most frequent pulmonary manifestations. Clubbing is not seen. It has been suggested that the primary pathologic finding in MCTD is a proliferative vasculopathy characterized by intimal thickening (King '89: 200, 201).

Ankylosing spondylitis (AS) is a chronic inflammatory disease with predominant involvement of the sacroiliac joints, spinal articulations and paravertebral soft tissue. The onset is insidious and occurs in persons under the age of 40. The cause remains unknown. There has been a definite association with the histocompatibility antigen, HLA-B27, with more than 90% of whites with AS having the HLA-B27 antigen inherited as an autosomal codominant characteristic, and only 20% of patients with HA-B27 develop ankylosing spondylitis. Pleuropulmonary involvement of ankylosing spondylitis is uncommon, manifestations include, (1) upper-lobe fibrocystic disease, (2) pleural disease, bronchopleural fistula, empyema, pleural thickening and spontaneous pneumothorax, (3) recurrent pneumonitis, (4) impaired chest-wall mobility, (5) infectious complications, especially typical and atypical mycobacterial infection and aspergillomas, and (6) miscellaneous processes such as bronchocentric granulomatosis, scar carcinoma, mediastinal fibrosis, and cricoarytenoid arthritis.

Psoriatic arthritis is an inflammatory arthritis characterized by involvement of the distal interphalangeal (DIP) and proximal interphalangeal (PIP) joints of the hands and feet and the absence of rheumatoid factor. An intermittent, oligoarticular, asymmetric synovitis is most frequent. An advanced nongranulomatous upper-lobe pulmonary fibrosis has been described in psoriatic spondylitis. **Wegener's granulomatosis** is a multisystem syndrome of unknown pathogenesis characterized by necrotizing granulomatous vasculitis of the upper and lower respiratory tracts, kidney (glomerulonephritis), and small blood vessels. It occurs at any age with a mean age of presentation being 40 years. Sinusitis, arthralgia or arthritis, fever, cough, otitis, rhinitis, hemoptysis, ocular inflammation and weight loss are common. Respiratory

involvement extremely common and manifested by (1) upper airway disease (rhinitis, refractory sinusitis, and otitis media), (2) tracheal stenosis, and (3) pulmonary infiltrates, with and without cavitary lesions. Chest radiographs classically demonstrate bilateral, well-circumscribed nodules 1 cm or greater in size. Tissue diagnosis is necessary in all cases. Cyclophosphamide in combination with prednisone is the treatment of choice for Wegener's granulomatosis (King '89: 201, 202).

Classic polyarteritis nodosa is a necrotizing vaculitis of small and medium-sized muscle arteries. Renal disease, hypertension, polyarthralgia, and hepatic disease are quite common. Lung involvement is extremely uncommon. **Allergic angiitis and granulomatosis** (Churg-Strauss syndrome) closely resemble classic polyarteritis nodosa but with certain clearly distinguishing features (1) lung involvement (the sine qua non of this syndrome), (2) allergic background and asthma with high levels of peripheral eosinophilia (usually greater than $1500/mm^3$), (3) eosinophilic tissue infiltration, (4) granulomatous reactivity and (5) involvement of capillaries and venules, in addition to muscular arteries. Pulmonary radiographic findings include diffuse alveolar infiltrates that may be transient, nodular pulmonary densities that may cavitate, pleural effusions and diffuse interstitial lung disease. Pathologically the lung shows eosinophilic granulomas, which are necrotizing lesions with frequent involvement of the pulmonary arteries. **Polyangiitis overlap syndrome** combines the features of the above diseases. Small vessels (capillaries and venules) as well as large and small arteries, may be involved. Lung disorders that can occur in this syndrome range from small vessel leukocytoclastic vasculitis to granulomatous vasculitis of medium-sized pulmonary vessels, hemorrhage, infiltrates, nodules, or cavitary lesions. Treatment of the polyarteritis nodosa group of systemic necrotizing vasculitis with corticosteroids has improved the survival rate of patients. In addition, the use of cyclophosphamide, either alone or in combination with preexisting corticosteroid therapy, is associated with a favorable response in some patients (King '89: 203).

Immunoblastic lymphadenopathy has generalized lymphadenopathy, hepatosplenomegaly, anemia, and polyclonal lypergammaglobulinemia as its major manifestations. Bilateral lower-lobe interstitial pneumonia and bilateral, usually exudative, pleural effusions are the main pulmonary complications, 50% patients have hilar and mediastinal adenopathy. **Lymphomatoid granulomatosis** is a necrotizing vasculitis with prominent lung involvement, similar radiographically to Wegener's granulomatosis, with frequent cavitation. Hemoptysis is not uncommon, and pleural effusions may or may be present. This disease is part of the spectrum of malignant lymphoma. If treated early in their course many patients respond to corticosteroids and cyclophosphamide. On the other hand, many of these patients have a relentless course, with death occurring within 2 years of presentation. **Bronchocentric granulomatosis** is a form of bronchitis characterized by secondary necrotizing vasculitis. Patients usually have asthma, eosinophilia, and allergic bronchopulmonary aspergillosis. The chest radiograph often reveals actelectasis, lobar collapse, nodules and parenchymal infiltrates. **Behcet's disease** is a multisystem disorder characterized by ulcer of the mouth and genitalia, relapsing iritis, joint manifestations, thrombophlebitis, migraines, erythemia nodosum, and CNS abnormalities. In general, the diagnosis of Behcet's disease requires the presence of three of the following (1) recurrent aphthous stomatitis, (2) genetical aphthous ulcers, (3) uveitis, (4) synovitis, (5) cutaneous vasculitis, and (6) meningoencephalitis. Vascular involvement is common. Obstruction of the inferior or superior vena cava occurs with relative frequency. Pulmonary involvement is uncommon. These patients often present with massive hemoptysis resulting from bronchial erosion secondary to aneurysms. The Hughes-Stovin syndrome is thought to be a manifestation of Becet's disease and venous thrombosis and pulmonary aneurysms are common

to both. Treatment with corticosteroids has been helpful in patients with acute lung disease, as well as with disease at other sites.

Relapsing polychondritis is a disease of unknown etiologic factors, characterized by inflammation and destruction of cartilage. Most patients have vasculitis of large and small arteries and a coexisting connective tissue disorder is common. Cardiovascular complications occur in 25% of patients and consist of (1) aortic insufficiency secondary to progressive dilation of the aortic ring in the ascending aorta, and (2) aneurysms involving the ascending, thoracic, and abdominal aorta that may rupture and cause sudden death. Pulmonary disease occurs in patients who have recurrent involvement of the laryngotracheal structure, causing upper airway obstruction and secondary pneumonia. Hoarseness, cough, dyspnea, laryngeal tenderness, wheezing and stridor should alert the physician to the possibility of this life-threatening complications. Corticosteroids may be beneficial for treatment of the acute laryngeal inflammation (King '89: 203-205).

Pulmonary alveolar proteinosis (PAP) is a disease of unkown etiology characterized by the intra-alveolar accumulation of lipo-proteinaceous material without alveolar wall inflammation. This acellular intra-alveolar material contains surfactant apoprotein, as well as the lipids which are found in normal lung surfactant. The peak ages of onset are between 30 and 50 years, with no known race or gender predilection. A history of occupational exposure is common. The usual presentation is an insidious onset of cough and dyspnea. The diagnosis is established by lung biopsy, which can usually be accomplished by transbronchial approach. Superinfection occurs in 15% of cases by Nocardia, Aspergillus and Cryptococcus. Another association is hematologic malignancies. **Goodpasture's syndrome** (GPS) refers to a disorder characterized by diffuse alveolar bleeding and glomerulonephritis. The majority of cases (60% to 80%) occur in men and the mean age of onset is 27 years. In 50% of patients hematuria is found. The onset of glomerulonephritis may be delayed up to 3 months. Particularly in non-smokers, only glomerulonephritis occurs, in 20%. Hemoptysis may be present. At least 90% of patients have circulating anti-glomerular basement-membrane antibody, and the highest levels are associated with rapidly progressive renal failure. The diagnosis of GPS is established by a compatible clinical picture, the presence of circulating anti-glomerular basement-membrane antibody and the demonstration of linear deposition of IgG. Treatment is generally unsatisfactory. Corticosteroids appear to have some effect on the pulmonary component but are not effective for the glomerulonephritis. The addition of cytotoxic drugs has a greater effects on the pulmonary than on the renal disease. Approximately 50% of patients with GPS survive for 24 months. The differential diagnosis of GPS includes idiopathic pulmonary hemosiderosis, systemic lupus erythematosis, Henoch-Schönlein purpura, Wegener's granulomatosis, D-penicillamine therapy and polyarteritis nodosa (Schwarz '89: 218-221).

Idiopathic pulmonary hemosiderosis (IPH) is a disease that is limited to the lungs and is characterized clinically by intermittent hemoptysis and morphologically by alveolar filling with red blood cells and hemosiderin-laden macrophages but without other anatomic changes in the lung. IPH is predominantly a disease of children with only 20% of cases occurring in adults. Symptoms include dyspnea, cough, and hemoptysis. Symptoms referable to iron deficiency anemia may also be present. Rale and finger clubbing can be found in chronic cases. Chest radiographs reveal recurrent alveolar and interstitial infiltrates. Patients have hypochromic microcytic anemia, peripheral eosinophilia is found in 10% of patients. Lung tissue is almost always required to rule out other conditions associated with diffuse alveolar bleeding. Tight mitral stenosis should be excluded by echocardiography. Although a combination of

corticosteroids and cytotoxic agents have been anecdotally claimed to be effective in IPH, failure is common, the mean survival is between 3 and 5 years. **Eosinophilic pneumonia** (EP) refers to an idiopathic condition in which eosinophils and other inflammatory cells infiltrate the alveolar walls and spaces. Asthmatic symptoms are prominent in 50% of cases. In the more acute cases dense bilateral alveolar nodules are present on chest radiographs, which clear a few days following corticosteroid therapy. These infiltrates tend to reappear with relapses or too rapid tapering of the corticosteroids therapy. Diagnosis can be established by the combination of broncho-alveolar lavage eosinophilia and a trans-bronchial lung biopsy that demonstrates the eosinophilic infiltration of the alveolar structures (Schwarz '89: 221, 222).

There are several types of interstitial lung disease. **Lymphangitic carcinomatosis** (LC) is a metastatic malignant disease of the lungs arising from primary adenocarcinomas in the breast, stomach, colon, prostate, lung or kidneys. The small muscular arteris and the peribronchial and perivascular lylmphatics fill with the malignant cells. Most pathologists believe that the primary event is small tumor emboli in the pulmonary vessels, which lodge distally and secondarily spread through vascular walls and obstruct the lymphatics. Clinically, the onset consists in progressive dyspnea and cough, marked hypoxemia and signs of cor pulmonale. The chest radiograph reveals interstitial infiltrate with Kerley-B lines at the lung bases. Diagnosis can best be established by transbornchial biopsy once LC is considered a possibility. LC originating from primary breast and prostate adenocarcinoma has occasionally responded to endocrine manipulation. **Lymphagniomyomatosis** (LAM) is an uncommon disease occurring only in premenopausal women and is characterized by the proliferation of smooth muscle in the lymphatics, interstitium, small veins, and small airways of the lung. Proliferation of smooth muscle in the interstitium of the lung results in progressive dyspnea. Smooth muscle obstructing pulmonary lymphatics is associated with chylous pleural effusions in 60% of cases. Although most patients survive for as long as ten years following diagnosis, clinical, radiographic, or physiologic stabilization or improvement has been reported following treatment with progesterone, tamoxifen, or oophorectomy (Schwarz '89: 223,-225).

Pulmonary histiocytosis X (PHX) is one of the three primary diseases that have an abnormal proliferation of histiocytic cells. The first two, Letterer-Siwe and Hand-Schüller-Christian disease, are found in pediatric and younger age groups. PHX occurs in adults and is primarily a pulmonary disorder. PHC is a granulomatous reaction scattered throughout the lungs and found primarily in the interstitium. The atypical histocyte in this disease is a proliferating cell that has been identified as the Langerhans cell normally residing in the skin. In addition, eosinophils, plasma cells, and lymphocytes are found in the granuloma. As the disease progresses stellate interstitial scars are formed which obliterate small airway lumens and lead to cystic dilation of distal alveolar structures. Most patients become symptomatic between the ages of 20 to 40. Cough and dyspnea are most frequently reported and 25% of patients who have PHX, recurrent spontaneous pneumothorax occurs secondary to ruptured cysts. In 10% to 15% of cases bone pain resulting from lytic bone disease involving the skull, ribs, or pelvis is present. A less frequent complication, with a poor prognosis, is diabetes insipidus due to granulomatous involvement of the posterior pituitary gland.

Pneumothorax and lytic rib lesions may be visible to radiograph. With chronic disease a cystic honeycomb appearance supervenes. Peripheral eosinophilia is not uncommon. Broncho-alveolar lavage demonstrates increased numbers of Langerhans cells, and electron microscopic examination reveals the typical pentiluminar Birbeck's granule in the cytoplasm. Diagnosis is usually made by either open-lung or bone biopsy. Responsiveness to corticosteroids has been

demonstrated in early nonfibrotic cases. Spontaneous remission and stabilization without treatment have been reported. **Churg-Strauss syndrome** (CSS) is a clinical syndrome consisting of asthma, fever, eosinophilia, and systemic vasculitis. Histopathologic examination reveals a vasculitis of blood vessels of various sizes, tissue eosinophilia and vascular, as well as extravascular granuloma involvement. Cardiac involvement is responsible for 50% of the mortality in CSS. High dose corticosteroid therapy affords a significant increase in survival, and cytotoxic therapy is sometimes required for refractory cases. **Necrotizing sarcoid granulomatosis** (NSG) is most likely a variant of nodular saroidosis. The granulomatous vasculitis that occurs in NSG is pathologically similar to the sarcoid granuloma. The hilar lymph odes are involved but systemic involvement is unusual. It is primarily a disease of young women whose chest radiograph revels multiple nodular lesions with occasional hilar adenopathy with a gratifying response to corticosteroid therapy (Schwarz '89: 225, 226).

The term "sarcoidosis" was coined by Boeck in the nineteenth century to describe skin lesions that he though resembles sarcomatous tissue and recognized the systemic nature of the disease. Although no agent or factor has yet been identified, most investigators suspect that sarcoidosis (or sarcoid) is initiated by a transmissible agent. Sarcoidosis is a multi-system granulomatous disease with worldwide distribution. The southeastern United States has a high incidence, possibly related to the greater percentage of blacks in the population. The attack rate of sarcoidosis in black neighborhoods of New York City was reported to be 64 per 100,000, whereas in predominantly white neighborhoods of the city it was 7 per 100,000. However, in Sweden where blacks are few, the attack rate is 64 per 100,000. In addition, sarcoidosis occurs infrequently in native Africans living in Africa. The disease appears most commonly in the second through the fourth decades, with the peak incidence in the third decade, cases in childhood and past the sixth decade are also seen. Women are more often affected than men(Schwarz '89: 207). It is hypothesized that sarcoidosis describes the peculiar respiratory infection, skin lesions and systemic illness caused by rodent borne infection.

The typical histologic lesion of sarcoidosis is a granuloma composed of macrophages, epithelioid cells (T lylmphocytes and plasma cells) and fibroblasts are found at the periphery of the granuloma. It is likely that blood monocytes, which are also cells of origin of the pulmonary macrophages, migrate to the site of granuloma formation and are the precursors of the epithelium cells and the Langhans' giant cells. Early studies of human sarcoidosis demonstate that before granuloma formation and alveolitis composed mainly of T-lymphocytes and alveolar macrophages is present within alveolar spaces. Inclusion bodies of the Schaumann or crystalline type are often present within giant cells. The granuloma of sarcoidosis does not caseate like those of mycobacterial disease and histoplasmosis. The fate of this granulomatous lesion is either complete resolution without structural change or hyaline fibrosis causing alteration in target organ function. The granuloma of sarcoidosis is essentially identical to that found in berylliosis, hypersensitivity pneumonitis, regional enteritis, and the non-caseating granulomas of tuberculosis and the fungal diseases. In addition, lymph nodes, which are primary drainage sites for certain chronic infections or malignant disorders, demonstrate histo-pathologic factors indistinguishable from sarcoidosis. Patients with sarcoidosis demonstrate both T- and B-lymphocyte abnormalities that are characteristic for this disease.

One of the clinical hallmarks of sarcoidosis is a quantitative increase in all three major immunoglobulin classes (IgM, IgG and IgA). Hemolytic complement activity is elevated. 40% to 60% of patients with sarcoidosis have a positive serum rheumatoid factor. The IgM is often elevated in patients with erythema nodosum. A persistent elevation of IgG often indicates

progression to a chronic disease state. The enhanced B-cell activity in sarcoidosis is also reflected by finding increased antibody titers to *Mycoplasma pneumoniae*, herpeslike virus (Epstein-Bar virus), measles, herpes simplex, and rubella. This capacity for overproduction of antibodies does not interfere with the expected B-cell response to infectious agents or vaccines. In patients with sarcoidosis, skin test reactivity is absent or diminished when compared with that of control populations. The majority of patients with active disease have decreased skin reactivity to tuberculin and other recall antigens including *Trichophyton*, mumps, and *Candida*. If active tuberculosis develops in a patient with sarcoidosis the tuberculin test result becomes positive. Lymphocytes from patients with active sarcoidosis undergo a higher rate of spontaneous blastic transformation when compared with control groups. In active sarcoidosis a peripheral T cell lymphopenia is seen. However, in sarcoidosis increased numbers of activated T lymphocytes (helper cells) as well as macrophages are found in the bronchoalveolar lavage of these patients. Activated macrophages release interleukin-1, which stimulates the expansion of the T lymphocyte helper cell population. T cells produce interleukin-2, which activates and increases the T cell population. T cells release monokines that are chemotactic for peripheral monocytes to migrate to the lung (macrophages) and stimulate the production of B cell growth factor, which increases the number of immunoglobulin-producing plasma cells. These two functions are the basis for granuloma formation and for the polyclonal increase in gammaglobulins. The alveolar macrophage is also capable of releasing fibronectin, a growth factor fibroblasts. Interleukin-1 and fibronectin attract and support the proliferation of fibroblasts, which causes collagen deposition resulting in lung fibrosis of nonresolving sarcoidosis (Schwarz '89: 209, 210).

The general symptoms of sarcoidosis include fatigue, weakness, malaise, fever and weight loss. The lungs and mediastinal lymph nodes are involved in over 90% of patients with proven sarcoidosis. Dyspnea and cough are the most common complaints, and hemoptysis is occasionally encountered . In 50% of patients with sarcoidosis, the initial lesions spontaneously resolve; the remainder of lesions may progress to diffuse parenchymal infiltration with partial or complete resolution of the nodal enlargement. As the fibrotic process progresses, dense bands of fibrous tissue retract the upper loves and cysts tend to form. Within these cystic spaces, a saprophytic colonization with *Aspergillus* species may proliferate and produce a fungus ball, which can be detected on the radiograph. Dermatologic manifestations are found in 10% to 30% of patients with sarcoidosis. Erythema nodosum with hilar adenopathy is common manifestations in Europe but not the black population in the United States. Another presentation is erythematous macropapular lesions occurring on the face, trunk and extremities. A more serious skin eruption is the nodular or plaque-like lesions that occurs anywhere on the body. Lupus pernio, volaceous plaques on the nose, cheeks, or ears, are also found with chronic protracted disease. Ocular disease, including conjunctival and lacrimal granulomas, is found in 25% to 50% of patients with sarcoidosis. Uveitis is the most common and potentially dangerous eye complication. Initially it involves the anterior chamber and may be self-limiting or may respond to corticosteroid treatment. Posterior segment involvement of chorioretinitis occurs later and coexists with central nervous system sarcoidosis in 10% to 30% of patients. It is chorioretinitis that threatens sight and is difficult to treat. Patients' sarcoidosis occasionally complain of dryness and redness of the eyes secondary to keratoconjunctivitis sicca. Another ocular complication is corneal calcification that can result from hypercalcemia. Palpable lymphadenopathy is found in 30% to 80% of patients with sarcoidosis. Hepatosplenomegaly in 25%. Liver biopsy shows noncaseating granuloma in 70% of patients with early sarcoidosis, but hepatic dysfunction is rare. Arthralgias and occasionally polyarthritis in chronic arthritis with periosteal bone resorption, which appears as cysts, may mimic rheumatoid disease. Uveoparotid

fever, a combination of parotid gland enlargement, uveitis, fever and facial nerve palsy, is a well-recognized presentation of sarcoidosis. Myocardial granulomas caused by sarcoidosis frequently involve the left ventricle, including the papillary muscles and the interventricular septum. This may result in ventricular arrhythmias, congestive cardiomyopathy, mitral insufficiency and left-ventricular aneurysm. Sudden death is rarer than the development of cor pulmonale. The most common cause of renal insufficiency is secondary to the effects of hypercalcemia.

Adrenal insufficiency may follow sarcoidal replacement of the adrenal cortex. Thyroiditis has been reported in the active phase of sarcoidosis. Hemoglobin values below 11 mg/dl are seen in 22% of patients. Usually the anemiais normocytic, normochromic similar to that seen in chronic disease states. In addition to T-cell lymphopenia, leukopenia occurs in 30% of patients and eosinophilia occurs in 24%. Thrombocytopenia is infrequent but may result from hypersplenism. Hypercalcemia and hypercalciuria are found in 10% to 20% of patients. The hypercalcemia of sarcoidosis has been attributed to increased gut absorption of calcium resulting from an increased sensitivity to vitamin D known as hypervitaminosis D. This is due to an increased production 1,25-dihydroxycholicalciferol vitamin D by the activated alveolar macrophages. Pulmonary function testing reveals a restrictive pattern with preservation of flow rates. The stress of exercise may accentuate these abnormalities. The nonspecific self-limiting symptoms of acute sarcoidosis such as fever, arthralgia, and erythema nodosum may be treated with any analgesic drug. Corticosteroid therapy should be reserved for the more serious manifestations including hypercalcemia, uveitis, involvement of the cardiac conduction system, impaired or progressive deterioration of pulmonary function, arthritis, myositis, and central nervous system involvement. The patient with chronic sarcoidosis should be reassured within 1 year approximately half of patients with only hilar adenopathy have normal chest radiographs. At 5 years nearly 80% have normal chest radiographs. Pulmonary infiltrates disappear in approximately one third of patients within 5 years. Treatment with corticosteroids has usually been recommended for infiltrates that are worsening or are persistent for more than 6 to 12 months. However, there is no direct proof that corticosteroids alter the natural history of the disease. Hospital admissions of sarcoidosis patients are infrequent and precipitated by neurologic, cardiac or pulmonary dysfunction (Schwarz '89: 210-217).

III.A.13 Pulmonary hypertension and cor pulmonale

Pulmonary arterial hypertension (PAH) is defined as the elevation of the mean pulmonary artery pressure above 25 mm Hg at rest or systolic pulmonary artery pressure is above 30 mm Hg at rest. Pulmonary artery pressure is lower than systemic arterial pressure and is normally 15 to 18 mm Hg. Latent pulmonary hypertension exists when a significant rise in mean pulmonary artery pressure (>5 mm Hg) occurs with mild exercise. Familial PAH is caused by mutations in the gene encoding the bone morphogenitic protein receptor type II (BPR2). Associated PAH is a leading cause of mortality in many connective tissue disorders (e.g. scleroderma) ad affects up to 1 in 200 individuals infected with HIV. Diet drugs, amphetamines, and cocaine also have been linked o an increased risk for PAH. COPD is the most common lung disease associated with PAH,abut any condition that causes chronic hypoxemia can result in pulmonary hypertension. Symptoms of fatigue, chest discomfort, tachypnea and dyspnea on exertion, palpitations and cough are common. Examination may reveal peripheral edema, jugular venous distention, a precordial heave, and accentuation of the pulmonary compartment of the second heart sound. Definitive diagnosis and accurate assessment of pulmonary artery pressure can be made only

with right-sided heart catheterization. Laboratory studies, including arterial blood gas testing, liver function testing, HIV serology, electrocardiography, chest x0ray and cT scanning, pulmonary function testing, polysomnography, ventilation-perfusion scanning and echocardiography are used to detect underlying causes of PAH. General therapies for PAH include administration of oxygen, diuretic and anticoagulants and avoidance of contributing factors such as air travel, decongestant medications, non-steroidal anti-iflammatory medications, pregnancy and tobacco use. Medications used in the treatment of PAH include prostacyclin analogs (epoprostenol, beraprost, iloprost), endothelin receptor antagonists (bosentan, ambriesentan) and phosphodiesterase-5 inhibitors. Those who fail medical therapy may be candidates for lung transplantation. The best treatment for secondary pulmonary arterial hypertension is treatment of the primary disorder. However, once pulmonary hypertension has persisted long enough hypertrophy of the medial smooth muscle layer to develop (as it does with chronic hypoxia) it is no longer reversible. Treatment relies on use of supplemental oxygen to reverse hypoxic vasoconstrition (McCance '14: 1277-1278))

The **pulmonary circulation** is a low pressure low resistance system. The resistance is 5 times less than in the systemic circulation. With an increase in cardiac output, as with exercise, a minimal rise in pulmonary artery pressure is followed by a fall in pulmonary vascular resistance (PVR = Pa – Pw/C.O.) because of capillary recruitment. The pulmonary circulation is unique because it is exposed to alveolar air, accepts the entire cardiac output, and empties into the left atrium. Each of these features can alter the behavior of the pulmonary vascular bed. Hypoxia cause pulmonary vasoconstriction and is a frequent cause of pulmonary hypertension. Agents that inhibit hypoxic vasoconstriction, such as bronchodilators, calcium antagonists, and nitro compounds, can worsen V/Q matching. Localized hypoxic vasoconstriction is beneficial and generalized hypoxic vasoconstriction leads to pulmonary hypertension and cor pulmonale. In chronic lung diseases, chemical mediators (mainly products of inflammatory cells) can cause vasoconstriction. Generally, chronic hypoxia causes mild to moderate pulmonary hypertension (Voelkel '89: 276). Blockage of abnormally-narrowed bronchial tubes, as well as lack of blood vessels around the alveoli, contributes to low oxygen levels. There's plenty of oxygen in the air, it just can't get through the lungs into the blood. When the oxygen in the blood gets low enough, the heart doesn't work as well as usual. This problem is called **cor pulmonale**, from two Latin words meaning heart lungs. The heart still pumps blood, but it doesn't empty as it should with every heart-beat. Blood eventually piles up behind the heart, just as water does behind a dam which is only partially open. When this happens, congestion with fluid accumulating first in the feet, then in other parts of the body may occur (Tucker et al '01: 29, 38).

Cor pulmonale is secondary to pulmonary artery hypertension and consists of right ventricular enlargement (hypertrophy, dilation, or both). Cor pulmonale develops as pulmonary artery hypertension creates chronic pressure overload in the right ventricle similar to that created in the eft ventricle by systemic hypertension. Pressure overload increases the work of the right ventricle, causes hypertrophy of the normally thin-walled heart muscle, and compromises right ventricular myocardial perfusion. Acute hypoxemia, such as might occur with pneumonia, can exaggerate pulmonary hypertension and dilate the ventricle as well. Right ventricular filling pressures are normal until failure occurs. The right ventricle usually fails when pulmonary artery pressure equals systemic blood pressure. The clinical manifestation of cor pumonale may be obscured by primary respiratory disease and appear only during exercise testing. The appears normal at rest, but with exercise, cardiac output falls. The electrocardiogram shows right ventricle hypertrophy. Chest pain is common. The pulmonary component of the second heart sound, which represents closure of the pulmonic valve, may be accentuated, and a pulmonic vale

murmur also may be present. Triscuspid valve murmur may accompany the development of right ventricular failure. Peripheral edema, hepatic congestion and jugular venous distention often may be detected. Treatment is the same as for pulmonary artery hypertension, and its success depends on reversal of the underlying lung disease (McCance '14: 1278).

The diagnostic hallmark of s**evere pulmonary hypertension** is the combination of high pulmonary artery pressure and low cardiac output. The cardiac output does not respond to exercise in severe pulmonary hypertension. The lower the cardiac output at the time of diagnosis the shorter the survival. The main symptom is dyspnea in patients with severe pulmonary hypertension. Fatigue, syncope, anginalike chest pain, nonproductive cough, and hoarseness also occur. A complete hemodynamic assessment is mandatory for patients with severe pulmonary hypertension. A drastic acute reduction in pulmonary vascular resistance with oxygen administration or infusion of incremental prostacyclin doses signals the long-term therapeutic benefit of chronic oxygen or vasodilator drugs. Ideally, vasodilator treatment is initiated as an acute trial in the catheterization laboratory. The assessment of vasodilator efficacy is preceded by the assessment of the vasodilator response to prostacyclin that appears to be the "gold standard" test for pulmonary vascular reversibility.

Pulmonary vascular disease can occur in each part of the vascular tree. Aneurysms of the main pulmonary outflow tract or benign dilation of the right main pulmonary artery or coarctation of the main pulmonary arteries are rare disorders. Inflammatory lesions (angiitis) occur in Wegener's granulomatosis and in periarteritis nodosa. Churg-Strauss syndrome, and sometimes sarcoidosis. The two most frequent causes of pulmonary vascular disease are vessel obliteration because of thromboembolic disease and alveolar hypoxia-induced pulmonary vaso-constricution resulting from COPD. Pulmonary embolisms and severe pulmonary hypertension are related, and right ventricular failure, and chronic unresolved lung blood clots are a frequent cause of pulmonary hypertension. The effects of pure left-sided heart failure are largely due to pulmonary congestion and edema. **Pulmonary embolism** (PE) is the most common cause of pre-capillary pulmonary vascular disease in the United States. The incidence of acute pulmonary embolism in the United States has been estimated as high as 500,000 cases per year resulting in about 50,000 deaths annually, mostly among hospitalized patients. Most pulmonary emboli arise from venous thrombosis in veins above the knee. Primary in situ pulmonary arterial thrombosis occurs in parenchymal inflammatory diseases that involve vessel walls or when lung parenchyma or tumor compress pulmonary vessels. A massive pulmonary embolism is defined as an occlusion of at least 50% of either peripheral pulmonary arteries or an equivalent amount of the central vessels (saddle embolus). The mortality from massive pulmonary embolism is 25%. **Pulmonary hypertension** resulting from pulmonary embolism occurs when at least 50% of the pulmonary vascular bed is occluded. The three most common symptoms in angiographically proven emboli are dyspnea (78%), cough (70%), and pleuritic pain (50% to 70%). Hemoptysis is present in 20% of cases, and fever is common. When the tentilation-perfusion scan is abnormal multiple segmental or larger defects in flow support the diagnosis. Findings in support of a diagnosis are hypoxemia, hypocapnia, and a widened alveolar-arterial oxygen gradient.

In submassive pulmonary embolism only 10% of patients show radiologic signs of cor pulmonale. Only 10% to to 15% of pulmonary emboli are complicated by pulmonary infarction. Angiography is needed to establish a diagnosis of lung malignancy or postoperative patients. The treatment of choice is continuous intravenous heparin for 7 to 10 days with a goal of prolonging the patients thromboplastin 1 ½ to 2 times baseline. Resistance to heparin therapy is encountered in patients with antithrombin III deficiency, severe liver disease and extensive

thrombosis and in patients who have pulmonary embolism associated with adenocarcinomas (Trousseau's syndrome). Thrombolytic therapy is reserved for patients with acute, massive pulmonary embolism who do not have contraindications (active bleeding, history of CVA, intracranial or intraspinal surgery within 2 months before embolism, trauma or surgery within 2 wees before embolism and diastolic blood pressure >100 mm Hg). Thrombendarterectomy has been performed successfully in specialized centers for the treatment of patients with chronic, major-vessel pulmonary embolism and resultant pulmonary hypertension (Veolkel '89: 272-276).

Hydralazine, Nitro-compounds, and ACE-inhibiors have produced favorable results in some patients. Because advanced, irreversible pulmonary hypertension occurs resulting from irreparable structural alterations some patients will be irresponsive to any vasodilator drugs. Few patients survive for long treated with either continuous intravenous prostacyclin or with other orally administered vasodilators. The value of anticoagulation has not been studied. A few patients with severe, unexplained pulmonary hypertension have undergone heart-lung transplantation, yet long-term follow-up data is not yet available. The overall prognosis in severe (primary) pulmonary hypertension is poor. After the disease has been diagnosed, survival is generally still a matter of months; a few cases have been documented to survive for several years in spite of very high pulmonary artery pressure. The severe reduction in cardiac output and the limitation to increased cardiac output with exercise, are known hemodynamic factors of poor survival. Patients die from progressive right ventricular failure, pulmonary hemorrhage, and syncope. Pulmonary angiography with rapid injection of a large load of contrast medium has resulted in death within 24 hours in a number of patients with "primary" pulmonary hypertension (Voelkel '89:278-283). Hawthorne may help, the FDA writes, to conduct clinical trials to study the efficacy of Hawthorne in the treatment of heart disease, high blood pressure, arrhythmia, congestive heart failure, and other cardiovascular medical conditions.

III.A.14 Cancer of the head, neck and lung

Although the **skin of the head and neck** region accounts for approximately 10% of the body surface area, most cutaneous tumors occur in this area. Benign lesions: Nevi, that develop soon after birth but may appear at any time in life, they reach their maximum size within a few years and do not continue to enlarge. Approximately 15% of congenital pigmented nevi give rise to malignant melanoma. Treatment consists of total removal. A blue nevus is a benign lesion that rarely becomes larger than 2 to 6 mm in diameter, it persists through life and has no malignant potential. A seborrheic keratosis is a light brown to black, greasy appearing, sharply demarcated papule or plaque. These are benign lesions that do not require treatment. Malignant lesions: Actinic keratosis is discrete, slightly scaling, pink macules and papules. They form on sun-exposed areas and are considered precancerous. Treatment consists of cryotherapy, trichloroacetic acid and topical imiquimod. Basal cell carcinoma is the most common skin cancer. More than 90% occur on the head and neck. Basal cell carcinomas tend to be slow growing and have a low incidence of metastasis, less than 0.1%. these cancers are easily treated by surgical excision with minimal margins. Squamous cell carcinomas also arise from keratinocytes. Metastatic potential is variable. Incidence of metastasis is 8% de novo squamous cell carcinoma, and between 20% to 30% in squamous cell carcinoma arising in scars, chronic ulcers, and burn and radiation therapy sites. Management is total local excision with a resultant high cure rate. Melanoma consists of three types: nodular, superficial spreading and lentigo maligna melanoma, depending on the the depth of the invasion. Once the diagnosis of melanoma is made, a wide and deep excision is warranted. In the management of neoplasms of the skin, the two primary optins are surgical treatment and radiation therapy. Topical agents

such as fluorouracil and imiquimod are also effective. A mole chart is a useful clinical tool for following lesions (Tran, Turk & Baldwin '04: 355, 356, 359, 360, 361).

Squamous cell carcinoma is the sixth most prevalent cancer and constitutes more than 90% of cancers arising in the upper aerodigestive tract. Approximately 5% of all malignant tumors among men and 2% among women arise in the head and neck. More than 50,000 new cases of head and neck cancer occur each year in the United States, and there are more than 15,000 deaths annually. Worldwide, squamous cell carcinoma of the head and neck affects more than 500,000 people annually. Other tumors that arise in the head and neck region include major and minor salivary gland neoplasms, cervical nodal lymphoma, pharyngeal lymphoma arising from Waldeyer's ring or other extranodal non-lymphoid sides and undifferentiated tumors. Approximately 80% to 90% of head and neck cancers may be attributed to exposure to chemical carcinogens such as alcohol and tobacco, which act synergistically. Other common carcinogenic factors include poor dental hygiene, tobacco chewing, betel nut chewing, glossitis (tongue cancer factor), woodworking (nasal and sinus cancer factor). Radiation exposure may likewise predispose a patient to a variety of carcinomas or sarcomas in the head and neck. Viral carcinogens have been implicated, particularly the Epstein-Barr virus in nasopharyngeal carcinoma. Premalignant oral lesions are characterized by thick, whitish plaques (leukoplakia). Approximately 12,000 new cases of laryngeal cancer are diagnosed annually and there are almost 4,000 deaths (Tran & Har-El '04: 305, 307, 310).

Because of the involvement of the respiratory tract, risk incurred by smoking and fact that twenty percent of patients with high-grade neoplasms of the head and neck develop distant metastases in the lung or bone and because the same treatment is much more effective in head and neck cancer than for lung cancer with survival rates ranging from 10% to 90% depending on the location and stage, cancers of the head and neck are treated, herein. The major cause of head and neck cancer is tobacco, and the relative risk increases with number of cigarettes smoked per day. Alcohol produces a synergistic effect. Other known agents associated with head and neck cancer include cigars and pipe tobacco, - lip and oral cavity; chewing tobacco – oral cavity; betel nut (mixed with tobacco and lime) – buccal mucosa and floor of mouth; syphilis – tongue; nickel exposure – nasal cavity and paranasal sinus; woodworking – nasopharyngeal; prolonged sun exposure – lip; Plummer-Vinson syndrome – hypopharyngeal and esophageal cancers. 95% of all head and neck carcinomas are of the squamous cell type, classified as well differentiated, moderately well-differentiated, poorly differentiated, or undifferentiated. Spread is predominantly local or to regional nodes. Late dissemination occurs to lung, liver or bone. Metastases are more common from nasopharyngeal or hypopharyngeal primaries (Jacobs '89: 212).

Staging System for Head and Neck Cancers

Primary Tumor (T)
For each of the head and neck regions the definition of the T classification varies.
Oral Cavity (lip, bucal muosa, alveolar ridge, retromolar trigone, floor of mouth, hard palate and anterior two third so the tongue)
Oropharynx (soft palate, uvula, tonsillar pillar, tonsillar fossa, tonsil, base tongue and pharyngeal wall)

T1	Greatest diameter <2 cm
T2	Greatest diameter 2 cm to 4 cm
T3	Greatest diameter >4 cm

T4 Diameter > 4 cm with deep invasion (oral cavity – to antrum, pterygoids, base of tongue, skin of neck; oropharynx – to bone, soft tissues of neck, root of tongue)
Hypopharynx (pyriform sinus, postcricoid area, and posterior hypopharyngeal wall)
Supraglottic larynx (false cords, arytenoids, epiglottis, aryepiglottic folds)

T1 Tumor confined to site of origin
T2 Extension of tumor to adjacent region without fixation of hemilarynx of vocal cords
T3 Extensin of tumor to adjacent region with fixation of hemilarynx or vocal cords
T4 Massive tumor invading bone, cartilage or soft tissues of neck , or extending beyond larynx for supraglottic or glottis cancers

Nasopharynx

T1 Tumor confined to one site of nasopharynx or no tumor visible (positive biopsy)
T2 Tumor involving two sites
T3 Extension of tumor into nasal cavity or oropharynx
T4 Tumor invasion of skull or cranial nerve involvement

Cervical Nodes (N)

N0 No clinically positive node
N1 Single clinically proven homolateral node < 3 cm in diameter
N2 Single clinically positive homolateral node > 3 cm but not more than 6 cm in diameter or multiple clinically positive homolateral nodes, none of which is more than 6 cm in diameter
  N2a Single clinically positive homolateral node > 3 cm but not more than 6 cm in diameter
  N2b Multiple clinically positive homolateral nodes, none of which is more than 6 cm in diameter
N3 Massive homolateral node(s), bilateral nodes, or contralateral node(s).
  N3a Clinically positive homolateral node(s), one > 6 cm in diameter
  N3b Bilateral clinically positive nodes
  N3c Contralateral clinically positive node(s) only

Distant Metastasis

MX Not assessed
M0 No (known) distant metastasis
M1 Distant metastasis present

Stage Grouping

Stage I: T1, N0, M0
Stage II: T2, N0, M0
Stage III: T2, N0, M0
  T1 or T2 or T3, N1, M0
Stage IV: T4, N0 or N1, M0
  Any T, N2 or N3, M0
  Any T, Any N, M1

Source: (Jacobs '89: 214, 215)

Proper staging is crucial for planning appropriate treatment and prognosis. Precise localization of the primary tumor and assessment o regional spread are key. Since metastases are rare at presentation, a limited metastatic evaluation is advised. Biopsies should be of full thickness an should be obtained from the non-necrotic portion of the tumor, areas at the edge of the tumor, and adjacent normal mucosa. Open biopsy of the neck node is contraindicated if one suspects squamous cell cancer. Needle biopsies are useful for unknown primaries presenting in the neck or salivary glands and for thyroid cancers. False-negatives are a novice pathological mistake.

Computed tomography (CT) and magnetic resonance imaging (MRI) are complementary for evaluation of the nasopharynx, sinuses, oral cavity and oropharynx. CT is superior for evaluating hypopharyngeal and laryngeal lesions, bony erosions of the base of the skull and metastatic adenopathy. For cancers of the nose, paransal sinuses and nasopharynx, sinus series and/or sinus CT tomography are necessary to evaluate the extent of disease and potential bony destruction. Patients with cancers of the pyriform sinus, posterior pharynx, or postcricoid area should have a barium swallow in order to rule out esophageal extension or second primaries. Prior to treatment, a chest film may reveal underlying pulmonary disease or metastatic spread. A complete blood count (CBC) and chemistry profile, including liver function tests, are part the initial evaluation. Epstein-Barr virus (EBC antibody titers (IgA and IgG anti-EBV viral apsid antigen and early antigen) are increased in patients with nasopharyngeal cancer, and the level correlates with disease activity (Jacobs '89: 212, 213).

About 60% of oropharyngeal cancers — cancers of the throat, tonsils and the base of tongue — are related to HPV. It is estimated that every year in the U.S., more than 2,370 new cases of HPV-related oropharyngeal cancers are diagnosed in women and about 9,356 are diagnosed in men; they are most common in white men. There are about 15 different HPV types that are established causes of cancer. The most common are HPV 16 and 18, accounting for about 70% of cervical cancers and oral infection. The Johns Hopkins School of Medicine estimates that 20 million people in the U.S. currently have HPV infection, and one in 49 people will contract a new HPV infection each year. Physicians recommend the HPV vaccine for both young boys and girls, to prevention infection from the disease (Sifferlin '13). Patients should undergo a thorough dental evaluation prior to treatment, and non-salvageable teeth should be extracted. Post-irradiation extractions are associated with increased risk of osteo-radionecrosis. Fluoride treatments should be prescribed. Patients with head and neck cancer are often nutritionally deficient because they have difficulty eating animal products, bread and protein. The patient should be brought into positive nitrogen balance to reduce postoperative complications and improve tolerance to radiotherapy and/or chemotherapy (Jacobs '89: 214).

The extent of surgical resection is dictated by the extent of tumor at staging. The primary lesions should be widely excised leaving negative margins. Primary closure of the surgical defect is preferable, but local or regional skin flap should be utilized when required. In the oral cavity a composite resection includes the primary, part of the mandible (if necessary) and cervical nodes. For patients in whom tumor approaches, but does not grossly involve, adjacent bone, a partial mandibulectomy may be performed. Gross bone invasion demands segmental mandibular resection, the extent of which depends on the degree of clinical involvement. In the oropharynx, if the lesion is below the level of the arytenoids, a total laryngectomy is recommended because of aspiration. In the supraglottic larynx a supraglottic laryngectomy can be performed if the cancer is confined to the supraglottic region and the forced expiratory volume (FEV) is more than 60%.

A total **laryngectomy** should be done if (1) tumor extends to the commissures, artyenoids, thyroid cartilage, or glottis, (2) there is impaired mobility or fixation of vocal cords. In the larynx, hemilaryngectomy is appropriate to T_{1-2} failures of radiation. For patients with known neck disease, a standard radical neck dissection should be performed. This includes the superficial and deep cervical fascia with its enclosed lymph nodes, the sternocleidomastoid and omohyoid muscles, the internal and external jugular veins, the spinal accessory nerve, and the submaxillary gland. . For patients with cancers of the oral cavity, oropharynx, and supraglottic larynx in whom surgical management of the neck is chosen, a functional neck dissection should

be performed. This leaves the sternocleidomastoid, the internal jugular vein and the spinal accessory nerve intact. In addition to the post-operative problems with postoperative infections and bleeding the long term problems include the following (1) cosmetic deformities, (2) speech impediment, (3) aspiration pneumonia and (4) shoulder droop and pain resulting from accessory nerve dysfunction following neck dissection (Jacobs '89: 216).

Radiotherapy for head and neck cancer is usually done with either teletherapy, brachytherapy or hyperthermia. In **teletherapy**, treatment with a linear accelerator (4-6 MeV energy) is preferred. Cobalt-60 units are acceptable if they operate at 80 SSD (source-to-skin distance). A combination of lateral opposed fields, anterior and lateral wedged fields, or isocentric multiple fields is used for the primary tumor site. A single anterior field with a midline block can be used to treat the neck, and lower neck fields should match the primary field at the skin. The accepted dose rate is 180 cGy to 200 cGy per day. The dose to tumor volume for primary treatment is approximately 6600 cGy to 7000 cGy in 6 to 7 weeks. The dose to a tumor bed following resection is 5500 cGy in 5 to 5 ½ weeks for negative margins, 6000 cGy for close margins and 6600 cGy-7000 cGy for positive margins. The maximum dose to the spinal cord should be no more than 4000 cGy when 200 cGy fractions are used. Postoperative radiation should not begin until postoperative healing is satisfactory (about 2 weeks). In **brachytherapy** insterstitial implantation of radioactive sources is a means of obtaining high localized radiation dose to the tumor bed while minimizing normal tissue injury. The most commonly used permanent implant source is iodine. The most commonly used removable brachytherapy source is Iridium seeds. The dose rate for removable implants is between 40 cGy to 100 cGy per hour. In previously untreated patients, the total dose of iodine for 1 year is approximately 15,000 cGy. Removable interstitial doses, when used as a booster after 5500 cGy external beam, should be limited to 25000 cGy to 4000 cGy. In hyperthermia ultrasound is used to heat tumors to 44°C. The toxic effects of radiotherapy include (1) xerostomia and loss of taste, (2) mucositis may delay treatment, (3) otitis media should be managed with decongestants but may require tube placement, (4) osteoradionecrosis of the mandible can often be prevented by appropriate preradiation dental extractions. Treatment is with antibiotics (penicillin) but in severe cases, hyperbaric oxygen and /or resection may be required, (5) laryngeal edema may follow radiation to the larynx, and a small percentage of patients may develop cartilage necrosis or a compromised airway. Conservative treatment includes antibiotics and/or steroids. Persistent edema following radiation is suspicious of tumor recurrence, (6) Lhermitte's syndrome, which is characterized by electric sensations in the spine, arms or legs or neck flexion, requires no treatment and (7) rarely hypothyroidism, heralded by an elevation of thyroid-stimulating hormone (Jacobs '89: 217, 218).

Chemotherapy can only rarely cure a patient with recurrent disease. The most active single agents for recurrent disease are methotrexate and cisplatin. Each produces response rate of approximately 30% (mostly partial responses) of 4 to 6 months' duration. Cisplatin responses usually occur more promptly. **Methotrexate** is generally given at 40 mg/m^2 intravenously weekly, and is also available in oral table 2.5 mg once a week in a dose too small to cause side effects such as alopecia (hair loss) and pulmonary infiltrates. There is no evidence that large doses are superior to standard doses. Because of renal excretion, the patients should have normal serum creatinine. Toxicities include mucositis, myelosuppression, hepatotoxicity, nephrotoxicity and severe fatigue. Elderly patients and those with poor nutritional status are more likely to have severe reactions. CBC and platelets should be monitored weekly, liver function tests and serum creatinine at least monthly. The cytotoxic effects of the drug can be reversed with a reduced folate, leucovorin. **Cisplatin** is an effective drug whose major route of excretion is renal, and its

use should be limited to patents with a creatinine clearance that is more than 50 ml/minute. The standard dose is 100 mg/m^2 every 3 weeks. Because of nephrotoxicity, a 24-hour infusion or mannitol diuresis is recommended. Typical standing orders are 12 hours prior to administration of cisplatin, pre-hydrate with 2 liters dextrose, 5%, in 0.5 normal saline plus 20 meq of potassium chloride. Three hours prior to administration of cisplatin, increase to 300 ml/hour. Just prior to administration of cisplatin, manitol, 12.5 g by rapid intravenous injection, followed by cisplatin (100 mg/m_2) in saline to a concentration of 1 mg/ml is infused over 30 minutes. Follow this with a continuous infusion of mannitol 10g/hour for 6 hours, with concurrent dextrose, 5% in 0.5 normal saline plus 20 meq potassium chloride per liter at 200 ml/hour for 6 hours. Toxicities include nephrotoxicity, mild myelosuppression, moderately severe nausea and vomiting, hypomagnesemia, ototoxicity, and neurotoxicity. Response rates in excess of 15% for recurrent disease have been reported with several other drugs, including bleomycin, 5-fluorouracil (5-FU), Adriamycin, cyclophosphamide, and hydroxurea.

Multiple combinations have been reported for recurrent head and neck cancer with complete and overall response rates higher than those of single agents, however there is no evidence that combination chemotherapy prolongs survival compared with single agent chemotherapy. Two commonly used regimens are (1) Cisplatin, 50 mg/m^2 on day 6, methotrexate, 40 mg/m^2 on days 1 and 15; Bleomycin 10 mg on days 1, 8, 15; response rate is 61%. (2) Cisplatin, 100 mg/m^2 on day 1; 5-FU, 1000 mg/m^2 for 4 days, response rate is 70%. Chemotherapy has been used prior to surgery in attempts to reduce tumor size and to decrease local or distal recurrence. When using chemotherapy in this manner, the optimal response is obtained after two to three cycles of chemotherapy. Reported response rates vary from 70% to 90% overall with 20% to 50% complete responses. Cure for squamous cancers of the head and neck is measured in terms of 5-year survival, although most relapses occur in the first 3 years following therapy. Follow-up should include a thorough head and neck examination every 1 to 2 months for the first year, with progressively longer intervals up to five years. A chest film should be obtained early. Approximate cure rates are for (1) oral tongue, T1, T2 – 70%-85%, T3, T4- 30%-40%; (2) floor of mouth, T1, T2-70%, T3, T4-45%; (3) tonsil, T1, T2-60%-75%, T3, T4-20%-35%; (4) pyriform sinus, T3, T4-25%; (5) glottis larynx, T1, T2-80%-90%, T3, T4-75%; (6) supraglottic larynx, T1, T2,-70%-85%, T3, T4-25%-40%; (7) base or tongue, T1, T2-50%-60% , T3, T4-20%-30%, and (8) nasopharynx, T1, T2-70%-75%, T3-55%, T4-<10% (Jacobs '89: 219, 220).

Cancers of the salivary gland account or less than 5% of head and neck neoplasms. The majority arise in the parotid gland and approximately 25% of parotid tumors are malignant. Of those originating in the submaxillary gland and minor salivary glands (palate, nasal cavity, and paranasal sinuses) half are malignant. These cancers usually present as painless masses and infrequently produce pain from nerve involvement. The most common histologic type is mucoepidermoid (low grad or high grade). Others include acinic cell, malignant mixed, adenoid cystic, adenocarcinoma, poorly differentiated carcinoma, squamous and anaplastic. The diagnosis can be made by needle biopsy at the time of parotidectomy. These cancers spread by direct extension, and some, like adenoid cystic, have a propensity to spread along nerve sheaths. Lymph nodes spread is found in up to 30% of high-grade cancers (adenocarcinoma squamous, undifferentiated, anaplastic and mid-grade mucoepidermoid). The most common site of metastatic spread is lung, and a chest film should be done prior to surgery. The staging system for salivary gland cancers is T1- <2 cm, T2- 2 cm to 4 cm, T3- 4 cm to 6 cm, T4a- > 6 cm, T4b – any size with local extension. NO- negative nodes, N1- regional lymphatic involvement, M0- no metastases, M1-metastatic sprea. Stage I – T1, T2, N0, M0. Stage II – T3, N0, M0. Stage III

T1-2, N1, M0; T4, N1, M0. Stage IV t3-4, N0, M0, M1. Surgery is the treatment of choice for salivary gland neoplasms.

For parotid cancers that are low-grade and involve only the superficial lobe, a superficial parotidectomy may be performed. For all others, a total partodiectomy is recommended. The facial nerve can often be preserved, but if it is involved and needs to be sacrificed, a nerve graft may preserve function. At the time of the surgery, if peri-parotid nodes are positive, a radical neck dissection should be performed. Treatment of minor salivary gland cancers includes a wide excision. Most would recommend postoperative radiation for patients with high-grade cancers, positive margin, perineural invasion, deep lobe involvement, and regional lymph node metastases, at a minimum dose of 5000 cGy to 5500 cGy or 6600 cGy for positive margins. Primary radiotherapy is reserved for inoperable patients. The best single agents are cisplatin, doxorubicin, 5-FU and methotrexate. Overall responses have been noted in up to 60% of patients. The major actors that influence outcome are histology, site of tumor, and tumor size. Local control is achieved in approximately 80% of low-grade cancers and approximately 30% of high-grade cancers. Twenty percent of patients with high-grade neoplasms develop distant metastases in lung or bone. Five-year survival for parotid cancers range form 30% in undifferentiated neoplasms to 92% in acinic cell cancer, but since salivary gland cancers can recur at 10 and 15 years, 5 year survival rats are unreliable (Jacobs '89: 220, 221).

Radiation therapy is based on directed ionizing radiation used to manage malignant and occasionally benign tumors. Ionizing radiation causes three types of injury – immediate cellular death, temporary mitotic arrest, and loss of reproductive capacity in biologic tissue through the formation of free radicals, which cause direct and indirect cellular damage. Radiosensitivity is the vulnerability of cells to lethal injury from ionizing radiation, and is unique to each type of tumor. A radiosensitive tumor adjacent to vital organs might require a dose of radiation that wil cause intolerable tissue damage ot the surrounding normal cells. Similarly, a radiosensitive tumor that has metastasized to vital organs might not be curable. Therapeutic ratio is defined s the radiation tolerance dose of normal tissue divided by the lethal dose of radiation of the tumor mass. A typical dosing schedule for the head and neck region involves a daily dose of 180 to 200 cGy, 5 days per week for a total of 6,000 to 7,000 cGy. Doses of radiation greater than 7,500 cGy do not correlate with better control and are associated with more complications. Radiation can be used to manage most T1-T2 and N0-N1 tumors of the head and neck. Almost all tumors of the nasopharynx are managed primarily by means of radiation therapy. However, almost all tumors of the salivary glands are managed primarily with surgical excision. Radiation therapy is contraindicated in the care of pregnant women. Most side effects of radiation therapy are caused by absorption in normal tissues surrounding the target. Superficially the skin shows an acute erythematous reaction caused by histamine release and vasolidatation. This condition resolves after several days. The dermal layers show injury to the basal cells, and mitotic arrest manifests itself as dry desquamation. Late skin effects include subepithelial fibrosis. Early mucosal injury is manifested as erythema that progresses to mucositis. Continued progression to ulceration occurs as a late effect. Xerostomia (dry mouth) is caused by fibrosis of the major and minor salivary glands with a resultant decrease in salivary output. The central nervous sytem can show demyelination, which usually resolvs. Ocular complication may include lacrimal gland injury and lens opacification (cataract). Cartilage and bone necrosis can occur. Osteoradionecrosis occurs in 30% to 45% of patents who undergo orthovoltage radiation (orthovoltage is almost never used) but among only 5% of patients who undergo megavoltage radiation therapy. The mandible is the most common site of injury. Although osteoradionecrosis is thought to occur as a late effect (years after therapy) it has been seen as early as 2 to 3 months after therapy.

Radiation therapy decreases the vascular supply to the bone. Therapy includes moisturizing the affected skin, rinsing with viscous lidocaine (swish and swallow), and taking oral analgesics to control odynophagia and the pain of mucositis. Parasympatheticomimetic drugs such as pilocarpine and cevimeline can improve salivary function for patients with enough remaining salivary tissue. Hyperbaric oxygen therapy may reverse the tissue changes cause by radiation therapy – hypocellularity, hypovascularity and hypoxia. Surgical debridement usually is necessary when hyperbaric oxygen therapy for osteo-radionecrosis fails.

Patients with large primary tumors (more than 4 cm in greatest dimension), primary tumors with extension onto other structures, multiple histologically positive neck nodes or nodes with extra-capsular spread, histologically positive or close surgical margins, or recurrent disease are candidates for post-operative radiation therapy. In the neck, radiation therapy is very effective for the clinical N1 lesions (no clinically palpable nodes). With a course of therapy over 5 weeks (4,500 to 5,000 cGy), the N1 lesion of the neck (single ipsilateral node less than 3 cm in greatest dimension) has a high cure rate with radiation therapy. A total dose of 6,400 cGy typically is administered over 6 to 7 weeks. In case of failure, surgical treatment can be used. Radiation is administered postoperatively for larger positive nodes, or if there is evidence of extracapsular spread. Lesions with N2 and N3 nodes usually are too large to manage only with radiation therapy; surgical treatment must be used. Radiation therapy can be used in organ-preservation protocols along with chemotherapy to manage locally invasive cancers (Schwartz, Har-El & Aziz '04: 453-457).

Lung cancer is the most common fatal neoplasm in the United States in both women and men. It has replaced tuberculosis as the major pulmonary cause of death. Approximately 150,000 new cases will be diagnosed in 1988. Over the past 40 years, long-term survival after the diagnosis of lung cancer has shown little or no improvement. The overall 5-year survival rate is approximately 10% to 15%. Chemotherapy for small cell lung cancer has advanced significantly, resulting in prolongation of life but few long-term survivors. Operative mortality has decreased from 10% to 3%. The incidence of discovery of unresectable tumor at the time of thoracotomy has decreased from 25% to 5%. Because of the disappointing results of surgical therapy for lung cancer treatment lies in prevention, through smoking cessation. One of 13 cigarette smokers develops bronchogenic carcinoma; smoking cessation results in a gradual normalization of risk over a period of 10 to 20 years. The shocking rise in incidence of lung cancer in the twentieth century has suggested that environmental or behavioral factors are responsible. Tobacco smoke, particularly from cigarettes, is the major factor for this precipitous disease. Cigarette smokers have at least a 10 times greater risk of developing lung cancer than do nonsmokers. Smokers with chronic obstructive lung disease are more likely to develop lung cancer than those without obstructive lung disease. Maintaining close contact with an active cigarette smoker, may be responsible for up to 5% of al lung cancer. Asbestos exposure is a potent risk factor for bronchogenic carcinoma, as well as mesothelioma. Asbestos exposure and cigarette smoking act synergistically; an asbestos worker who smokes has a 50-100-fold increased chance of developing lung cancer. Whether asbestos exposure alone can be regarded as a cause of lung cancer has not been determined. Exposure to radon daughters, which emit radioactive gas, may act synergistically with cigarette smoke to yield a risk 50 to 100 times greater than that of the normal population. Exposure to radon occurs near uranium mining operations in the western United States and also when homes are built on or near hard rock formations. A variety of other environmental and occupational factors that increase lung cancer risk have been identified. These include exposure to arsenic, nickel, chromium, chloromethyl ethers, hydrocarbons, and mustard gas. Disease that causes lung scarring, such as pulmonary

tuberculosis or interstitial fibrosis, may predispose to "scar carcinomas" usually peripheral adenocarconomas of bronchiolo-alveolar cell carcinomas (Miller & Johnston '89: 319-321).

The patient with **bronchogenic carcinoma** is generally past age 35. Only 3% of cases are diagnosed patients before 35 years of age. Cough is the commonest symptom. Either the onset or a change in the nature of a chronic cough is the most common symptom. Hemoptysis is a particularly suggestive sign and should never be ignored, particularly in patients over 35 with a history of smoking. Vague non-pleuretic chest pain added to a worsening cough and hemoptysis is a common triad seen in these diseases. Dyspnea may occur, secondary either to an obstruction of an airway or to lymphangitic spread of the tumor. Recurrent pneumonia may be the first evidence of the presence of endobronchial obstructive lesion. All pneumonias should be subjected to radiographs at intervals of 6 weeks to 2 months to document complete clearing. If an infiltrate persists, increases in size, does not fully resolve on serial radiographs or recurs in the same location, further diagnostic steps should be taken. Persistent infiltrate with evidence of volume loss is particularly worrisome. Weight loss and anorexia may be initial symptoms and most often signify extensive disease on diagnosis. A variety of symptoms may be caused by extension of the tumor within the thorax. Most of these signal advanced disease. Chest pain may be the result of pleural or rib involvement. Hoarseness is a sign of recurrent laryngeal nerve involvement. Extension to the autonomic nervous system can produce Horner's syndrome: ptosis, miosis, and anhydrosis on the affected side. Brachail plexus invasion, causing arm pain and parensthesias and often accompanied by Norner's syndrome, is referred to as Pancoast's syndrome. Bockag of the superior vena cava produces facial suffusion, edema and mental changes. Distant metastases to bone, brain, and liver often produce symptoms that prompt the first visit to the physician. Paraneolastic syndromes frequently occur with lung cancer and occasionally produce the initial symptoms. Pulmonary tumors produce a variety of endocrinopathies. Hypercalcemia may be caused by parathyroid hormone-like peptides, osteoclast-activating factor, or bony metastases. Inappropriate secretion of antidiuretic hormone (SIADH) may be produced particularly by small cell carcinomas and may cause hyponatremia. ACTH is commonly produced by lung cancers but rarely cause full-blown Cushing's syndrome. More common is hypokalemia, based on an excess of secondary mineralocorticoid. Some hormones act to stimulate growth of tumor cells. Less understood are the neuromuscular paraneoplastic syndromes, which include Eaton-Lambert syndrome, myopathies, neuropathies, cerebellar degeration, and dementia. One of these endocrinopathies is found in 5% to 10% of patients with bronchogenic carcinoma. Digital clubbing and hypertrophic pulmonary osteoarthropathy can occur together, but clubbing alone is more common. Hypertrophic pulmonary osteoarthropathy is manifested by periosteal elevations over the long bones, particularly the tibia and radius. This is frequently painful. Hypertrophic osteoarthropathy can also occur wit nonmalignant antrathoracic processes such as lung abscess, bronchiectasis, chronic interstitial pneumonitis, bacterial endocarditis or cyanotic heart disease. It rarely occurs with extra-thoracic processes such as ulcerative colitis, cirrhosis and thyroiditis. Migratory thrombophlebitis, often in unusual sites and resistant to treatment, is seen in lung cancer as in various other malignancies, but is not common. Thrombocytosis, thrombocytopenic purpura, fibrinolysis, hemolysis and red cell aplasia have also been described (Miller & Johnston '89: 321-322).

The **four major lung cancer cell types** (adenocarcinoma, squamous, large cell and small cell) theoretically originate from a common stem cell. Adenocarcinoma of the lung is characterized by gland formation and intracellular mucin. Although incidence varies between series, this cell type appears to be increasing in frequency and is probably the most common, accounting or

approximately 40% of cases. Squamous cell carcinoma is characterized by intracellular bridges and keratin synthesis, often with typical keratin "pear" formations, and currently accounts for about 30% of al lung cancer. Small cell lung cancer (formerly oat cell carcinoma) accounts for 20% of lung cancers. A characteristic chromosomal abnormality, has been identified in the majority of small cell lung cancers. Bomesin, or g-satrin-releasing peptide, has been shown to have a high correlation to increased expression of the c-myc oncogene. Less common primary malignant tumors of the lung include large cell carcinoma and bronchioloalveolar cell carcinoma (a subset of adenocarcinoma) which accounts for 5% to 8% of lung cancers. The most consistent abnormality in involving oncogenes in non-small cell lung cancer is a mutation of the Ki-ras oncogene that gives it the ability to transform rodent fibroblasts. Rare cell types include giant cell carcinoma, clear cell carcinoma, and pulmonary blastoma, which account for less than 2% of lung cancers. Bronchial adenomas and carcinoid tumors are classified as benign lung tumors, although they have a rare but significant tendency to metastasize (Miller & Johnston '89: 319-321).

The **solitary pulmonary nodule** (SPN) is defined in radiographic terms as an opacity on the chest radiograph that is single, is round to ovoid, is less than 6 cm in diameter, (large nodules are usually called chest masses, has distinct margins (is surrounded by aerated lung parenchyma and therefore not abutting chest wall, diaphragm, or mediastinum), and may or may not contain calcium obvious on the plain radiograph. The vast majority of SPNs do not cause symptoms or signs. Rare symptoms include hemoptysis, cough, clubbing and endocrinopathy. Up to a third have vague or nonspecific chest pain. About one third of SPSs in patients who have undergone operation are malignant (bronchogenic carcinoma, solitary metastasis, or bronchial adenoma). However, by selection of patient populations, the malignant percentage has varied from as low as 3% to as high as 80%. The overwhelming number of benign SPNs are granulomas caused by tuberculosis, histoplasmosis, or coccidioidomycosis; however, hamartoma cysts, and a host of rare benign neoplasms and other lesions have been reported. The crux of patient management involves removing primary malignant tumors and adenomas after carefully excluding all evidence of extrathoracic metastases. Some 25% to 50% of patients with "localized" bronchogenic carcinoma (appearing as SPNs) have 5 year cures. Most patients with benign lesions do not need an operation. The chance of an SPN being a primary bronchogenic carcinoma in patients less than 35 years of age is about 1%. Previous chest radiographs are extremely helpful because the growth rate of primary bronchogenic carcinoma is well known, with the average doubling time for most cell types being 4 to 7 months. More important, almost all of primary malignant bronchogenic SPNs double in volume within 1 to 16 months. If the nodule has not doubled in volume, within 16 months the lesion is not malignant. SPNs that double in volume within 30 days are almost always inflammatory. Calcification almost always indicates a benign lesion. The patient's smoking history is statistically very helpful. Oat cell, squamous cell and undifferentiated bronchogenic carcinomas are all highly related to cigarette smoking and rarely occur in nonsmokers. Adenocarcinoma, bronchial adenoma, and alveolar cell carcinoma are not closely related to smoking. Overall, nonsmoking patients with SPNs have about a 9:1 chance of having a benign disease (Neff & Perry '89: 312-314).

In the majority of cases of lung cancer, the chest radiograph is abnormal at the time of diagnosis. A common radiographic abnormality is the solitary pulmonary nodule, by definition less than 3 cm in diameter and completely surrounded by lung tissue. Larger lesions are termed masses. The importance of solitary pulmonary nodule is that it represents the most curable group of lung tumors with a 5-year survival rate of 70% to 90% if metastases are absent. Lung tumors, particularly squamous cell carcinomas, may cavitate. Therefore cavitary lesions should be

considered potentially neoplastic. Lung abscesses can be due to underlying neoplasm, particularly in smokers. Pneumonitis that fails to resolve over 6 to 8 weeks may be a manifestation of a tumor. Atelectasis is highly suggestive of a malignant endobronchial obstruction. Alveolar infiltrates may represent bronchioloalveolar carcinoma, and interstitial markings with Kerley B lines can be caused by lymphangitic spread of a tumor, either primary (in the lung) or metastatic. Dense, central, concentric or "popcorn" calcification seen on plain radiographs or conventional tomography is a reliable sign that a nodule is benign. Lesions that double in volume in less than 30 days are most often inflammatory. The most reliable sign of a benign tumor is lack of growth over a 2 year period. Dense, central, concentric, or "popcorn" calcification seen on plain radiographs of conventional tomography is a reliable sign that a nodule is benign. However, lesions containing only a fleck of calcification may represent scar carcinomas growing near an old calcified lesion. Malignant tumors are not common in patients under 35. Sputum cytology is noninvasive and is easily performed. Approximately two thirds of central lesions and one third of peripheral lesions can be diagnosed by this means, but the exact cell type is difficult to determine (Miller & Johnston '89: 323-326).

If a lesion is associated with a pleural effusion, thoracentesis with cytology and possibly needle pleural biopsy is a logical early step in workup. Negative cytologic results in sputum or pleural fluid do not definitely exclude malignancy. More invasive techniques for diagnosis include flexible fiberoptic bronchoscopy and trans-thoracic needle biopsy. Flexible fiberoptic bronchoscopy with transbronchial biopsy has several advantage over the trans-thoracic needle biopsy. It is a low-morbidity procedure: mortality is less than 0.05% and risk of pneumothorax is less than 1%. The diagnostic yield ranges from 50% to 90%, depending on the location of the lesion. Furthermore, endo-bronchial biopsies should be obtained at potential surgical margins of the bronchial tree to rule out submucosal spread of tumor. Trans-thoracic needle biopsy has the advantage of a higher yield (approximately 90% to 95% accuracy) than bronchoscopy. However, the risk of pneumothorax is between 20% and 30% and one third of these require chest tube insertion. An aspiration technique is most commonly used and yields tissue for cytology and microbiologic testing only. Identification of cell type of tumors is not as accurate as with tissue biopsies. False identification of cancers as benign lesions occurs and can delay therapy. (Miller & Johnston '89: 326-328).

Staging System for Lung Cancer

PRIMARY TUMOR (T)

TX	Tumor either proven by the presence of malignant cells in bronchopulmonary secretions but nor visualized roentgenographically or bronchoscopically or cannot be assessed.
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*
T1	Tumor 3 cm or less in greatest diameter, surrounded by lung or visceral pleura and without invasion proximal to a lobar bronchus.
T2	Tumor more than 3 cm in greatest diameter or a tumor of any size that either invases visceral pleura or has associated atelectasis or obstructive pneumonitis extending to the hilum. The proximal extent must be within a local bronchus or at least 2 cm distal to the carina. Any associated atelectasis or obstructive pneumonitis must involve less than an entire lung, and there must be no pleural effusion.

T3 Tumor of any size with direct extension into adjacent structures such as parietal pleura or chest wall, diaphragm, or the mediastinum and its contents; a tumor involving a main bronchus less than 2 cm distal to the carina; any tumor associated with atelectasis obstructive pneumonitis of the an entire lung; or a pleural effusion.

NODAL INVOLVEMENT (N)

NX Minimal requirements to assess regional nodes cannot be met

N0 No evidence of involvement of regional lymph nodes

N1 Metastasis to lymph nodes in peribronchial or ipsilateral hilar region including direct extension

N2 Metastasis to lymph nodes in the mediastinum

DISTANT METASIS (M)

MX Minimum requirement to assess presence of distant metastasis cannot be met

M0 No evidence of distant metastasis

M1 Distant metastasis present

STAGE GROUPING

Occult Stage: TX, N0, M0

Stage 1: Tis, N0, M0 (carcinoma *in situ*)
T1, N0, M0
T1, N1,, M0
T2, N0, M0

Stage II: T2, N1, M0

Stage III: T3 with any N or M
N2 with any T or M
M1 with any T or N

Source: Idhe '89: 191 Table 25-1

Non small cell lung cancer (NSCLC) - squamous (epidermoid) carcinoma, adenocarcinoma and large cell carcinoma of the lung comprise approximately 75% of all cases of lung cancer in the United States. Squamous cell carcinoma is most clearly related to cigarette smoking, and possibly candidiasis. Adenocarcinoma is more common in women and is the most frequent type of lung cancer in nonsmokers. Squamous cancer usually presents as a central endobronchial lesion, and regional lymph nodes are the most common site of metastatic disease. Adenocarcinoma more often arises in the periphery of the lung and relatively infrequently invades the pleural space, causing a pleural effusion. Distant metastases at diagnosis are common. The 5-year survival of all patients with NSCLC is only approximately 10% and there has been no marked improvement over the past few decades. The five year survival with distant metastatic NSCLC is less than 1%. Pathologically confirmed stages I and II are surgically resectable. Stage III includes extrapleural invasion. Patients are divided into three groups of approximately equal size: patients with tumor confined to the lung and hilar nodes that can be surgically resected; those with more advanced locoregional disease that is managed with radiotherapy, surgery, or both, and a third group with distant metastases who are treated with palliative irradiation or sometimes with chemotherapy. There is no evidence that different cell types of NSCLC differ in their responsiveness to chemotherapy. There is no proven role for postoperative adjuvant immunotherapy, radiotherapy of chemotherapy after complete surgical resection. Radiotherapy may reduce local occurrence of Stage II tumors, but no survival benefit is noted. Following complete resection of State I NSCLC, 5 year survival is 40% to 50%, in Stage II patients it is 15% to 30% (Ihde, '89: 189, 193). Surgical therapy is offered as the best chance for cure in non-small cell carcinoma of the lung. For patients with non-small cell lung cancer who are not surgical candidates radiation therapy can be effective, particularly for

palliation of symptoms of bronchial obstruction, bone pain, superior vena cava syndrome, or spinal cord compression. Radiotherapy has occasionally been curative, but most patients suited for cure by radiation are also surgical candidates and receive surgery. Potentially curative doses of radiation will cause loss of pulmonary function, which is often comparable to loss from resection (Miller & Johnston '89: 328, 332).

Radiotherapy alone is the usual treatment given to most patients with advanced locoregional NSCLC with a 5 year survival of only 5% to 10%. Irradiation is not begun in patients with poor performance status, malignant pleural effusion or bulky tumors and poor pulmonary function, or those with early progressive tumor or distant metastases. Potentially curative radiotherapy is customarily administered to a total dose of 55 Gy to 60 Gy (5500-6000 rad) in continuous fractionation using megavoltage equipment. In the 40 Gy to 60 Gy range, increasing tumor dose is associated with a higher rate of complete response and decreased frequency of local recurrence, but no definitive improvement in survival due to the high probability of occult distant metastases at the time of irradiation. The role of chemotherapy has yet to be established. Chest irradiation provides the best available palliation for symptoms due to locoregional NSCLC, and it is especially effective in ameliorating pain, hemoptysis, superior vena cava obstruction, and pneumonitis distal to an incompletely obstructed bronchus. Atelectasis and vocal cord paralysis are less often relieved.

Surgical resection is integrated into the management of some intra-thoracic Stage III NSCLC with advanced primary tumors and absence of mediastinal node involvement with a 5 year survival as high as 20% to 35%. Bulky peripheral tumors that directly invade adjacent structures with no or only hilar nodal metastases can be resected with curative intent. Patients with only parietal pleural (not chest wall) involvement and those without nodal metastases have a better prognosis. Empiric preoperative irradiation is sometimes given to improve the likelihood of resectability. Postoperative irradiation is often administered and reduces the rate of local recurrence, but survival benefit has not been conclusively shown. Prospects for prolonged survival are dismal in patients with distant metastatic NSCLC. Median survival of fully ambulatory patients is 6 months and is only 1 to 2 months for bedridden patients Five-year survival is less than 1%. Since there is no convincing evidence that any form of therapy improves survival in this setting, palliation of symptoms is the most important goal in management of Stage III M1 disease. Radiotherapy plays a major role in this regard. Single-agent chemotherapy of NSCLS yields only 5% to 20% response rates and does not affect survival. Recently, combination chemotherapy regimens have produced higher response rates (20% to 40%) in patients with good performance status, but complete responses are uncommon, but complete responses of 2 years' duration have been documented. Outside a clinical trial setting, individual patients may be offered a published chemotherapy regimen provided that the patients (1) is of good performance status, (2) has evaluable tumor lesions so that response to treatment can be assessed and therapy stopped if it proves ineffective, and (3) understands the limitations of chemotherapy but still wants treatment (Ihde '89: 192-194).

Lobectomy, pneumonectomy, segmentatectomy or wedge resection and sleeve resection may be indicated by the surgeon's intraoperative findings. The chosen procedure will remove all of the tumor with adequate margins of resection and maximum conservation of normal lung tissue. Postoperative mortality of 3% for lobectomy and 5% to 8% for pneumonectomy can be anticipated. The five year survival rate following complete resection of Stage I NSCLC is 40% to 50% and for State II 15% to 30%. Surgeons must take precautions that they do not remove too much parenchymal tissue to cause respiratory insufficiency. The predicted postoperative

FEV_1 should exceed 800 ml. Loss of pulmonary function is roughly proportional to the percentage of total lung resected. The five year survival rate by clinical stage is as follows I (45-50%), II (25-30%), IIIa (15-20%), IIIb (5%), IV (2%).

Patients with stage I, II, or IIA disease are usually assigned surgical therapy, whereas those in stages IIIb and IV are generally not believed to be candidates for curative surgery. Metastasis to contralateral mediastinal or hilar nodes places a patient in a nonsurgical category. Direct chest wall extension and selected instances of mediastinal invasion in the absence of mediastinal nodal metastasis are potentially surgically curable. Cervical mediastinoscopy is a minor procedure that is usually performed under general anesthesia. A small incision is made in the suprasternal notch, and the pretracheal space is entered. An instrument similar to a laryngoscope is inserted and advanced into the middle mediastinum. Paratracheal, high parabronchial and subcarinal lymph nodes can be routinely sampled. Since the trachea lies posterior to the aortic arch and main pulmonary arteries, the surgeon does not have access to the anterior and superior mediastinum. Mediatinoscopy carries a less than 2% complication rate and changes the clinical staging in 30% of lung cancer patients. It is the most important factor in increasing the resectability rate to well over 90% in patients undergoing exploratory thoracotomy (Miller & Johnston '89: 328-331).

Chemotherapy for non-small cell carcinoma is disappointing. Response rates vary from 10% to 40%. Cure is not expected, and prolongation of life has been demonstrated only when chemotherapy is used as an adjuvant to resection. Chemotherapy for small cell lung cancer is effective, achieving an 80% initial response rate and increasing mean survival from 13 weeks to 13 months. It has been reported that up to 5% are potentially cured. Disease limited to the thorax and supraclavicular nodes is termed "limited and has a better prognosis than "extensive" disease., such as extrathoracic metastases. A recent series describes a 20% 4-year survival in optimally treated "limited" small cell lung cancer. Brain metastases are so common that prophylactic cranial irradiation is often recommended for patients with limited disease who achieve complete intrapulmonary responses to chemotherapy. Recurrence at the site of the primary pulmonary tumor occurs frequently and may be a major reason or failure of current regiment. Trials comparing radiotherapy with surgery for local control of primary disease are under way (Miller & Johnston '89: 332). Blogging-survivors ask for more prompt chemotherapy, with pneumococcal vaccination, antibiotic and antifungal prophylaxis without having to first cough up a section of lung for a surgeon, permanently losing a significant percentage of lung function.

Small cell lung cancer (SCLC), sometimes called oat cell carcinoma, differs from other types of cancer and the response to therapy so it is treated differently. Compared with other types of lung cancer, SLC has a rapid clinical course with shorter duration of symptoms prior to diagnosis and median survival in the absence of treatment of only 2 months for disseminated and 4 months for localized disease. Almost 70% of patients will have distant metastases in autopsies performed within 30 days of putatively curative surgical resection, and are rarely cured with the localized therapeutic modalities of surgery or radiotherapy. SCLC exhibits features of neuroendocrine or APUD (amine precursor uptake and decarboxylation) differentiation, including neurosecretory granules on electron micrographs, production of various polypeptide hormones both in vitro and in vivo, and much higher frequency of such paraneoplastic syndromes as ectopic Cushing's syndrome and inappropriate secretion of antidiuretic hormone than occurs in other types of lung cancer. Most importantly, patients with SCLC are markedly more responsive to chemotherapy than are patients afflicted with other lung cancer cell types. Effective combination therapy has

led to four- to fivefold improvement in median survival compared to untreated patients and a small fraction apparently enjoying a long-term cure (Ihde '89: 195).

Staging is not important for SCLC treatment. However assessing the extent of tumor dissemination is useful to establish a prognosis. Common sites of distant metastases in SCLC are the liver, bone, bone marrow, brain, lymph nodes and subcutaneous tissue, for which imaging studies are commonly performed. The three most important prognostic factors in SCLC are tumor extent (limited or extensive stage), performance status and weight loss. The morbidity and mortality of optimal doses of combination chemotherapy are greatly increased in fully bedridden patients and tumor responses lasting over a year are virtually nonexistent in this group, that is better treated with reduced doses of chemotherapy, which will often ameliorate symptoms and sometimes increase survival. The major survival benefits of treatment is to patients whose tumors exhibit compete clinical disappearance It is uncommon to observe further improvement in response status after 12 weeks of chemotherapy in SCLC patients. Several studies have shown that combination chemotherapy is more effective than single-agent treatment in SCLC, both in terms of response rate and survival. Moderately intensive drug doses associated with nadirs of leukopenia in the range of 1000 to 2000 cells/µl yield superior results to regiments producing more modest myelosuppression. Chemotherapy programs utilized in SCLC generally include three or four drugs selected from known active single agents such as cyclophosphamide, doxorubicin, vincristine, methotrexate, etoposide (VP-16), cisplatin, or a nitrosuourea such as moustine (CCNU). The major toxicities produced by all combination chemotherapy programs used in SCLC are related to myelosuppression, specifically neutropenia-assocaited fever, infectin and bleeding. Nausea, vomiting and alopecia are sen with many drugs. Toxicities peculiar to specific drugs, such as congestive heart failure with doxorubicin and neuropathy with vincristine. With current commonly used chemotherapy regiments, treatment-associated death rates of 1% to 4% in liminted and 3% to 8% in extensive stage disease can be anticipated, however the survival benefits of chemotherapy greatly exceed the survival detriments produced by its toxicities (Ihde '89: 196, 197).

Combination Chemotherapy Regimens Commonly Used in Small Cell Lung Cancer

Regimen and Drugs	Dose (MG/M^2)	Schedule
VAC Regimen (Q.3 Weeks)		
Vincristine	1 (2 mg maximum)	Days 1,8,15 in first cycle, Day 1 only thereafter
Doxorubicin (Adriamycin)	40	Day 1
Cyclophosphamide	1000	Day 1
CMC Regimen (Q.3 Weeks)		
Cyclophosphamide	1000 (500 reduced dose 2^{nd} cycle)	Day 1, 22
Methotrexate	15 (10 reduced dose 2^{nd} cycle), p.o.	Days 1, 4, 8, 11, 22, 25, 29, 32
Lomustine (CCNU)	100 (50 reduced dose 2^{nd} cycle)	Day 1
CAVp Regimen		
Cyclophosphamide	1000	Day 1
Doxorubicin (Adriamycin)	45	Day 1
Etoposide (VP-16)	50	Day 1-5
CMCV Regiment (Q.4		

Weeks)		
Cyclophosphamide	700	Day 1
Methotrexate	20, p.o.	Days 18, 21
Lomustine (CCNU)	70, p.o.	Day 1
Vincristine	1.3 (2 mg maximum)	Day8, 15, 22, in first cycle; Day 1 only thereafter
CAVVp Regiment (Q.3 weeks)		
Cyclophosphamide	1000	Day 1
Doxorubicin (Adriamycin)	50	Day 1
Vincristine	1.5 (2 mg maximum)	Day 1
Etoposide (VP-16)	60	Days 1-5
VP-16/Platinum Regiment (Q.3 Weeks)		
Etoposide (VP-16)	100	Days 1-3
Cisplatin	25	Days 1-3

Source: Ihde '89: 198 Table 26-1

Combination chemotherapy is the cornerstone of management of limited state SCLC. Overall response rates of 80% to 95%, complete response rates of 40% to 70%, median survival of 12 to 16 months, 2-year survival of 10% to 25% and 5 years survival (with probable cure of the original SCLC) of 6% to 12% can be expected when chemotherapy, with or without chest irradiation, is delivered. SCLC responds much more readily to chest irradiation, with overall response rates o fup to 90%. In most patients treated with radiotherapy alone, however, distant metastases ensue within a few months. In the 1970s studies demonstrated that chemotherapy plus chest irradiation improved survival compared with radiotherapy alone in limited stage SCLC. Randomized trials have conclusively shown that combined therapy reduces the failure rate at the primary tumor site but is associated with more hematologic, pulmonary and esophageal toxicity, and combined modality programs have not shown better survival compared with chemotherapy given alone. Approximately 10% to 15% of limited stage patients present with surgically resectable disease using standard criteria employed for non small cell lung cancer. Particularly if a preoperative diagnosis of SCLC is unavailable, proceeding with tumor resection in patients without mediastinal node involvement at thoracotomy is perfectly appropriate. Postoperatively, a standard combination chemotherapy program with or without chest radiotherapy should be administered (Ihde '89: 197-199).

Chest irradiation has no impact on survival in patients with extensive stage disease. Therefore, combination chemotherapy alone is customarily administered, although with results inferior to those obtained in limited disease. Overall response rates of 65% to 85%, complete response rates of 15% to 30%, median survival of 7 to 11 months, 2 year survival of 0% to 5% and only anecdotal 5 year survival can be anticipated when effective combination chemotherapy programs are employed in disseminated SCLC. Radiotherapy can be useful in control of brain metastases, palliation of symptoms from pathologic bone fractures, painful bony metastases, and spinal cord compression, and in treatment of bronchial obstruction or superior vena cava syndrome that is unresponsive or has recurred after chemotherapy. Chemotherapy and chemotherapy with chest irradiation yield fairly similar results in the initial treatment of superior vena cava syndrome. SCLC is the type of lung cancer most likely to metastasize to the brain, and early studies of both chest irradiation and chemotherapy documented that the brain was a frequent site of relapsing tumor in responding patients. Therefore, prophylactic cranial irradiation, either concurrently

with initial therapy or after response, tends to diminish the frequency of clinically detectable brain relapse, however, no survival benefit has been demonstrated, because brain metastases is an uncommon cause of death, and other studies have indicated that cranial irradiation is only beneficial for those patients with a complete response to systemic treatment. Due to unresolved neuropsychological impairment in long term survivors with SCLC prophylactic cranial irradiation should be given in low doses per fraction, preferably only to patients in complete remission, and may be omitted (Ihde 89: 198, 199).

Chemotherapy, the management of disease with chemical sustances, is used to manage primary as well as recurrent cancers. Neoadjuvant or induction chemotherapy is delivered before radiation therapy or induction chemotherapy is delivered before radiation therapy or a surgical procedure to attempt to decrease the tumor burden and make it more amendable to the primary therapy. Concomitant chemotherapy is given simultaneously with the definitive form of therapy. Adjuvant chemotherapy is given after radiation or surgical treatment to help control remaining microscopic disease. In some malignant diseases such as leukemia and lymphoma, chemotherapy may be the primary therapy, whereas in head and neck cancer chemotherapy is provide in conjunction with a primary therapy. Despite response rates exceeding 75% with the use of induction chemotherapy, it has not been shown to improve survival rates. Chemoprevention is the administration of drugs to prevent the development of invasive carcinoma. Because second primary cancers develop at an annual rate of 5% it is desirable to find a way of decreasing or suppressing these new cancer. Isotretinoin activity in suppressing premalignant lesions showed fifty-five percent to 100% of leukoplakic lesions showed regression during therapy with the retinoid drugs. Most lesions that initially responded to therapy progressed after the medicine was stopped. Despite continual advancement in chemotherapeutic management of head and neck cancer, overall survival rates have not changed significantly during the past 30 years (Schwartz, Har-E; & DiPillo '04: 459, 462).

Toxicity profile for selected chemotherapeutic agents

Chemotherapeutic agent	Common toxic profile
Methotrexate	Bone marrow suppression, gastrointestinal ulcers, hepatotoxicity, pulmonary infiltration, mucositis, pulmonary infiltration, mucositis, neutropenia-thrombocytopenia, anemia, diarrhea, stomatitis
5-Fluorouracil	Nausea, vomiting, diarrhea, bone marrow suppression, photosensitivity, cerebellar toxicity, mucositis, neutropenia-thrombocytopenia, skin reaction, alopecia
Cisplatin	Bone marrow suppression, tinnitus and hearing loss, nausea and vomiting, renal failure, potassium and magnesium wasting, peripheral neuropathy, anemia, anorexia
Bleomycin	Pulmonary fibrosis, pneumonitis, little innumosuppression or bone marrow suppression, erythema, hyperpigementation, ulceration, fever, chills, allergic reaction
Mitomycin-C	Bone marrow depression, gastrointestinal, renal and pulmonary toxicity, alopecia, stomatitis, nausea and vomiting, diarrhea, potential for hemolytic-uremic syndrome

Source: Schwartz, Har-E; & DiPillo '04: 462 Table 53-2

Chemotherapeutic drugs exert their effects by interfering with cell proliferation or the processes of DNA, RNA or protein synthesis. Most anticancer drugs indiscriminately attack

rapidly dividing cells and damage both normal host tissues and cancer cells. Many chemotherapeutic drugs act at specific phases during the cell cycle and are termed cycle-specific agents. Agents that interfere with DNA synthesis are called S-phase specific, and those that interfere with microtubules to disrupt mitosis are called M-phase specific. DNA-alkylating drugs are considered cell-cycle nonspecific because they damage cells whether or not they are dividing, making these agents more effective against slow-growing and solid tumors. A chemotherapeutic agent will not affect tumor cells if the drug does not reach the cells, the cells are not in the proper phase of the cell cycle for the drug to work, or the cells are resistant to the effects of the drug. Cancer cells can gain resistance by reducing drug uptake, enhancing the repair of its DNA, producing altered drug-resistant enzymes, decreasing the amount of prodrug converted into active drug, and inactivating agents working within the cells. Also, multi-drug resistance can develop and may be caused by a cellular pump that decreases drug levels. Antimetabolites are drugs that interfere with DNA or RNA synthesis such as methotrexate with or without leucovorin, 5-flurouracil, 6-mercaptopurine, cytarabine (Ara-C) and thioguanine. Mitotic inhibitors are drugs that bind to tubulin and depolymerize microtubules such as vincristine and vinblastine. Alkylating agents are drugs that cross link DNA and preventDNA replication and RNA transcription such as Cisplatin, busulfan, nitrogen mustards (cyclophosphamide, mechlorethamine). Antibiotics with inhibition activity are drugs that affect synthesis of DNA such as bleomycin, mitomycin-C, actinomycin D, and doxorubicin. Nitrosoureas are drugs that are lipid soluble, penetrate the blood-brain barrier and inhibit DNA and RNA such as BCNU, CCNU and streptozotocin. Hormones are drugs that affects testosterone and estrogen-sensitive tumors, lymphoma and leukemia such as estrogen, progestins, androgens, leuprolide, flutamide, and adrenocorticotropic steroids.

Single agent chemotherapeutic drugs for the head and neck are methotrexate, 5-Fluorouracil, Cisplatin, Bleomycin, Dozorubicin, Cyclophasphamide, Vincristine, Mitomycin-C, Paclitaxel (Taxol) and Carboplatin. Multiple agent combinations for the head and neck are Cisplatin and 5-Fluorouracil and Carboplatin and 5-Fluorouracil (Schwartz, Har-E; & DiPillo '04: 459-463). Regimens used in the treatment of SCLC are the VAC Regimen, vincristine, doxorubicin (adriamycian), cyclophosphamide; the CMC regimen, cyclophosphamide, methotrexate, lomustine (CCNU); CAVp regimen, cyclophosphamide, doxorubicin (Adriamycin), etoposide (VP-16)' CMCV regimen, cyclophosphamide, methotrexate, lomustine (CCNU), vincristine' CAVVp regimen, cyclophosphamide, doxorubicin (Adriamycin), vincristine, etoposide (VP-16) and VP-16/Platinum Regimen, etoposide (VP-16) and Cisplatin (Ihde '89: 198). Methotrexate 2.5 mg available online without prescription and marathons might produce better results with fewer side-effects, infections, and at 70 cents a pill, once a week, less cost.

III.A.15 Congenital defects and cystic fibrosis

Congenital disorders of respiratory function, ear, nose and throat range from respiratory distress at birth, to subtle changes in appearance, or communication. Congenital disorders may be divided into genotypic and phenotypic abnormalities. Genotypic abnormalities may be caused by a single gene mutation such as a point mutation or dislocation or by a chromosomal abnormality such as trisomy 21. Phenotypic abnormalities are morphologic defects that may be further classified by type and pattern. Types of phenotypic abnormalities include malformations, deformations and disruptions. **Malformations** are caused by an abnormal developmental process, such as incomplete morphogenesis (e.g., cleft lip and cleft palate). Malformations initiated earlier in organogenesis produce more severe results than those occurring later. **Deformations** are abnormal forms or positions of a portion of the body. They generally are

caused by restricted fetal movement from intrauterine mechanical forces (e.g. congenital torticollis and clubfoot associated with oligohydramnios). Deformation usually occur late in development and may improve postnatally when the mechanical restriction is eliminated. **Disruptions** are morphologic defects caused by intrauterine interference with an otherwise normally developing organ or region of the body (e.g., phocomelia associated with thalidomide use). Disruptions are usually sporadic. Patterns of phenotypic abnormalities include sequences, syndromes and associations. **Sequences** result from one primary developmental defect that causes a chain of secondary anomalies that may lead to another group of defect. For example, in Robin sequence the hypoplastic mandible (primary defect) prevents the tongue from descending. This prevents closure of the palatal shelves and causes cleft palate (secondary defect). **Syndromes** are groups of multiple anomalies (malformations or sequences) thought to be pathogenetically related but not represented by a single sequence (e.g., Down syndrome). **Associations** are nonrandom clusterings of anomalies that are not known to be a sequence or a syndrome (Song & Goldsmith '04: 370, 377).

The larynx, trachea, and lungs begin to form from the anterior surface of the foregut early in the fourth week of gestation. This laryngotracheal ridge grows caudally, forms major bronchi, and becomes infiltrated by splanchnic mesenchyme, which forms the connective tissue and vessels of the lung. As the lung matures from a simple tube surrounded by mesenchyme to a complex system of airways and alveoli interfacing with an enormous vascular network, it undergoes five stages of development – (1) embryonic, 4^{th} - 6^{th} weeks the major airways and lobes develop; (2) pseudoglandular, 7^{th}-16^{th} weeks, completion of formation of all conducting airways: number of acini determined; (3) canalicular, 17^{th}-28^{th} weeks, acini develop and become vascularized and the alveolar lining epithelium thins; (4) saccular, 29^{th}-36^{th} weeks, decrasing interstitial tissue, secondary saccular crests form and surfactant appears; and (5) alveolar, 37^{th} week – birth, true alveoli are seen. The complete development of the bronchial tree by the sixteenth week of gestation has been described as Reid's first law of lung development. Reid's second law of lung development states alveoli develop after brith, increasing in number until the age of 8 years and in size until growth of chest wall finishes with adulthood. 50 million alveoli are the mean number of alveoli at a term birth. Reid's third law of lung development states the pre-acinar vesses (arteries and veins) follow the development of airways, the intra-acinar that of the alveoli. Muscularization of the intra-acinar arteries does not keep pace with the appearance of new arteries (Sobonya '89: 15-17).

Developmental defects of the lung include (1) agenesis or hypoplasia of both lungs, one lung, or single lobes; (2) tracheal and bronchial anomalies; (3) vascular anomalies; (4) congenital lobar overinflation (emphysema); (5) congenital cysts; and (6) intralobar and extrapulmonary lobar sequestrations. Congenital cysts represent and abnormal detachment of a fragment of primitive foregut, and most consist of bronchogenic cysts. **Bronchogenic cysts** may occur anywhere in the as single or, on occasion, multiple cystic spaces from microscopic size to more than 5 cm in diameter. They are usually found adjacent to bronchi or bronchioles but may or may not have demonstrable connections with the airways. Complications include infection of the secretions, with suppuration, lung abscesses, or rupture into bronchi, causing hemorrhage and hemoptysis or rupture into the pleural cavity, with pneumothorax or interstitial emphysema. **Bronchopulmonary sequestration** refers to the presence of lobes or segments of lung tissue without a normal connection to the airway system. Blood supply to the sequestered area arises not rom the pulmonary arteries but form the aorta or its branches. Intralobar sequestrations are found within the lung substance and are usually associated with recurrent localized infection or bronchiectasis. Extralobar sequestrations are external to the lung and may be found anywhere in

the thorax or mediastinum. Found most commonly in infants as abnormal mass lesions, they may be associated with other congenital anomalies (Kobzik & Schoen '94: 675).

Atelectasis refers either to incomplete expansion of the lungs or to the collapse of previously inflated lung substance, producing areas of relatively airless pulmonary parenchyma. Significant atelectasis reduces oxygenation and predisposes to infection. Acquired atelectasis may be divided into obstructive (or absorptive), compressive, contraction (from scarring), and patchy atelectasis. **Obstructive atelectasis** is the consequence of complete obstruction of an airway, which in time leads to absorption of the oxygen trapped in the dependent alveoli, diminishing lung volume. Obstructive atelectasis is caused principally by excessive secretions or exudates within smaller bronchi and is most often found in bronchial asthma, chronic bronchitis, bronchiectasis, and postoperative states and with aspiration of foreign bodies. **Compressive atelectasis** results whenever the pleural cavity is partially or completely filled by fluid exudate, tumor, blood, or air (pneumothorax), or tension pneumothorax, when air pressure impinges on and threatens the function of lung and mediastinum, especially the major vessels, most commonly encountered in patients in cardiac failure who develop pleural fluid and in patients with neoplastic effusions within the pleural cavities. **Patchy atelectasis** develops when there is loss of pulmonary surfactant, as in neonatal and adult respiratory distress syndrome. Because the collapsed lung parenchyma can be re-expanded, atelectasis is a reversible disorder. However, atelectatic parenchyma is prone to developing superimposed infections (Kobzik & Schoen '94: 675, 676).

The **face of an infant and child** is not merely a scaled-down version of that of the adult. Newborns have a small face relative to cranial size. The **newborn face** also appears round and relatively flat with large, wide-set eyes. Throughout childhood, the face elongates because of maxillary and mandibular growth. As facial height increases, the ratio of face to the cranium changes from 1:3 for infants to 1:2 for adults. Concurrent growth of the skull base causes increased facial projection. The chin and cheek bones become more prominent, and the pyriform aperture of the nose is displaced inferiorly relative to the orbits. **Sinonasal growth** is closely related to maxillary and facial growth. The vertical height of the nose increases substantially during adolescence. Growth of the external nose completed at about 15 years of age for girls and 18 years for boys. Elective nasal operations are consequently deferred until adolescence. The immature pinna (external **ear**) has adult morphologic features at birth but it is soft and pliable. Operations to correct excessive protrusion of the ear (otoplasty) can be performed safely by 4 to 5 years of age, when most of the pinna growth has occurred. Adult size is attained by 9 years of age. The tympanic membrane has its full dimensions at birth, but is thick and lies in a nearly horizontal position. With ossification of the ear canal by 2 years of age, the tympanic membrane assume its vertical orientation. The ossicles (malleus, incus and stapes) are of adult size and configuration at birth. The Eustachian tube is only half its adult length at birth and is nearly horizontal (infant 10 degrees, adult 45 degrees). By age 7 the Eustachian tube assumes its adult size and configuration, and the incidence of otitis media is greatly reduced. Newborns have a small **oral cavity** because the mandible is foreshortened, producing relative macroglossiea, causing the newborn to be an obligate nasal breather until 6 to 12 weeks of age. The **larynx** is fully formed at birth but is located higher in the neck at the level of the fourth cervical vertebrae. With growth of the neck, the larynx gradually reaches its adult position at C5 to C7 at the time of puberty. **Hearing loss** occurs in 1 of 500 live births; severe impairment occurs among about one-half of patients. **Cleft palate** is a defect in the structures that divide the nasal and oral cavities. It may occur with or without a cleft lip deformity, and is estimated to occur in 1 of 680 births (Song & Goldsmith '04: 380). There are a number of **behavioral milestones** in the

development of children, particularly regarding speech and language (Francis, Rosenfeld & Goldsmith '04: 385, 386).

Communication milestones for infants and children

Age	Hearing and receptive language	Expressive language
0 to 3 months	Alerts to speech. Startles to loud sounds.	Cries to express needs. Throaty noises
3 to 6 months	Recognizes change in tone. Watches speaker's face.	Laughs. Makes guttural sounds (cooing).
6. to 9 months	Turns toward novel sounds. Stops action in response to no.	Babbles. Varies pitch. Says "Dada" or "Mama".
9 to 12 months	Follows instructions with gesturing. Turns to name.	Makes speech sounds (p, b, m) in different pitches. Says 1 to 2 words.
12 to 18 months	Knowns the names of familiar objects. Identifies sounds from another room.	Uses jargon. Says 2 to 3 words.
18 to 24 months	Identifies 2 or more body parts. Identifies 5 common objects.	Mixes jargon with words. Says more than 20 words.
24 to 30 months	Follows 2-step directions. Understands possessive terms.	Uses 2-word sentences. Knows more than 50 words. 50% of speech intelligible.
30 to 36 months	Follows simple conversation	Uses 2 to 4 word sentences. Knows 800 to 1,000 words. 50%-75% of speech intelligible.
3 to 4 years	Understands with background noise. Categorizes.	Uses 3 to 5 word sentences. Knows 1,500 words. Produces p, b, m, n, h, w, k, g, d, f, y
4 to 5 years	Able to listen for long periods. Follows 3-step directions	Knows more than 2,000 words. 90% grammar acquisition. Inconsistently produces r, l, s, z, v, th, /d/

Source: Francis, Rosenfeld & Goldsmith '04: 387 Table 44-2

Adolescence is defined as the period beginning with the appearance of secondary sexual characteristics and ending with completion of growth. The healthcare problems of adolescents tend to fall into three major categories – the consequences of puberty, the consequences of psychosocial development, and the consequences of specific diseases that involve only this age group, such as infectious diseases (mumps, infectious mononucleosis, sexually transmitted diseases), neoplasms (Hodgkin's disease, thyroid cancer), and systemic disease (sarcoidosis, lupus erythematosus). During puberty changes in the hypothalamic-pituitary access increases levels of **sex hormones** such as estrogen, progesterone and testosterone and cause physical changes. These changes include the growth spurt that occurs anywhere from 12 to 14 year of age, dental changes such as the development of molars, including wisdom teeth, the appearance

of secondary sexual characteristics, and the change in voice. Adolescents are not merely small adults or large children, and their successful care requires a strong appreciation of the particular physical and psychological changes that occur during this critical period. Although any disease may affect an adolescent, certain disease must be strongly considered when one deals with this population (Goldsmith '04: 393). **Strep throat**, caused by Group A β-hemolytic streptococcus (*Streptococcus pyogenes*), is particularly intriguing because although it tends to affect the throats of adolescents with healthy hearts and brains, sometimes causing rheumatic fever, particularly in younger children, and also causes rheumatic heart disease in susceptible, typically older, people.

Cystic fibrosis (CF) is a multi-system disease characterized by a triad of suppurative pulmonary disease, pancreatic insufficiency and elevated sweat chloride concentrations. Formerly called mucoviscidosis, it is transmitted as an autosomal recessive trait and is the most common fatal inherited disease of whites, occurring in 1 in 2000 live births. About 5% of the white population carries the disease. The CF gene has been localized on the long arm of human chromosome 7. CF was once exclusively a pediatric disease. However, because of improved awareness of the disease, diagnosis of mildly affected individuals, and aggressive treatment, median survival has increased from less than 2 years in 1950 to almost 20 years of age in 1990. The hallmarks of CF are malabsorption of food from pancreatic insufficiency and progressive, suppurative and destructive pulmonary disease. Early on, the clinical picture is dominated by symptoms referable to pancreatic insufficiency and other gastrointestinal manifestations. As the patient's age advances, respiratory manifestations tend to predominate. The disease varies greatly in age of onset, organ system involvement and rapidity of progression. The sweat chloride concentration is an excellent diagnostic discriminator of patients with CF, 90% of them have seat chloride concentrations greater than 60 mEq/L. The remainder of them have values between 50 and t0 mEq/L and about 1 in 1000 have values less than 50 mEq/L. A determination greater than 60 mEq/L in adults is considered diagnostic. A normal range of sweat chloride does not exclude the diagnosis. The majority of patients with CF have a chest radiograph that demonstrates cystic bronchiectatic changes and honeycombing, particularly in the upper lung fields. Only 2% of adults with CF have a normal chest radiograph. The upper lobes are affected more often than the lower, and the right lung more than the left (Gerber '89: 301-303).

Clinical manifestations of adult cystic fibrosis are (1) respiratory manifestations: chronc rhinosinusitis, nasal polyposis, chronic bacterial bronchitis, bronchiectasis, bronchopneumonia, lobar actelectasis, pneumothorax, hemoptysis, cor pulmonale, reactive airway disease and allergic bronchopulmonary aspergillosis; (2) gastrointestinal manifestations: pancreatic insufficiency, malabsorption, vitamin deficiency, intestinal obstructive syndrome, intussusception, volvulus, fatty liver infiltration, focal biliary cirrhosis, hepatic cirrhosis, portal hypertension, recurrent acute pancreatitis, appendicitis, periappendiceal abscess, microgallbladder, cholelithiasis, cholecystitis, hiatal hernia, gastroesophageal reflux, and rectal prolapse; (3) exocrine manifestations: abnormal sweat electrolytes, abnormal mucosal electric potential differences, heat prostration, metabolic alkalosis; (4) endocrine manifestations: glucose intolerance, iodide goiter, thyroid amyloidosis; (5) renal manifestations: renal tubular acidosis, secondary systemic amyloidosis, nephrotic syndrome; (6) hematologic manifestations: iron deficiency anemia, thrombocytosis, hypoprothrombinemia and vitamin deficiency coagulopathy; (7) reproductive manifestations: obstructive azoospermia, thickened cerbical mucus and pregnancy complications; (8) musculoskeletal manifestations: clubbing, hypertrophic osteoarthropathy, idiopathic arthralgias, erythema nosum, rickets, and osteomalacia; (9) nervous system manifestations: brain abscess, pseudotumor cerebri, exudative retinopathy, amyloidosis

peripheral neuropathy, and nervous system autonomic dysfunction and (10) psychosocial manifestations (Gerber '89: 302)..

Symptoms of rhinosinusitis are seen in nearly all individuals with CF. Spontaneous pneumothorax is a relatively frequent complication (up to 50%) in CF and occurs in a setting of severe pulmonary impairment. Mortality is 30% to 60% and is causd by the severe underlying parenchumal decompensation rather than the pneumothorax itself. Hemptysis occurs in approximately 7% of Cf patients. Cor pulmonale is a frequent sequelae of severe pulmonary involvement. Pancreatic insufficiency, manifested by abdominal bloating and cramps, frequent and voluminous loose stools, and malabsorption, is present in 85% of children with CF. In adolescents pancreatic insufficiency abates and in adults is well controlled with prancreatic enzyme supplementation. Malabsorption may be present, as evidence by weight loss and the sequelae of the fat-soluble vitamin deficiencies. Childhood acute pancreatitis occurs in 1% to 5% of children and is much higher in adults. Intestinal obstruction caused by either fecal impaction or intussusception is a frequent complication of CF.increasing with age. The symptoms of obstruction include crampy abdominal pain, constipation or watery stools, nausea and tender mass on abdominal exam. Contrast enemas usually delineate the obstruction or intussusception and are also therapeutic in that they can evacuate the impacted feces or reduce the intussusception. Digital clubbing is a nearly universal clinical finding in CF that an be complicated by hypertrophic osteoarthropathy of the joints, such as the knee, ankle and wrist. Nearly all post-pubescent males with CF are infertile on the basis of obstructive azoospermia caused by maldevelopment of the epididymis, vas deferens and seminal vesicles. However, approximately 2% to 3% of men with CF have normal fertility and some have fathered children. The reproductive tract of women with CF is anatomically normal. However, these women have decreased fertility because of their chronic illness, relative malnutrition, and anovulatory cycles. The cervix is often impacted with thick, tenacious mucus, which acts as a mechanical obstruction to sperm (Gerber '89: 304-306).

Most individuals with CF are diagnosed in infancy or childhood, but 20% of young adults with CF are not diagnosed until after age 15. The diagnosis of CF is usually quite obvious. Historically, CF was often mistaken for pulmonary tuberculosis because of the chronic productive cough fever, weight loss and apical cystic lesions on chest radiographs. Currently CF is most commonly mistaken for asthma. Asthma and CF share the features of chronic cough, bronchospasm, hyperinflation, rhinosinusitis, occasional nasal polyposis, aspergillus colonization and increased IgE levels. But asthmatic people rarely develop chronic bacterial bronchitis, a persistently abnormal chest radiograph, clubbing, hemoptysis, spontaneous pneumothorax, cor pulmonale, or a deteriorating course with extrapulmonary disease. Adult CF patients have also been misdiagnosed as having emphysema chronic bronchitis, bronchiectasis, eosinophilic granuloma, sarcoidosis, immotile cilia syndrome, or one of the immunoglobulin deficiencies. In making the differential diagnosis of CF one must rule out (1) respiratory analogues: asthma, chronic bronchitis, bronchiectasis, emphysema, tuberculosis, eosinophilic granuloma, sarcoidosis, alpha-1- antitrypsin deficiency, immotile cilia syndrome, agammaglobulinemia, IgA deficiency, Young's syndrome, or ankylosing spondylitis; (2) gastrointestinal: inflammatory bowel disease, infectious enteritis or gluten-sensitive enteropathy. Occasionally there is confusion between CF and the immotile cilia syndrome. CF causes obstructive azoospermia due to maldevelopment and obstruction of the reproductive ductal system. In the immotile cilia syndrome, sperm is present but immotile because of ultrastructural abnormalities. Patients with the **immotile cilia syndrome** have a much slower progression of disease and a normal life expectancy. They do not have multiorgan complications, chronic *S. aureus* or *P. aeroginosa*

bronchitis, or other findings characteristic of CF. The CF gene has been localized to the long arm of chromosome 7. DNA markers are being used for linkage analysis of certain CF families. These markers, called restriction fragment length polymorphisms (RFLPs) , make it possible to follow the transmission of the gene from one generation to the next, thus making it possible to tell if the fetus has inherited a CF gene from a parent or if a sibling of an affected individual is a carrier of the CF gene (Gerber '89: 306-308).

Respiratory complications account for the major morbidity and mortality of patients with CF. Treatment, although only palliative, is directed primarily at pulmonary hygiene and management of chronic infection. Treatment must also be directed toward other organ system complications. Overproduction of mucus exacerbates the airway obstruction, bacterial infction and deterioration seen in CF. Removal of these secretions is facilitated by bronchial hygiene, breathing exercises, and exercise therapy. Mucomyst (N-acetylcysteine) although its effectiveness is questionable, is occasionally used to liquefy tenacious secretion. With progressive pulmonary deterioration, CF patietns develop exercise-induced, and, eventually, resting arterial oxygen hypoxemia. This hypoxemia exacerbates the patient's incipient cor pulmonale. Oxygen administration alleviates the dyspnea associated with exercise and often improves the patient's appetite and level of activity. Airway hyper-reactivity is a common accompaniment to CF's chronic inflammation, infection and mucus overproduction. As many as 25% of adults with CF have some degree of exercise-induced bronchospasm. Aerosolized beta agonists and atropine derivatives are efficacious in CF patietns with airway hyper-reactivity. In mild to moderately severe disease, theophylline has proven to be beneficial in improving pulmonary function, but blood levels must be monitored. Treatment of CF in children with alternate-day prednisone has been shown to improve their height, weight and pulmonary function and to reduce hospital admissions. It is currently common practice to use corticosteroids not only chronically but also for acute exacerbations of CF, as in status asthmaticus. No evidence of worsening bacterial infection has been reported in patietns treated concurrently with short-term, high-dose corticosteroids and antipseudomonal antibiotics. Continuous oral antibiotics are useful in decreasing the number of pulmonary exacerbations and hospitalizations of CF patients. Their principal efficacy is activity against *S. aureus* and *H. influenza*. Trimethoprim-sulfamethoxazole and chloramphenicol occasionally have in vitro activity against *P. aeruginosa* organisms. Penicillin or the antiviral amantadine (symmetrel) are most effective against *H. influenza* and doxycycline is best for S. aureus in children over 8, younger children benefit most from penicillin, if the are not allergic. Intravenous antibiotics are indicated when a patient has severe deterioration despite aggressive treatment. Deterioration is usually manifested by increased cough, fatigue, malaise, anorexia, weight loss, low-grade fever, occasional chills, decreased pulmonary function and radiographic changes. Two-drug therapy (an aminoglycoside and another anti-pseudomonal antibiotic) is directed against *P. aeruginosa* and *S. aureus* organisms. The penicillin derivatives often exhibit synergy with high doses of aminoglycosides against *P. aeruginosa*. The duration of multi-drug antibiotic therapy is empirically set at 10 to 14 days (Gerber '89: 308-310).

Type A influenza infections can cause significant morbidity in CF patients. Therefore yearly influenza vaccination is recommended for all CF patients over 6 months of age. Amantadine hydrochloride can be used if begun in 24 to 48 hours after the onset of symptoms. Tamiflu is also highly effective prescription flu remedy. Proper nutrition is important to treatment. Patients with pancreatic insufficiency have increased energy requirements because of fecal losses from malabsorption. For most patients a well-balanced diet of appropriate caloric and vitamin content is usually sufficient. Fat restriction is usually not necessary. Exogenous pancreatic enzymes are administered to patients with symptoms of malabsorption caused by exocrine

pancreatic insufficiency. They are usually begun at 2 to 5 tablets with each meal; the dosage is titrated to the level at which symptoms are most relieved. These enzymes require an alkaline environment and are inactivated by pepsin and stomach acid. Thus enteric coating of the pancreatic enzymes improves their efficiency. The histamine H2 blocker, such as cimetidine and ranitidine, also improve the effectiveness of pancreatic enzymes by decreasing the acid production. H2 blocker also help relieve the symptoms of gastro-esophageal reflux caused by theophylline and corticosteroids. CF patients require supplementation of vitamins A, D, E, and K. In most routine situations this can be achieved by administering one multivitamin twice a day and an additional 200 international units of vitamin E. In individuals with an elevated prothrombin time, an extra 5 mg of vitamin K is given each week (Gerber '89: 310, 311).

III.B Cardiovascular Conditions

III.B.1. Ischemic Heart Disease

Ischemic heart disease (IHD) is the leading cause of death in the United States and many industrialized nations. **Sudden cardiac death** (SCD) strikes about 300,000 to 400,000 annually. Coronary atherosclerosis with greater than 75% stenosis, involving more than one of the three major vessels is present in 80 to 90% of victims; only 10 to 20% of cases are of non-atherosclerotic origin. Usually there are high-grade stenosis (greater than 90%). Acute coronary changes such as, thrombosis, plaque fissuring, intra-plaque hemorrhage, are commonly found in 75 to 80% of fatal heart attacks. A healed myocardial infarct is present in about 40%, but in those who have been rescued by prompt therapy from sudden cardiac arrest new myocardial infarction is found in 25% or less. The ultimate mechanism of death is almost always a lethal arrhythmia. Cardiovascular diseases, including stroke, are the No. 1 killer in the United States for both men and women. Coronary heart disease, is America's No. 1 killer. Stroke is No. 3 and a leading cause of serious disability. Of the estimated 50 million, 166 out of 1,000, with unhealthy levels of lipoprotein in their blood, 7 million Americans feel angina (23 in 1,000), 1.5 million will suffer an acute myocardial infarction (heart attack) for which 550,000 will be hospitalized (1.8 out of 1,000) and of the 2.4 million people who died in 2004, 666,000 died from heart disease (2.2 out of 1,000) and 150,000 from stroke. People suffering chronic angina pectoris have about a 20% chance of suffering a fatal heart attack over ten years. depending on how many and how complete the occlusion of the arteries is, the five year survival ranges from 50 to 98% (Heger '04: 113).

In the United States during 1972 more than one million people died from major cardiovascular disease, a majority from heart attacks and strokes. Between 1940 and 1960 there was a marked increase in deaths from cardiovascular diseases among American males over 45 years of age (Elvin-Lewis ’77). Since then heart attacks and strokes in North America have declined by 60 percent (after adjusting for age). Myocardial infarction may occur at any age, but the frequency rises progressively with old age. Five percent of myocardial infarctions occur in people under age 40 years, and 45% occur under age 65. Blacks and whites are affected equally often. Throughout life men are at significantly greater risk of myocardial infarction than women. However, the use of oral contraceptives, increases the risk of myocardial infarction, especially in smokers older than age 35. Newer formulas have reduced estrogen content with reduced risk at all ages. Moreover, epidemiologic evidence strongly suggests that estrogen replacement therapy protects menopausal women against myocardial infarction (Schoen ’94: 529). The **risk of heart attack** is four times greater to a man in his fifties than to one in his thirties, and greatest among men in the 50 to 60 year age group. For the most part, this improvement has been due to a

reduction in the traditional risk factors identified in the Framingham Heart Study, in which the population of Framingham, Massachusetts, just west of Boston, has been followed for more than fifty years, with regular research examinations. In that study it became apparent that independent predictors of risk included age, sex, congenital defects, lipidemia, high blood pressure, thickening of the heart muscle (left ventricular hypertrophy), glucose intolerance (diabetes and prediabetes) and sedentary lifestyle (Spence '06: 75). The cardinal risk factors for coronary disease in the United States are hypercholesterolemia, hypertension, and inactivity (Elvin-Lewis '77: 179).

Angina pectoris is characterized by paroxysmal attacks of substernal or precordial chest discomfort (variously described as constricting, squeezing, choking, or knife-like) caused by transient (15 second to 15 minutes) myocardial ischemia that falls short of inducing the cellular necrosis that defines myocardial infarction, heart attack, which causes chronic angina until the necrotic myocardial tissue is scarred over and healed after about 5 days to 7 weeks (Schoen '94: 527). Angina is chest pain or discomfort that occurs when an area of your heart muscle doesn't get enough oxygen-rich blood. It's thought that nearly 7 million people in the United States suffer from angina. About 400,000 patients go to their doctors with new cases of angina every year. Angina may feel like pressure or squeezing in your chest. The pain also may occur in your shoulders, arms, neck, jaw, or back. It can feel like indigestion. Angina itself isn't a disease. Rather, it's a symptom of an underlying heart problem. Angina is usually a symptom of **coronary artery disease** (CAD), the most common type of heart disease. CAD occurs when a fatty material called plaque builds up on the inner walls of the coronary arteries. These arteries carry oxygen-rich blood to your heart. When plaque builds up in the arteries, the condition is called **atherosclerosis**. There are three overlapping patterns of **angina pectoris** (1) stable or typical angina, related to cardiovascular exercise (2) Prinzmetal's or variant angina, coronary artery spasm at rest that responds to nitroglycerin and calcium channel blockers and (3) unstable or crescendo angina that falls short of inducing infarction, and is sometimes referred to as pre-infarction angina or acute coronary insufficiency (Schoen '94). **Chronic angina** lasts until the tissue has satisfactorily healed and scarred over, from 5 days to 7 weeks from the last heart attack.

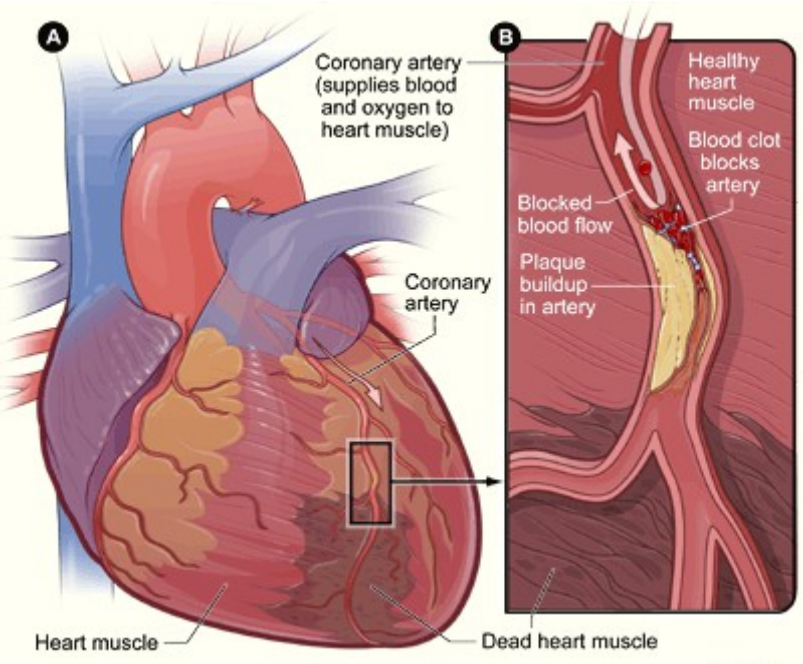
Nitrates are the most commonly used medicines to treat angina and in conjunction with statin drugs seems to be the most successful prescription drug available for the treatment of congestive heart failure. They relax and widen blood vessels. This allows more blood to flow to the heart while reducing its workload. Nitroglycerin is the most commonly used nitrate for angina. Nitroglycerin that dissolves under your tongue or between your cheeks and gum is used to relieve an angina episode. Nitroglycerin in the form of pills and skin patches act too slowly to relieve pain during an angina attack (Sanders '08). Nitrates are safe and affective for the treatment of stable angina pectoris. Short acting nitrates are used for the relief of the acute attacks, whereas long-acting nitrates are used for anti-anginal prophylaxis. With continuous application of the drug at a constant rate, tolerance can develop within 24 hours so a nitrate-free interval is the strategy for preventing tolerance With oral **isosorbide dinitrate**, dosing at 7am, noon and 5 pm appears to avoid tolerance problems With a patch-free interval of 10 to 12 hours, patches retain their effectiveness (Heger et al '04: 114). The **acute coronary syndromes** of unstable angina, acute myocardial infarction and sudden death share a common pathophysiological basis, with coronary atherosclerotic plaque rupture as the pathologic hallmark and associated intraluminal platelet-fibrin thrombus. **Typical angina** commonly results from myocardial oxygen deficiency caused by stenosed (blocked) coronary arteries. In **unstable angina**, a relatively small fissure or disruption of an atherosclerotic plaque may lead to a sudden

change in plaque morphology, with platelet aggregation or mural thrombus and frequently vasoconstriction leading to transient reduction in coronary blood flow. **Sudden coronary death** frequently involves a rapidly progressing coronary lesion, in which plaque disruption and often partial thrombus (and possibly embolization) lead to regional myocardial ischemia that induce a **fatal ventricular arrhythmia** (Schoen '94: 528).

A **heart attack** (myocardial infarction) occurs when blood flow to a section of heart muscle becomes blocked. If the flow of blood isn't restored quickly, the section of heart muscle becomes damaged from lack of oxygen and begins to die. Heart attack is a leading killer of both men and women in the United States. But fortunately, today there are excellent treatments for heart attack that can save lives and prevent disabilities. Treatment is most effective when started within 1 hour of the beginning of symptoms. Heart attacks occur most often, about 90% of the time, as a result of a condition called coronary artery disease (CAD). In CAD, a fatty material called plaque builds up over many years on the inside walls of the coronary arteries (the arteries that supply blood and oxygen to your heart). Eventually, an area of plaque can rupture, causing a blood clot to form on the surface of the plaque. If the clot becomes large enough, it can mostly or completely block the flow of oxygen-rich blood to the part of the heart muscle fed by the artery. During a heart attack, if the blockage in the coronary artery isn't treated quickly, the heart muscle will begin to die and be replaced by scar tissue. This heart damage may not be obvious, or it may cause severe or long-lasting problems. **Diabetes** is a risk factor for heart attack. Some 21 million Americans have diabetes, meaning their bodies can't properly regulate blood sugar, or glucose. Diabetics already are at increased risk of heart disease. Type 2 diabetes, the most common form, is linked to obesity, which in turn harms the heart. Plus, high blood sugar over time damages blood vessels. In other words, fat and sugar, may induce ischemia in inactive people with compromised cardiovascular health and should be avoided.

Blood supplying the heart muscle comes entirely form two coronary (heart) arteries, both lying along the outside surface of the heart. If one of these arteries or any part of one suddenly becomes blocked the portion of the heart being supplied by the artery dies. The death of a portion of the heart muscle is called a heart attack, **myocardial infarction**. The amount of the heart affected by the sudden occlusion will depend on the severity of this attack and will determine whether the individual dies or survives. If the heart continues to function, the dead portion is eventually walled off as new vascular tissue supplies the needed blood to adjacent areas (Elvin-Lewis '77: 177). When coronary angiography was performed within 4 hours of the onset of apparent myocardial infarction, a **thrombosed coronary artery** was found in almost 90% of cases. The incidence of acute occlusion, however, fell to about 60% when angiography was delayed until 12 to 24 hours after onset. Thus with the passage of time, at least some occlusions appear to clear spontaneously because of lysis of the thrombus or relaxation of spasm or a combination of the two. The progression of ischemic necrosis in the myocardium begins in the subendocardial zone. With more extended ischemia, a wavefront of cell death moves through the myocardium to involve progressively more of the transmural thickness of the ischemic zone. **Necrosis** is usually complete in 3 to 6 hours in experimental models. Provided exposure to environmental and dietary cardiotoxins, namely animal products, is eliminated, and toxic insult ceases, the necrotic muscle elicits **acute inflammation** and pain, typically most prominent at 2 to 3 days, thereafter macrophages remove the necrotic myocytes, in 5 to 10 days, and the damaged zone is progressively replaced by the ingrowth of highly vascularized granulation tissue, at 2 to 4 weeks, which progressively becomes less vascularized and more fibrous. In most instances, scarring is well advanced by the end of the sixth week, but the efficiency of repair depend on the size of the original lesion (Schoen '94: 528, 530).

Heart With Muscle Damage and a Blocked Artery



Credit: American Heart Association

Only **severe ischemia**, with blood flow of 10% or less of normal, lasting at least 20 to 40 minutes or longer leads to irreversible damage (necrosis) of some cardiac myocytes. After the onset of an acute ischemic event, one of several pathways may be followed. One is brief and marked by **sudden cardiac death** (SCD) within 1 to 2 hours in 20% of patients (probably an overestimate because most patients are silent about their heart attacks), accounting for about half of ischemic heart disease deaths. If the patient with acute myocardial infarction reaches the hospital, 10-20% of cases are uncomplicated and 80 to 90% are complicated. Common **complications** include cardiac arrhythmias (75-95% of complications), left ventricular congestive failure and mild-to-severe pulmonary edema (60%), cardiogenic shock, pump failure from a large infarct, usually greater than 40% of left ventricle, with nearly 70% mortality rate accounting for two-thirds of in-hospital deaths (10 to 15%), rupture of free wall, septum or papillary muscle (1-5%) and thromboembolism (15 to 40%). The overall total **mortality** within the first year is about 35%, including those victims who die before reaching the hospital. The early mortality rate during hospitalization is approximately 10 to 15% and in the year following infarction is another 7 to 10%. Thereafter there is a 3 to 4% mortality among survivors with each passing year (Schoen '94: 528, 537 539).

The clinical diagnosis of **acute myocardial infarction** is mainly based on three sets of data: (1) symptoms, (2) electrocardiographic (ECG) changes and (3) elevation of specific serum enzymes, particularly creatine phosphokinase (CPK) and lactate dehydrogenase (LDH), although other diagnostic modalities, such as echocardiography (for visualization of abnormalities of regional wall motion), radioisotopic studies (such as radionuclide angiography (for chamber configuration), perfusion scintigraphy (for regional perfusion) and magnetic resonance imaging (for structural characterization, are available. The CPK serum level rises above baseline within 4 to 8 hours and may peak very early or not for several days, falling to baseline in about 4 days. The LDH level does not begin to rise until about 24 hours, peaks in 3 to 6 days, and may not

return to normal until the end of the second week. There are two types of myocardial infarction the transmural infarct and the subendocardial (nontransmural) infarct. The more common type is the **transmural infarct**, in which the ischemic necrosis involves the full or nearly full thickness of the ventricular wall in the distribution of a single coronary artery. This pattern of infarction is usually associated with coronary atherosclerosis, plaque rupture, and superimposed thrombosis. In contrast, **subendocardial (nontransmural) infarct** constitutes an area of ischemic necrosis limited to the inner one-third or at most one-half of the ventricular wall, often extending laterally beyond the perfusion territory of a single coronary artery (Schoen '94: 537).

In **chronic ischemic heart disease** the pericardial surface of the heart may have adhesions as a result of healing associated with past myocardial infarcts. Invariably there is moderate to severe stenosing atherosclerosis of the coronary arteries and sometimes total occlusions resulting from organized thrombi. Discrete, gray-white scares of healed previous infarcts are usually present. The mural endocardium is generally normal except for some superficial, patchy, fibrous thickenings. The clinical diagnosis of chronic ischemic heart disease is generally made largely by the insidious onset of congestive heart failure (CHF) in patients who have past episodes of myocardial infarction or angina attacks, and excludes millions of people who have suffered constant angina pectoris for more than six months (the typical definition of chronic disease). Before necrotic heart tissue has fully scarred, 7 weeks from last infarction, the chronic ischemic heart disease patient has an auto-immune predisposition to infectious endocarditis, nearly always of bacterial origin, usually *Streptococcus pyogenes* (rheumatic heart disease), *S. faecalis*, *S. sanguis*, that respond best to penicillin, and erythromycin, *Peptostreptococcus*, *Bactroides fragiles* that respond best to metronidazole (Flagyl ER) or *Staphylococcus aureus* whose resistant strains can only be treated with doxycycline or clindamycin (Cleocin) for pregnant women and children under 8. Viruses and fungi rarely infect the heart and should be treated with corticosteroids.

One-quarter of adults over age 45 take cholesterol-lowering statin drugs. Statin drugs are the best prescription medicine for heart disease. 17 percent of patients taking the pills reported side effects, including muscle pain, nausea, and problems with their liver or nervous system. About two-thirds of people with side effects quit taking statins. All in all, half of all the people who been prescribed the drugs quit them at last temporarily. Twenty percent quit for more than a year. The vast majority of people don't have side effects. Many of the people in this study who quit the drug were able to get back on statins. The FDA has warned that taking statins slightly increases the risk of diabetes, cancer, dementia and nerve damage, even in people at a healthy weight and with no other risk factors. No research has been done to see if the diabetes, cancer, dementia and nerve damage go away when patients stop taking statins. Long-term statin use may cause nerve damage, that damage often reverses when statins are discontinued, but the process can take months. Not continuing the drug has a lot more to do with people just not wanting to take drugs for a lifetime (Shute '13).

A 1994 study called the Scandinavian Simvastatin Survival Study (also called 4S) found that lowering cholesterol can prevent heart attacks and reduce death in men and women who already have heart disease and high cholesterol. For over 5 years, more than 4,400 patients with heart disease and total cholesterol levels of 213 mg/dL to 310 mg/dL were given either a cholesterol-lowering drug or a placebo (a dummy pill that looks exactly like the medication). The drug they were given is known as a statin, and it reduced total cholesterol levels by 25 percent and LDL-cholesterol levels by 35 percent. The study found that in those receiving statin, deaths from heart disease were reduced by 42 percent, the chance of having a nonfatal heart attack was reduced by

37 percent, and the need for bypass surgery or angioplasty was reduced by 37 percent. A very important finding is that deaths from causes other than cardiovascular disease were not increased, and so the 42 percent reduction in heart disease deaths resulted in a 30 percent drop in overall deaths from all causes (Sanders '08: 28). In 1996 the results of the Cholesterol and Recurrent Events (CARE) Study also showed the benefits of cholesterol lowering in heart disease patients. This study reported that even in patients with seemingly normal cholesterol levels (average of 209 mg/dL), cholesterol lowering with a statin drug lowered the risk of having another heart attack or dying by 24 percent. A study published in 1998, the Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) study, examined the effects of cholesterol lowering in people with CHD (those who had already experienced a heart attack or had been hospitalized for angina) and who had relatively average cholesterol levels. The LIPID study used a statin drug to lower cholesterol levels in the treatment group. All study participants were counseled about following a cholesterol-lowering diet. The LIPID results showed that a drop of 18 percent in total cholesterol and 25 percent in LDL-cholesterol produced a 24 percent decrease in deaths from CHD among the treatment group compared with the control group (Sanders '08: 28, 29).

Eating the standard American diet that's based on meat and dairy products, with plenty of white flour and white sugar, one-third of the women and one-half of the men in the US population die of heart disease. Meanwhile, vegetarians and vegans (vegetarians who consume no dairy products or eggs) not only have far less heart disease, but also have lower rates of cancer, hypertension, diabetes, gallstones, kidney disease and obesity. Not only is mortality from coronary artery disease lower in vegetarians than non-vegetarians, but vegetarian diets have been successful in arresting coronary artery disease. The daily intake of cholesterol by non-vegetarians is 300-500 mg/daily, lacto-ovo-vegetarians 150-300 mg/ daily and vegans zero, their cholesterol levels were 210, 161 and 133 respectively, safe levels of cholesterol are less than 150. The ideal ratio of total cholesterol to HDL (high-density lipoproteins) is 3.0 to 1 or lower, the average American male's ratio is 5.1 to 1 and the average vegetarian's ratio, on the other hand, is 2.9 to 1. When it comes to heart disease the evidence is against animal products. Vegans live on average six to ten years longer than the rest of the population and in fact seem to be healthier on every measurement we have of assessing health outcomes. A low-fat plant based diet would lower the heart attack rate about 85 percent, and cancer rate 60 percent (Robbins '01: 14 , 15, 21, 22, 47).

Modified nutritional habits of high-risk American men, substituting diets moderate in calories, total fat, and carbohydrate, low in saturated fat, cholesterol, and simple sugars reduced heart disease mortality by about one-half and the sudden death rate was only one-fourth as great, and total mortality was lower by 40%. In a study of coronary heart disease in seven countries only the concentration of cholesterol in the blood proved to be the outstanding risk factor within and between national groups. As these data indicate, Japanese men have the lowest incidence of coronary heart disease of any industrialized nation, they smoke heavily and they have high blood pressure, but they eat a low cholesterol diet. The death rate from heart disease is 300% higher in cigarette smokers than in non-smokers in the United States. Curiously, the effects of cigarette smoking are equivocal: the practice is not related statistically to heart disease among, for example, Japanese men who smoke heavily. Reasons for an increased risk include lowered ability of the lungs to exchange oxygen and carbon dioxide, toxicity form nicotine (which makes the heart beat faster and causes small arteries to narrow thereby increasing blood pressure and the work load on the heart). Obesity (10-20%) above ideal weight adds to the work load of the heart and is to be avoided. Lack of regular daily exercise is a factor in coronary disease. Men

engaging in heavy physical work seem to have a significantly lower death rate from coronary disease than more sedentary job holders (Elvin-Lewis ’77: 182, 183).

A 30 percent reduction in heart attacks has been found in people who follow a Mediterranean diet, as good as statin drugs (Shute '13). Not only is mortality from coronary artery disease lower in vegetarians than non-vegetarians, but vegetarian diets have been successful in reversing coronary artery disease by osmosis of lipids in the bloodstream. The daily intake of cholesterol by non-vegetarians is 300-500 mg/daily, lacto-ovo-vegetarians 150-300 mg/ daily and vegans zero, their cholesterol levels were 210, 161 and 133 respectively, safe levels of cholesterol are less than 150. The ideal ratio of total cholesterol to HDL (high-density lipoproteins) is 3.0 to 1 or lower, the average American male’s ratio is 5.1 to 1 and the average vegetarian’s ratio, on the other hand, is 2.9 to 1. When it comes to heart disease the evidence is against animal products. Vegans live on average six to ten years longer than the rest of the population and in fact seem to be healthier on every measurement we have of assessing health outcomes. A low-fat plant based diet would lower the heart attack rate about 85 percent, and cancer rate 60 percent (Robbins ’01: 14 , 15, 21, 22, 47).

Besides a vegan diet, an athletic level of cardiovascular exercise is necessary. **Statin** cholesterol lowering drugs are an essential medicine for reducing the risk of death from heart attack or ischemic stroke but recovery is not given as a reason for discontinuing statin use. Statin drugs reduce the risk of death in patients with hyperlipidemia by around 50 percent and the stroke risk by 30 percent but the reasons given for quitting statins does not include a cure. Nitrates and Nitrites can be effective at restoring normal blood flow within 5 minutes and lead to a complete recovery from angina pectoris or congestive heart failure in some patients, it should be tried in an office visit to see if a prescription is wanted. The treatment of congestive heart failure would be much improved with the use of the supreme herb for the heart - **Hawthorne** leaves, berries and flowers as an herbal tea infusion, tincture or syrup are good for the heart and kidneys. Hawthorne works in part by dilating the arteries and veins, enabling blood to flow more freely and releasing cardiovascular constrictions and blockages. It strengthens the heart muscle while helping to normalize and regulate blood pressure. It also helps maintain healthy cholesterol levels. Hawthorne is outstanding both to prevent heart problems and to treat high or low blood pressure, heart disease, edema, angina and heart arrhythmia. Hawthorn doesn’t store in the body and isn’t accumulative in action, it’s important to take on a regular basis if using as a heart tonic (Gladstar '12).

Drugs used to treat coronary artery disease

Supreme herb for the heart
Hawthorne is outstanding both to prevent heart problems and to treat high or low blood pressure, heart disease, edema, angina and heart arrhythmia.
Lipid-lowering drugs
HMG-CoA reductase inhibitors (statins): Used to prevent cholesterol buildup in the coronary arteries. Can also prevent the inflammatory response that could cause atheromatous plaques to rupture in the heart and precipitate a heart attack. Side effects include muscle and liver injury.
Niacin (nicotinic acid), cholestyramine, gemfibrozil, clofirate: Used to treat high cholesterol and high triglycerides.
Vasodilator
Nitroglycerine: used to treat chest pain (called angina) from coronary artery disease. Can lower blood pressure. Should not be used by patients using sildenafil (Viagra).
Antiplatelet Medications

Acetylsalicylic acid (aspirin): Used to help prevent and treat heart attacks.
Clopidogrel (Plavix): Used with acetylsalicylic acid (aspirin) after placement of a stent to prevent the stent and coronary artery from occluding.
Rare Diseases
Rituxan (rituximab) or cyclosphamide IV and prednisone for Wegener's granulomatosis, microscopic polyangiitis and Polyarteritis nodosa (PAN)
Gamma globulin IV administered with aspirin for Kawasawki Disese

Source: Cohen '05

Dissolution of a clot in an unwanted location, **thrombolysis**, was originally used for the treatment of deep vein thrombosis and pulmonary embolism but is now also used for treating acute peripheral arterial thrombosis and embolism and for thrombosed prosthetic heart valves, catheters and shunts. Thrombolytic agents used currently act directly or indirectly as plasminogen activators. Thrombolytic therapy with various fibrinolytic agents such as streptokinase or tissue-type plasminogen activator (tPA) is used in about 15% of myocardial infarcts, in an attempt to dissolve the thrombus that initiated the infarct, to re-establish blood flow to the area at risk for infarction, and possibly to rescue the ischemic heart muscle. Thrombolysis re-establishes the patency of the occluded coronary artery in about 70% of cases, and significantly improves survival rates. Reperfusion of the myocardium with blood, sufficiently early, within 15 to 20 minutes, after onset of ischemia may prevent all necrosis. Reperfusion after a longer interval can salvage at least some myocytes that would have died with more prolonged or permanent ischemia. However, reperfusion injury can cause cell death of myocytes that were still viable before reperfusion. Persistance of total occlusion with failure of clot lysis occurs in approximately 30% of patients undergoing thromblytic therapy. The major complications of thrombolytic therapy that lessen enthusiasm for its use in patients with occlusive vascular disorders include hemorrhage due to the systemic fibrinolytic state (15% of patients) and thrombotic reocclusion (15 to 35% of patients). Reocclusion is related to the continued presence of the factors, responsible for the original thrombus initiation (Schoen ’94: 535, 537, 512).

Because platelet aggregation has been strongly implicated in the pathogenesis of unstable angina pectoris and myocardia infarction, Aspirin, a platelet inhibitor, shows a 51% lower incidence of myocardial infarction and death in the aspirin group (324 mg/day) than the placebo group, although it is generally conceded that lower doses (1mg/kg) work as well and are less inhibitory to the arterial endothelium's production of prostacyclin than higher doses. Aspirin causes irreversible acetylation of platelet cyclooxygenase, thereby preventing the formation of thromboxane A_2 an extremely potent vasoconstrictor and platelet activator. The thienopyridine drugs ticlopidine and clopidogrel (Plavix) are also effective antiplatelet drugs used to prevent stent closure, generally, clopidogrel is preferred, because it is safer, more potent, and faster acting and can be taken once a day. Plavix is used with acetylsalicylic acid (aspirin) after placement of a stent to prevent the stent and coronary artery from occluding. Glycoprotein (GB) IIb/IIIa Receptor Antagonists prevent fibrinogen binding and platelet aggregation and is used by patients at high risk and those undergoing percutaneous coronary intervention. Three GP IIb/IIIa receptor antagonists are currently available – abciximab (long lasting 12 hours affect on platelets) an, eptifibatide, and tirofiban that have short half live of 2 to 3 hours. Severe thrombocytopenia (less than 20,000/mL) is seen in 0.5% of patients. Unfractionated heparin (UFH) reduces the risk of sudden cardiac death, myocardial infarction and recurrent ischemic events when combined with ASA in the setting of unstable angina pectoris. Unless there is a contraindication, full-dose heparin anticoagulation appears to be a logical therapy in the earl

coronary care unit setting followed by chronic low-dose aspirin in patients with intermediate or high risk unstable angina pectoris. Most of the benefit is short term and most trials have limited heparin use to 2 to 5 days. Severe thrombocytopenia (less than 100,000/mL) occurs in 1 to 2% UFH auto-immune induced thrombocytopenia with thrombosis occurs in less than 0.2% of cases. Low-molecular-weight heparin (LMWH) is safer and alleviates the need for partial thromboplastin time testing (Heger et al '04: 124-126).

Clinical trials testing three new drugs appear to offer some promise to heart patients. Two of the drugs, cangrelor and inclacumab, might improve outcomes for patients undergoing cardiac interventions such as angioplasty or stenting, while a third drug, Inspra, seems to lower heart patients' odds for death and heart failure following a heart attack. All three trials were funded by the respective drugs' makers, and all three were presented Sunday at the annual meeting of the American College of Cardiology (ACC) in San Francisco. In the first trial, researchers compared an as-yet approved blood thinner called cangrelor against the current standard medication, Plavix (clopidogrel), for patients who have recently had a stent implanted in an artery to help improve blood flow. According to the ACC, more than 600,000 coronary artery stent procedures are conducted in the United States each year, but doctors have long sought safer alternatives to Plavix to help prevent clots. Plavix comes with one big drawback for patients rushed to the hospital with suspected heart attack: It is taken in pill form, and its anti-clotting effects (with accompanying bleeding risk) may not wear off for up to a week. Cangrelor may help get around that issue. Even though it is delivered intravenously and begins acting quickly, its anti-clotting effects also fade quickly — within an hour — should any bleeding complications occur. So, doctors might feel free to give heart patients cangrelor upon admittance to the hospital and then send them immediately for angioplasty — a minimally invasive procedure to reopen clogged vessels — or stenting, if needed. In the trial, which was funded by cangrelor's maker, New Jersey-based The Medicines Company, researchers compared short-term outcomes for 11,000 patients who underwent stent placement at one of 153 centers around the world. Some of the patients got cangrelor, while others got Plavix. The research team reported that cangrelor reduced by 22 percent the odds of a patient dying, having a heart attack or having a clot develop in the stented vessel within two days of the procedure, compared to patients who took Plavix. Safety profiles were similar: Severe bleeding at 48 hours after the stenting procedure occurred in 0.16 percent of those on cangrelor and 0.11 percent of those given Plavix. More than 1 million Americans each year undergo angioplasty. But angioplasty can also trigger damage to heart tissues, and it was thought that the new drug might help minimize that risk. cangrelor's price has not yet been set, but it likely will carry a much higher price tag than Plavix.

A second study focused on the drug eplerenone, marketed by Pfizer as Inspra. The drug is currently FDA-approved to help lower high blood pressure and to ward off heart failure after heart attack. In the new Pfizer-funded trial, slightly more than 1,000 patients who had had a heart attack caused by complete blockage of an artery took either Inspra or a placebo in addition to standard treatments. Patients were followed for an average of a bit more than 10 months. Those taking Inspra were 38 percent less likely than those on a placebo to have outcomes such as death by cardiovascular causes, rehospitalization due to heart failure, irregular heart rhythms or other indicators of heart failure. A third and smaller trial, published simultaneously online in the *Journal of the American College of Cardiology*, looked at another still-unapproved drug, the anti-inflammatory agent inclacumab, for use in patients undergoing angioplasty. More than 1 million Americans each year undergo angioplasty. But angioplasty can also trigger damage to heart tissues, and it was thought that the new drug might help minimize that risk.

In the study, which involved 322 patients with a common form of heart attack, participants got either various doses of inclacumab or a placebo about an hour before their angioplasty.
The research team assessed changes in levels of troponin I — a protein found in the blood that indicates heart damage — as a means of telling whether the drug was effective or not.
The researchers reported that 24 hours after the procedure, patients who had gotten the highest dose of inclacumab saw their troponin I levels drop by more than 24 percent compared to those on a placebo — indicating less heart tissue damage. Levels of another marker of heart tissue damage, called CK-MB, fell by more than 17 percent over 24 hours compared to placebo, the team added. There was also "no bad signal [from the data] in terms of increased rates of bleeding or infection" with the use of inclacumab (Mundell '13).

Decade-old heart attack scars healed after being injected with stem cells from a patients' own bone marrow. So far, eight patients have received the experimental treatment in an ongoing clinical trial. All eight had suffered heart attacks an average of 5 1/2 years prior; one of the patients had his heart attack 11 years earlier. All had dangerously enlarged hearts, with areas of scar tissue from their heart attacks. The researchers harvested bone marrow progenitor cells from four patients and adult stem cells from another four patients. Using a catheter, they then injected the cells into the walls of the patients' hearts. Within three months, the scarred areas of the patients' hearts began to work again. About six months after treatment, and for a year later -- the length of the study so far -- all eight hearts regained a more normal size. They shrank 15% to 20%, three times more than current treatments can achieve. Whether just plain old bone marrow or [adult stem] cells, injected into the scar, and three months later, the area that was completely dead started to contract again. Stem cells are being explored in the treatment of people with recent heart attack damage -- but the "landmark area" is the use of stem cells to treat end-stage heart failure. Stem cells actually reverse the enlargement and their propensity to get worse (DeNoon '11).

Since 1963 Congress and the American Heart Association (AHA) has required the president to proclaim February "American Heart Month." The AHA recommends that patients with acute heart disease should take the ambulance, otherwise they are likely to be turned away. Social Security implemented Compassionate Allowances in October 2008 to provide benefits quickly, within a month, to applicants whose medical conditions are so serious that their conditions obviously meet disability standards of medicine and finance. There currently are 88 specific diseases and conditions that qualify as a Compassionate Allowance. On November 9, 2010, the sixth Compassionate Allowances Outreach hearing was hosted in Baltimore, MD at the University of Maryland Baltimore County. The subject of the hearing was cardiovascular disease and multiple organ transplants. Commissioner Astrue joined Susan B. Shurin, Acting Director of the National Heart, Lung, and Blood Institute, National Institutes of Health, and other Social Security officials in listening to testimony from some of the leading experts on cardiovascular disease and multiple organ transplants. It was estimated that in 2010 150,000 people with cardiovascular disability would benefit from the fast-track disability processes. Cardiovascular disease is the leading cause of death for both men and women in America. More than 95,000 people are currently waiting for an organ transplant and nearly 4,000 are added to the waiting list each month (Lassiter '10).

III.B.2 Arteriosclerosis

The most common form of heart disease is coronary artery disease. The heart is nourished through the coronary arteries, which arise from the proximal (first part of the) aorta. The

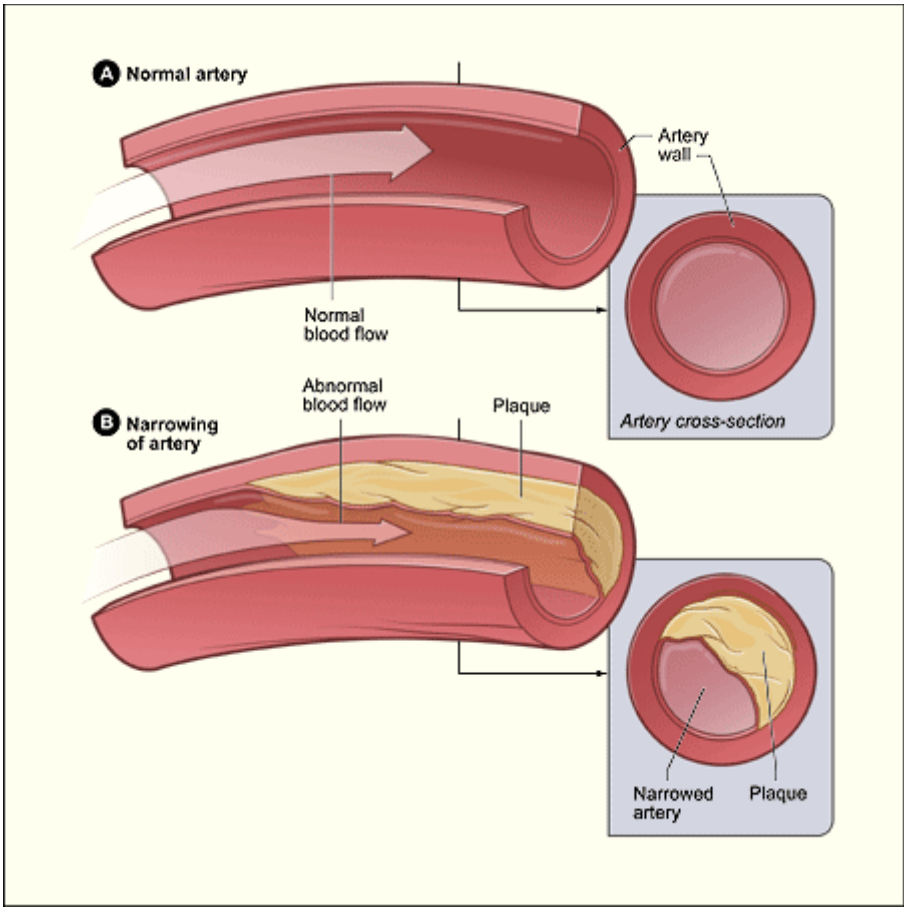
coronary arteries consist of a left coronary artery (which branches into the left anterior descending and the left circumflex coronary arteries) and a right coronary artery. Blockages in these arteries (or in their branches) may lead to a lack of blood flow and oxygenation of heart tissue (called ischemia). This occurs when there is inflammation of the artery wall and scar tissue forms. When the blockage is severe and lasts long enough (usually following plaque rupture), the person may have a heart attack (also called a myocardial infarction) when the heart muscle tissue dies as the result of not getting enough oxygen (Cohen '10: 1-7). Coronary artery disease (CAD) which may manifest itself as chest pain (angina), heart attack, arrhythmias, or sudden cardiac arrest. When blood supply to the brain and limbs is impaired, atherosclerosis can cause mini-strokes, strokes and peripheral artery disease. Two-thirds of Americas have some plaque buildup by age 35. Each year approximately 800,000 Americans have their first heart attack and 500,0000 Americans will have a recurring attack according to the American Heart Association. There is a link between atherosclerosis and sudden cardiac arrest. Atherosclerosis is the buildup of calcium and fatty deposits in the arterial walls. CAD with a prior heart attack is a leading risk factor for sudden cardiac arrest. Sudden cardiac arrest kill nearly 300,000 Americans each year (Cohen '10: 45). According to the U.S. government, one in every 300 Americans will be killed by a blocked artery in 2007. Every 34 seconds an American dies as the result of a blocked cardiac artery. As an American, there's a 90 percent chance that poor circulation will trigger a serious health problem at some point in your life. More than 6.8 million Americans undergo heart bypass, balloon angioplasty and other circulation-related procedures each year. 700,000 Americans will suffer a sudden blockage of blood flow to the brain in 2007-83 every hour of the day. Each year, about 1.1 million people in the United States have heart attacks, and almost half of them die. Mortality differs significantly by race or ethnic group as measured by age adjusted death rates. In 1998 these death rates per 100,000 people from heart disease in the United States were 211.8 for black non-Hispanics, compared to 145.3 for white non-Hispanics, 101.5 for Hispanics, 106 for American Indians and 78 for Asians (Sanders '08).

Arteriosclerosis means "hardening of the arteries" and includes three morphologic variants: (1) atherosclerosis, characterized by intimal thickening and lipid deposition; (2) Moncheberg's medial calcific sclerosis, characterized by calcification of the media of muscular arteries; and (3) arteriolosclerosis, marked by proliferative or hyaline thickening of the walls of small arteries and arterioles. **Atherosclerosis** is a process in which the wall of an artery fills with fat, fibrous tissue and, in later stages, grains of calcium. If the "plaque" gets large enough, it limits the flow of blood. When that happens and tissue downstream from the blockage dies, the result is a heart attack or stroke (Brown '13). Atherosclerosis is by far the most common and important form of arteriosclerosis causing 90% of all heart disease. Atherosclerosis overwhelmingly accounts for more death and serious morbidity in the Western world than any other disorder. Nearly 50 percent of deaths in the United States can be attributed to atherosclerosis related disease such as myocardial infarction (heart attack), cerebrovascular accident (stroke), or aortic aneurysm. The death rate related to atherosclerosis in the United States is among the highest in the world, lower than for Finland and Scotland, but above that of other well-developed affluent countries, such as Canada, France and the other Scandinavian countries. The rates are comparably low in Asia, Africa and South and Central America. For example death rates from ischemic heart disease in Japan are one-sixth of those in the United States. Japanese who migrate to the United States and adopt the lifestyles and dietary customs of their new home acquire the predisposition to atherosclerotic diseases of the American population (Schoen '94: 473, 474).

Arteriosclerosis and its offspring atherosclerosis are the primary contributors to death and disability in this country. This condition of progressive arterial damage leading to varying

degrees of narrowing and even complete obstruction of major arteries. History tells us that some of the earliest knowledge about arteriosclerosis and its very advanced form, atherosclerosis, came from dissections of the human body done in Renaissance Italy. Credit generally is given to Leonardo da Vinci for the first of these dissections in the 15th century. Abnormalities in arterial walls were found early on and related to social standing, for the most severe abnormalities were found in the wealthy classes of merchants and professionals. In the 19th century Karl Rokitansky compiled a comprehensive handbook of tissue changes he had observed. He suggested that elements of the blood, including blood clots and serum, formed layers on the arterial linings. Over time, a hardened, calcified layer resulted that came to be called arteriosclerosis. In the late 19th century Rudolph Virchow, who introduced tissue microscopy to the field of pathology, elaborated further on the process of this arterial change. **Mucoid degeneration** was a term he used to describe the very earliest sign of arterial change. In this condition, a mucoid substance is deposited within the intima, the tissue lining the inside of the artery. Subsequently he noted the accumulation of fatty substances from the blood within this mucoid deposit. He called these raised, swollen areas atheromas. This word, from the Greek athere, for porridge, reflected the porridge-like appearance of the fatty mucoid substance to Virchow's critical eye. The term atherosclerosis refers to the advanced for of the human disease where multiple plaques of this process are present. Arteriosclerosis refers to generalized hardening of the arterial walls by a collection of fibrous connective tissue and calcium salts. The two conditions frequently co-exist with atheromatous plaques developing in arteries already lined with sclerotic changes. Virchow suspected an infectious factor when he noted that leukocytes, the cells of infection, occasionally were present in the bases of atheroma plaques (Graveline '04: 57-59).

Formulated in 1973 and modified in 1986 and 1993 the contemporary view of the pathogenesis of atherosclerosis is called the **response to injury hypothesis**. The injury postulated is a form of endothelial dysfunction without necessary denudation, which increases permeability to plasma constituents, including lipids, and permits blood monocytes and eventually platelets to adhere to endothelium. Monocytes adhere and subsequently enter the intima, transform into macrophages and accumulate lipid to become foam cells, contributing to the evolution of the lesion. Single or short lived injurious events can be followed by restoration of endothelial function and regression of the lesion. Repeated or chronic injury, however, results in the development of an atheromatous plaque. Endothelial injury has been induced in experimental animals by mechanical denudation, hemodynamic forces (AV fistula), immune complex deposition, irradiation, and chemicals to cause intimal smooth muscle proliferation and in the presence of high-lipid diets, typical atheromas. **Endothelial cells** (EC) have a number of properties and functions for the maintenance of the permeability barrier namely (1) the elaboration of anticoagulant and antithrombotic molecules such as prostacyclin, thrombomodulin, plasminogen activator and heparin-like molecules; (2) elaboration of prothrombotic molecules Von Willenbrand factor (Factor VIIIa), tissue factor, plasminogen activator inhibitor and (3) extracellular matrix production (collagen, proteoglycans). In some situations, EC dysfunction comprises a loss of surface heparin-like proteoglycan molecules that prevent thrombus formation and inhibit smooth muscle cells growth, thereby promoting thrombosis and intimal thickening, and depressed release of EC-derived relaxing factors, leading to abnormal vasoconstriction. These changes can result in acute occlusion of a vessel by spasm or a localized thrombotic event and may contribute to atherosclerosis (Schoen '94: 480, 470, 471).



Credit: American Heart Association

Atherosclerosis is a slow progressive disease caused by hyperlipidemia (Schoen '94: 473) after initial damage to the endothelium. Sclerosis, means scarring and ather, the ancient Greek word for gruel or porridge, because the material that makes up plaque – the lesions of an affected artery looks like oatmeal. Plaque is grungy, yellowish and crumbly, with cholesterol crystals in it. It can induce clotting of the blood or can break off an embolize downstream, where it blocks branches and stops the flow of blood to whatever part of the brain, foot bowel, kidney or heart the branches supply. Most people imagine that an atherosclerotic plaque is a deposit of cholesterol and fat in the artery wall, like a collection of egg yolk and butter fat that has been left there from excess fat in the blood. It is actually more like scar tissue in the artery wall. Plaque is made up of inflammatory cells, fibrous tissue and smooth muscle cells that grow into the artery lining where it is injured, much like scar tissue (Spence '06: 28). **Hyperlipidemia** is a major risk factor in atherosclerosis. Atherosclerotic plaques are rich in cholesterol and cholesterol esters, which are derived largely from lipoproteins, such as LDL (low density lipoprotein) cholesterol, triglycerides, C-reactive protein and homocysteine, in the blood. The dietary intake of cholesterol and saturated fats, such as those present in egg yolk, animal fats, and butter, raises the plasma lipoprotein levels, conversely a diet without cholesterol or fat found in animal products or vegetable oils, lowers the plasma lipoprotein levels, enabling atheromas to be reabsorbed into the bloodstream, by osmotic process of lipoprotein levels, in the blood. Greenland Eskimos, who have a high dietary fat consumption, were thought to have low rates of ischemic heart disease, because of the high content of omega-3 fatty acids in their diets (present in fish and fish oils) (Schoen '94: 474, 475, 476). In a recent study of 137 mummies probable or definite" atherosclerosis was evident in 34 percent of the mummies. Only 4 percent, however, had atherosclerosis in the coronary arteries, where it can cause heart attacks. The 51 ancient

Peruvians, who in life presumably ate a lot of beans and complex carbohydrates such as sweet potatoes and manioc, had atherosclerosis in 25 percent of their mummies. Three of the five Aleutian hunter-gatherers, who ate a "paleo diet" high in meat and devoid of sweets and grains, showed atherosclerosis. One woman who died in her late 40s had "the kind of disease we see in people with bypass surgery (Brown '13).

Besides releasing hormones, damaged platelets also release substances that stimulate growth of the artery wall and cause the inner lining, the endothelium, to thicken. Damage to the endothelium, the lining of the artery, sets off a series of unhappy events. First, it attracts platelets and white blood cells to attach to the normally smooth endothelium. Next, it leads some white blood cells (monocytes) to migrate under the endothelium into the innermost layer of the artery itself (the intima), where they transform into macrophages that eat cholesterol and accumulate cholesterol forming a fatty streak. Finally smooth-muscle cells migrate from the middle muscular layer of the artery (the media), grow in the intima, and cause it to thicken further, forming a plaque. Although it would seem logical to assume that when plaque develops in the artery wall, it should stick out into the opening in the tube-like vessel and cause it to narrow, what actually happens is that the artery enlarges to accommodate the plaque so the flow rate along its wall remains constant. This growth is termed compensatory enlargement or vascular remodeling. At some point, an event occurs, such as a rupture of the plaque or a hemorrhage into the plaque. The scar formation in the plaque causes it to encroach on the artery's flow channel. The plaque become inflamed, and infected, and if it ruptures, the protective fibrous cap of the plaque cracks open and the granular contents of the plaque may embolize downstream or provoke the local formation of clot, blocking the artery completely. In other cases, a hemorrhage into a plaque, rather than an outward rupture, cause a sudden blockage of the artery. Virtually all heart attacks and about 70 to 80 percent of strokes, begin with a plaque rupture (Spence '06: 31, 32, 35).

The basic lesion – the atheroma, or fibrofatty plaque- consist of a raised focal plaque within the intima, having a core of lipid (mainly cholesterol and cholesterol esters) and a covering fibrous cap. **Atheromas** are sparsely distributed at first, but as the disease advances, they become more and more numerous, sometimes covering the entire circumference of severely affected arteries. As the plaques increase in size, they progressively encroach on the lumen of the artery as well as on the subjacent media. Consequently, the small arteries, plaques are occlusive, compromising blood flow to distal organs and causing ischemic injury, but in large arteries they are destructive, weakening the affected vessel wall, causing aneurysms or rupture or favoring thrombosis. Moreover, extensive atheromas are friable, often yielding emboli of their grumous contents into the distal circulation (**atheroemboli**), most commonly noted in the kidneys, and in **cerebrovascular accidents** (CVA, strokes) (Schoen '94: 473). **Atheromatous plaques** appear white to whitish yellow and impinge on the lumen of the artery. Plaque formation is often presaged by a fatty streak composed of lipid-filled foam cells. Plaques vary in size from 0.3 to 1.5 cm in diameter but sometimes coalesce to form larger masses. The superficial surface of these lesions tend to be firm and white (the fibrous cap). The centers of larger plaques may contain a yellow, grumous debris, called an atheroma, Greek for gruel. The distribution of atherosclerotic plaques in humans in the abdominal aorta is much more involved than the thoracic aorta, and aortic lesions tend to be much more prominent around the ostia of its major branches. The most heavily involved vessels are the coronary arteries (usually within the first 6 cm), the popliteal arteries, the descending thoracic aorta, the internal carotid arteries, and the vessels of the circle of Willis. Vessels of the upper extremities are usually spared, as are the mesenteric and renal arteries, except at their ostia. Atherosclerotic lesions usually involve the

arterial wall only partially around its circumference and are patchy and variable along the vessel length and the severity of atherosclerosis in one artery does not predict the severity in another. In advanced atherosclerosis, progressive fibrosis may convert the fatty atheroma to a fibrous scar. Almost always, atheromas in advanced disease undergo patchy or massive calcification, causing brittleness, that can be detected by intravascular ultrasound or ultrafast computed tomographic scanning (Schoen '94: 477, 478).

In general **vascular abnormalities** cause clinical disease by (1) progressive narrowing the lumina of vessels and producing ischemia of the tissue perfused by that vessel; (2) provoking intravascular thrombosis, causing acute obstruction or embolism (or both); or (3) weakening the walls of vessels, thereby leading to dilation and rupture. **Congenital anomalies** of blood vessels may predispose the myocardium to infarction or may cause sudden death. Among these diverse vascular anomalies, two have particular importance: developmental or berry aneurysms (involving the cerebral vessels) and arteriovenous fistulas or aneurysms. Abnormal communications between arteries and veins can arise as developmental defects, from rupture of an arterial aneurysm into the adjacent vein, from penetrating injuries that pierce the walls of artery and vein and produce an artificial communication, or from inflammatory necrosis of adjacent vessels. The connection between artery and vein may consist of a well-formed vessel, a vascular channel formed by the canalization of thrombus, or an aneurysmal sac, which can induce cardiac failure. **Thrombosis** is a complication of late-stage atherosclerosis that can lead to embolism as the fibrinous thrombosis becomes superimposed by plaque. Plaques may be equivalent to benign monoclonal neoplastic growths (such as leiomyomas) perhaps induced by exogenous chemical (e.g. cholesterol). Both herpes virus and cytomegalovirus have been detected in human atheromatous plaques that have existed long enough to be exposed. In larger vessels, such as the aorta, the important complications of these plaques are large mural thrombi that may dislodge and yield peripheral emboli, aneurysmal dilation due to destructive impingement of the atheromatous plaques on the media, or rupture of cholesterol emboli into the bloodstream. In smaller arteries, the narrowing of the lumen by atheromatous plaques, especially if accompanied by thrombosis or hemorrhage, can lead to occlusion, causing myocardial infarction or stroke (Schoen '94: 482-484, 467, 472, 473).

A **stroke** occurs when a blood vessel that brings oxygen and nutrients to the brain bursts or is clogged by a blood clot or some other particle. Because of this rupture or blockage, part of the brain doesn't get the blood and oxygen it needs. Deprived of oxygen, nerve cells in the affected area of the brain can't work and die within minutes. And when nerve cells can't work, the part of the body they control can't work either. The devastating effects of stroke are often permanent. There are four main types of stroke. Two are caused by blood clots or other particles (ischemic strokes), and two by bleeding (hemorrhage). Cerebral thrombosis and cerebral embolism are caused by clots or particles that plug an artery. They account for about 70–80 percent of all strokes. Ruptured blood vessels cause cerebral and subarachnoid hemorrhages. These (bleeding) strokes have a much higher fatality rate than strokes caused by clots. Stroke is a medical emergency. Every second counts! Stroke affects different people in different ways. It depends on the type of stroke, the area of the brain affected and the extent of the brain injury. Brain injury from a stroke can affect the senses, motor activity, speech and the ability to understand speech. It can also affect behavioral and thought patterns, memory and emotions. Paralysis or weakness on one side of the body is common. Cerebral thrombosis results when a blood clot blocks a cerebral vessel that has been narrowed by atherosclerotic deposits. Cerebral hemorrhage is bleeding of a vessel into the brain. Progressive cerebrovascular sclerosis occurs when arteries supplying the brain are progressively narrowed, resulting in chronic cerebrovascular insufficiency and giving

rise to dizziness, transient paralysis, forgetfulness and senility. Atherosclerosis is the underlying cause, either by weakening the artery walls with subsequent rupture and bleeding or by narrowing of the arteries predisposing to sudden occlusion by blood clots (Elvin-Lewis ’77: 178).

About 75 percent of strokes can be prevented in high-risk patients. In most cases the symptoms are transient, or the stoke is mild enough that a good recovery is likely. Treatment with the clotbuster drug tPa within three hours after the stroke increases by 40 percent the chance of someone who has suffered a stroke going home without a severe disability. tPA (tissue plasminogen activator) is a naturally occurring substance the body makes to dissolve clots. This can be manufactured and used as a clot-busting drug to open up blocked arteries in people who are experiencing a stroke or heart attack ,but to be effective it has to be used soon after the artery becomes blocked. In difficult cases, new approaches can make a big difference in controlling blood pressure, lowering cholesterol, and preventing arterial disease. The key to controlling difficult high blood pressure is a simple blood test to measure the activity of one kidney enzyme called renin, and an adrenal gland hormone called aldosterone. The levels of fat in the blood after a meal turn out to be more important than the level of cholesterol measured in a fasting cholesterol test. Most people who have muscle problems from cholesterol-lowering drugs in the family called “statins” can resolve them by reducing the dose, adding ezetimibe (a generic drug marketed as Zetia or Ezetrol)_ and taking CoQ10, a dietary supplement. The Most neglected treatable cause of artery disease is high levels of an amino acid called homocysteine, which can be treated with vitamins (Spence ’06: viii).

The measures recommended for stroke prevention are quitting smoking, controlling blood pressure adhering to a Mediterranean diet (plus exercise) and taking cholesterol-lowering drugs, opening up blocked arteries, taking drugs (Aspirin) that reduce blood clotting and treating homocysteine with vitamins. Drugs that lower the level of cholesterol in the blood probably reduce by about 30 percent in four year the risk of any stroke, and by about 50 percent the risk of strokes due to atherosclerosis – plaque deposits, often called “hardening of the arteries” – as opposed to strokes due to high bod pressure. Opening up blocked arteries via either surgery on the carotid (neck) artery or stenting (inserting a metal expanding sleeve into a narrowed artery to hold it open) reduces stroke risk substantially: in persons in whom the carotid artery is narrowed by 70 percent or more and who have had warning symptoms of stroke, surgically removing the inner layer of the artery with the plaque that is blocking the artery (endarterectomy) – reduces stroke or death by two-thirds over two years. (For patients with a narrow carotid artery who have not yet had warning symptoms of a stroke, surgery is only for those at high risk of stroke, as evidence by the particles breaking off the plaque (microemboli) that can be detected by ultrasound of the brain arteries (transcranial Doppler) (Spence ’06: ix, X).

Transient blockage of the carotid artery or its major branches, the anterior and middle cerebral arteries, commonly causes weakness and numbness on the opposite side of the body (face, arm, and leg). This may be accompanied by thickening of speech from either side, or by aphasia, if it is the carotid artery on the dominant side. Occasionally the numbness or weakness may spare the face or leg; rarely if the anterior cerebral artery alone is affected the leg alone may be affected. Ischemia (blocked blood flow) in the brainstem due to a problem with the vertebral arteries or basilar artery may cause numbness or weakness down one side of the body, but commonly the symptoms have a variation such as numbness on both sides of the face, or around the mouth, or the face on one side and the arm and leg on the opposite side. When numbness or weakness affects only the leg, then the problem may be in the spinal cord or in the nerve roots in

the lower back – the sciatic nerve or one of its branches. Similarly, numbness in one hand alone is commonly from a problem with the median nerve (carpal tunnel syndrome) or form a disc in the neck that affects a nerve root that goes down the arm or the nerve that winds around the elbow, the ulnar nerve (funny bone). Weakness in both legs simultaneously, particularly if accompanied trouble with bladder control, often indicates a problem with the spinal cord. When something is compressing the spinal cord and causing symptoms, the compression must be relieved to avoid permanent paralysis (Spence '06: 22, 23).

The arteries that run up through the bones in the back of the neck are the vertebral arteries. The vertebral arteries penetrate the base of the skull, and then join up to form the basilar artery which supplies the brainstem. Then the basilar artery branches to form the two posterior cerebral arteries, which supply the back part of the brain (the occipital lobes) and the interior mesial (underneath, toward the center) temporal lobes. The blood vessels supplying this part of the brain are called the vertebrobasilar system. Visual symptoms (flashing lights, zigzag lines, loss of vision in both eyes or in the visual field off to one side) point to involvement of the occipital lobes. Impaired visual processing, for example, being unable to recognize familiar faces, or becoming lot in familiar surroundings, indicate involvement of the nearby cortex that serves visual association. Permanent impairment of short-term memory suggests permanent damage in both temporal lobes; temporary impartment of short-term memory, which is called transient global amnesia, points to temporary loss of blood flow to the mesial temporal lobes. Double vision points to involvement of the top part of the brainstem (the midbrain), vertigo or facial numbness, to involvement in the middle party (the pons) and the thickening of speech (dysarthria) and trouble with swallowing to the lowest party (the medulla). Numbness or weakness on one side or both sides of the body may occur when lesions in any part of the brainstem affect the nerves that run from the spinal cord to the brain, or vice-versa. Clumsiness and staggering suggest involvement of the cerebellum. Sudden loss of blood flow to the cranial nerve nuclei and their connections to the brainstems may cause facial numbness and weakness, double vision, difficulty swallowing, thickness of speech, vertigo, tinnitus (ringing in the ear) and deafness (Spence '06: 24).

The artery that supplies blood to the eye (ophthalmic artery) is a branch of the internal carotid artery (the main artery that carries blood to the front part of the brain) and a typical attack would involves sudden loss of vision in one eye, recovering over minutes. This is called **amaurosis fugax**, which translates as "fleeting blindness". It is important to distinguish between loss of vision in one eye and loss of vision in one half of the visual field, because this is what determines where the problem is coming from. If the problem is only in one eye, it originated in the carotid artery on the same side; if the loss of vision is off to one side in both eyes, it may be from a problem in the vertebral arteries of the basilar artery, which together supply blood to the back part of the brain on the side of the brain opposite the visual loss. Getting the diagnosis wrong could lead to an unnecessary operation on a narrowed carotid artery that is not causing symptoms - surgery for asymptomatic carotid narrowing (Spence '06: 19, 20).

Vascular inflammatory injury, often with necrosis of blood vessels (**vasculitis**) is encountered in diverse diseases and clinical settings. The terms arteritis, vasculitis and angiitis are used interchangeably. In many patients with vasculitis the serum reacts with cytoplasmic antigens in neutrophils by immunofluorescence and immunocheimical assays, indicating the presence of antineutrophil cytoplasmic autoantibodies (ANCA). Classification and characteristics of vasculitis are organized into large vessel, medium-size vessel and small vessel vasculitis. Large vessel vasculitis includes Giant cell (temporal) arteritis and Takayasu's arteritis. Medium sized

vessel vasculitis includes Polyarteritis nodosa (classic polyarteritis nodosa) and Kawasaki disease. Polarteritis nodosa, also known as classic polyarteritis nodosa, presents as a necrotozing inflammation of medium-sized or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries or venules. Small vessel vasculitis includes Wegener's granulomatosis, Churg-Strauss syndrome, microscopic polyangiitis (microscopic polyarteritis), Henoch-Schonlein purpura, essential cryoglobulinemic vasculitis and cutaneous leukocytoclastic angiitis.

Giant cell (temporal) arteritis is the most common form of vasculitis, it involves granulomatous arteritis of the aorta and its major branches, with a predilection for the extracranial branches of the carotid artery, that often involves the temporal artery and usually occurs in patients older than 50. It is often associated with polymyalgia rheumatic, a flu-like syndrome with joint stiffness often with claudification of the jaw and visual symptoms including blindness. A genetic predisposition exists in those exhibiting increased HLA-DR4 antigen. Clinical improvement almost always achieved with corticosteroid treatment. **Takayasu's arteritis** presents as a granulomatous inflammation of the aorta and its major branches and usually occurs in patients under 50, predominantly females 15 to 40 years old, most common in Asia. This granulomatous vasculitis of medium and larger arteries was described in 1908 by Takayasu as a clinical syndrome characterized principally by ocular disturbances and marked weakening of the pulses in the upper extremities (pulseless disease), related to fibrous thickening of the aortic arch with narrowing or virtual obliteration of the origins of the great vessels arising in the arch. The salient clinical features include weakening of the pulses of the upper extremities with markedly lower blood pressure in the upper extremities; ocular disturbances, including visual defects, retinal hemorrhages, and total blindness; hypertension; and various neurologic deficits, ranging from dizziness and focal weakness to complete hemiparesis (Schoen '94: 494).

Polyarteritis nodosa (PAN) group is characterized by systemic involvement with the vasculitic process and includes the classic type of vasculitis also called macroscopic form of PAN. Classic PAN is manifested by necrotizing inflammation of small or medium-sized muscular arteries typically involving renal, coronary and visceral vessels and sparing the pulmonary circulation. PAN is a disease of young adults, although it may occur in children and older individuals. The most common manifestations are fever of unknown cause and weight loss; hypertension, usually developing rapidly; abdominal pain and melena (bloody stool) due to vascular lesions in the alimentary tract; diffuse muscular aches and pains and peripheral neuritis, which is predominantly motor. About 30 percent of PAN patients have hepatitis B antigen in their serum. Angiography shows vascular aneurysms or occlusions of main visceral arteries in 50 percent of cases. Untreated, the disease is fatal but therapy with corticosteroids and cyclophosphamide results in remissions or cures in 90 percent. Effective treatment of the hypertension is a prerequisite for a favorable prognosis. **Kawasaki disease** is an arteritis involving large, medium-sized, and small arteries and associated with mucocutaneous lymph node syndrome, the coronary arteries, aorta and veins may be involved, it usually occurs in children and infants under four years old. The acute illness is manifested by fever, conjunctival and oral erythema and erosion, edema of the hands and feet, erythema of the palms and soles, a skin rash often with desquamation, and enlargement of cervical lymph nodes. It is usually self-limited. Epidemic in Japan, the disease has been reported in Hawaii and increasingly in the United States. Approximately 20 percent of patients develop cardiovascular sequelae, with a range of severity from asymptomatic coronary artery extasia or aneurysm formation to giant coronary artery aneurysms (7 to 8 mm) with rupture or thrombosis, myocardial infarction or sudden death. It is the leading cause of acquired heart disease in children in the United States. Acute fatalities

occur in 1 to 2 percent of patients. Intravenous gamma globulin administered with aspirin appears to reduce the prevalence of long-term coronary artery abnormalities (Schoen '94).

Wegener's granulomatosis causes a granulomatous inflammation involving the respiratory tract and necrotizing vasculitis and often necrotizing glomeronephritis, affecting small to medium-sized vessels. The peak incidence is in the fifth decade. Typical clinical features include persistent pneumonitis with bilateral nodular and cavitary infiltrates (95%), chronic sinusitis (90%), mucosal ulcerations of the nasopharynx (75%) and evidence of renal disease (80%). Other features include skin rashes, muscle pains, articular involvement, mononeuritis or polyneuritis and fever. Untreated the course of the disease is malignant, 80% of patients die within 1 year. This grim prognosis is improved dramatically by the use of immunosuppressive cytotoxic drugs, such as cyclophosphamide, up to 90% of patients demonstrate significant improvement. **Churg-Strauss syndrome** presents as eosinophil rich granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small to medium-sized vessels and associated with asthmas and blood eosinophilia. **Microscopic polyangiitis**, also known as microscopic polyarteritis, appears as necrotizing vasculitis and pulmonary capillaritis, with few or no immune deposits affecting small vessels of the skin, mucous membranes, lungs, brain, heart, gastrointestinal tract, kidneys and muscle. The major clinical features are hemoptysis, hematuria, and proteinuria; bowel pain or bleeding; and muscle pain or weakness. **Cutaneous vasculitis** is manifested by palpable purpura. Most patients respond well simply to removal of the offending agent. **Henoch-Schonlein purpura** is vasculitis with IgA- dominant immune deposits affecting small vessels. Typically involves skin, gut and glomeruli and associated with arthralgias or arthritis. **Essential crypglobulinemic vasculitis** is with cryoglobulin immune deposits affecting small vessels, associated with crypglobulins in serum, skin and glomerluli are often involved. **Cutaneous leukocytoclastic angiitis** is isolated cutaneous leukocytoclastic angiitis without systemic vasculitis or glomerulonephritis (Schoen '94: 489).

Thromboangiitis obliterans (Buerger's disease) is a distinctive disease characterized by segmental, thrombosing, acute and chronic inflammation of intermediate and small arteries and sometimes veins of the extremities. The condition has occurred almost exclusively in men who were heavy cigarette smokers. Buerger's disease begins before the age of 35 years in most patients and before 20 years in some, in some cases it affects the arms as well as the legs. Small microabscesses within the thrombus create a pattern quite distinct from the bland thrombosis of atherosclerosis. The early manifestations are a superficial nodular phlebitis, cold sensitivity of the Raynaud type in the hands, and pain in the instep of the foot induced by exercise. Eventually patients suffer from vascular insufficiency that often leads to excruciating pain and ultimately gangrene of the extremities. Remissions and relapses correlate with cessation or resumption of smoking (Schoen '95: 498).

Raynaud's disease refers to paroxysmal pallor or cyanosis of the digits of the hands or feet, and infrequently the tips of the nose or ears (acral parts). It is caused by intense vasospasm of local small arteries or arterioles, principally of young, otherwise healthy women. The fingers turn from white to blue to red. Later in the course, intimal proliferation can appear in the artery walls. Raynaud's disease reflects an exaggeration of normal central and local vasomotor responses to cold or emotion. In contrast, Raynaud's phenomenon refers to arterial insuffiency of the extremities secondary to the arterial narrowing induced by various conditions, including systemic lupus erythematosus, systemic sclerosis (scleroderma), atherosclerosis, or Buerger's

disease. Indeed Raynaud's phenomenon may be the first manifestation of any of these conditions (Schoen '94: 499).

Peripheral artery disease refers to changes in the aorta and its branches, the arteries. Aortic aneurysms can form along any part of this main blood vessel, or one of its branches. Sometimes the force of blood under high pressure will rip the lining of the aorta, this is called aortic dissection, or a dissecting aneurysm if it occurs in one of the enlarged areas. A number of changes can occur in the arteries, the veins and the optic nerve that connect to the eye, and the retina, where vision is detected on the back surface of the eyeball. Treatment for severe diabetic eye complications is more successful when blood pressure is normal (Wilson & Childre '06: 9, 40). Varicose veins and phlebothrombosis/thrombophlebitis together account for at least 90% of clinical venous disease. **Varicose veins** are abnormally dilated, tortuous veins produced by prolonged, increased intraluminal pressure. The superficial veins of the leg are the preponderant site of involvement, however, portal hypertension, usually due to cirrhosis of the liver, leads to varices in the esophageal and hemorrhoidal veins. It is estimated that 10 to 20% of the general population eventually develop varicose veins in the lower legs. The condition is much more common over age 50, in obese persons, and in women, a reflection of the elevated venous pressure in the lower legs caused by pregnancy. Occupations that require long periods of standing and long automobile or airplane rides frequently lead to marked venous stasis and pedal edema, even in normal individuals. Varicose dilation of veins renders the valves incompetent and leads to venous stasis, congestion edema, and thrombosis. Despite thrombosis of superficial varicose veins, embolism is very rare. Distention of the veins is often painful, but most patients have no symptoms until marked venous stasis and edema develop. Some of the most disabling sequelae are the development of persistent edema in the extremity and trophic changes in the skin that lead to stasis dermatitis and ulcerations. Because of the impaired circulation the tissues of the affected part are extremely vulnerable to injury. Wounds and infections heal slowly or tend to become chronic varicose ulcers. Because **venous thrombosis** inevitably leads to inflammatory changes within the vein wall, thrombophlebitis and phlebothrombosis are two designations for a single entity. Cardiac failure, neoplasia, pregnancy, obesity, the postoperative state, and prolonged bed rest or immobilization predispose to venous thrombosis. The deep leg veins account for more than 90% of cases of thrombophlebitis (Schoen '94: 504, 505, 506).

An **aneurysm** is an abnormal bulge or "ballooning" in the wall of an artery. Arteries are blood vessels that carry oxygen-rich blood from the heart to other parts of the body. An aneurysm that grows and becomes large enough can burst, causing dangerous, often fatal, bleeding inside the body. Most aneurysms occur in the aorta. The aorta is the main artery that carries blood from the heart to the rest of the body. The aorta comes out from the left ventricle of the heart and travels through the chest and abdomen. An aneurysm that occurs in the aorta in the chest is called a thoracic aortic aneurysm. An aneurysm that occurs in the aorta in the abdomen is called an abdominal aortic aneurysm. Aneurysms also can occur in arteries in the brain, heart, intestine, neck, spleen, back of the knees and thighs, and in other parts of the body. If an aneurysm in the brain bursts, it causes a stroke. About 15,000 Americans die each year from ruptured aortic aneurysms. Ruptured aortic aneurysm is the 10th leading cause of death in men over age 50 in the United States. Many cases of ruptured aneurysm can be prevented with early diagnosis and medical treatment. Because aneurysms can develop and become large before causing any symptoms, it is important to look for them in people who are at the highest risk. Experts recommend that men who are 65 to 75 years old should be checked for abdominal aortic aneurysms. When found in time, aneurysms can usually be treated successfully with medicines or surgery. If an aortic aneurysm is found, the doctor may prescribe medicine to reduce the heart

rate and blood pressure. This can reduce the risk of rupture. Large aortic aneurysms, if found in time, can often be repaired with surgery to replace the diseased portion of the aorta.

An **aneurysm** is a localized abnormal dilatation of any vessel. Aneurysms may occur in any artery or vein of the body, most commonly the aorta. A true aneurysms is bounded by generally complete but often attenuated arterial wall components, with quantitatively or qualitatively altered structure. The blood within a true aneurysm remains within the confines of the circulatory system. Atherosclerotic, syphilitic and congenital aneurysms are of this type. **False aneurysms**, also called pseudoaneurysms or "pulsating hematoma, is an extravascular hematoma that communicates with the intravascular space. The vascular wall has been breached, and the wall of the aneurysmal sac consists of only outer arterial layers or periarterial tissue. A leak at the junction (anastomosis) of a vascular graft with a natural artery produces this type of lesion. **Arterial dissections**, usually of the aorta, arise when blood enters the wall of the artery, dissecting between its layers and creating a cavity within the vessel wall itself. The two most important causes of true aortic aneurysms are atherosclerosis and cystic medial degeneration. Syphilis also causes aortic aneurysms. Aneurysms are often classified by macroscopic shape and size. A **berry aneurysm** is a small spherical dilatation, rarely exceeding 1 to 1.5 cm in diameter, that is most frequently found in the brain. **Saccular aneurysms** are essentially spherical, involving only a portion of the vessel wall, and vary in size from 5 to 20 cm in diameter, often partially or completely filled with thrombus. A **fusiform aneurysm** is a gradual, progressive dilation of the complete circumference of the vessel up to 20 cm in length. Infection of a major artery that significantly weakens its walls is called a **mycotic aneurysm**. Mycotic aneurysms may originate either (1) from the lodgement of a septic embolus at some point within a vessel usually as a complication of infective endocarditis, (2) as an extension of an adjacent suppurative process or (3) by circulating organisms directly infecting the arterial wall. **Syphilitic aneurysms** are almost always confined to the thoracic aorta and usually involve the arch. Thoracic aortic enlargements give rise to signs and symptoms referable to (1) encroachment on mediastinal structures, (2) respiratory difficulties due to encroachment on the lungs and airways., (3) difficulty in swallowing due to compressure of the esophagus, (4) persistent cough due to irritation of or pressure on the recurrent laryngeal nerves, (5) pain caused by erosion of bone, (6) cardiac disease as the aortic aneurysm leads to dilation of the aortic valve or narrowing of the coronary ostia, and (7) rupture of the aneurysm (Schoen '94: , 499, 501).

Atherosclerotic aneurysms usually occur in the abdominal aorta, most frequently between the renal arteries and the iliac bifurcation, or in the common iliac arteries, but the arch and descending parts of the thoracic aorta can be involved. Large aneurysms shorten longevity primarily owing to rupture, a danger directly related to the size of the aneurysm. The risk of rupture for a small abdominal aortic aneurysm (less than 4 cm) is about 2%, aneurysms larger than 5 cm are the most dangerous, with a risk 5 to 10% per year. Timely surgery is key, operative mortality for untreated aneurysms is approximately 5% whereas emergency surgery after rupture carries a mortality rate of more than 50%. **Aortic dissection** are based largely on aortic angiography, but the noninvasive techniques, two-dimensional cardiac ultrasound (especially transesophageal echocardiography), computed tomography (CT, and magnetic resonance imaging (MRI) are increasingly useful. At one time, aortic dissection was almost invariably fatal, but the prognosis has markedly improved. The development of surgical procedures involving the aortic wall and the early institution of intensive antihypertensive therapy permit salvage of 65 to 75 percent of patients (Schoen '94: 500, 504).

III.B.3 Endocarditis

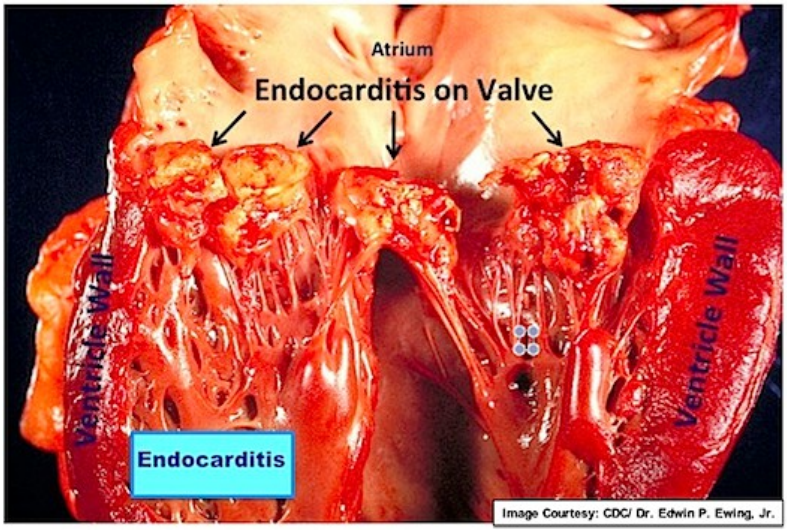
Bacterial endocarditis results from actual colonization of the endocardium by infectious agents through the interstitial capillary bed beneath the endothelium and the blood within the endocardial lumen. *Chronic angina pectoris* that doesn't fully go away after a day or two, week, month or year, usually happens when dead heart muscle from a myocardial infarction (heart attack) becomes infected with pyogenic organisms most obviously *Streptococcus pyogenes*, in about 50% of cases of endocarditis, which causes strep throat and rheumatic fever in children and **rheumatic heart disease** in adults with necrotic heart attack damaged cardiac muscle that doesn't go away like most infections, attacks the valves, creates huge septic vegetations over the myocardium and burdens the vegetarian patient with a 25 percent chance of dying over 10 years, if untreated by antibiotics. Untreated or drug resistant infection is the main reason that the body doesn't heal and acute injury progresses to chronic disease in six months, generally. Some streptococcal illnesses of the heart may last up to 6 weeks without antibiotics and can be severe. Organisms most commonly recovered from such infections are *Streptococcus sanguis*, *S. faecalis*, and in heroin addicts, also *Candida parapsilosis*. It has been reported that 90% of atherosclerotic plaques contain *Chlamydia pneumoniae*. **Infective endocarditis** is one of the most serious of all infections, it is characterized by colonization or invasion of the heart valves or the mural endocardium by a microbiologic agent, leading to the formation of bulky, friable **vegetations** laden with organisms. Not only the valves, but also the aorta (infective endoaortitis), aneurysmal sacs, or other blood vessels can also become infected.

Virtually every form of microbiologic agent, including fungi, rickettsieae (Q fever) and chlamydiae, has at one time or another been responsible for these infections, but most cases are bacterial, hence the usual term, **bacterial endocarditis**. More than half of cases are attributable to various streptococci – most prominently *Streptococcus pyogenes*, a group A strep the viridans, not the group A responsible for rheumatic fever – β hemolytic streptococcus. They are the dominant cause of subacute disease, and as organisms of relatively low virulence, they generally gain a foothold only in heart having some underlying disease or predisposition. Although relatively rare in members of the affluent population who are treated with antibiotics rheumatic fever is an often overlooked important cause of atrial fibrillation, systemic embolism, pulmonary edema, pulmonary hypertension and dyspnea with pregnancy or minimal exertion that is easily treated with broad spectrum antibiotics (Heger et al '04: 197, 198). *Staphylococcus aureus* accounts for about 20 to 30% of cases, it can infect normal valves and pericardium with Staph lesions, and is a leading cause of **acute endocarditis**, and can lead to death within days to weeks of more than 50% of heart failure patients, if a lesion occludes an artery, they are not promptly treated with doxycycline and instead admitted to a hospital. Septic thrombophlebitis, often associated with bacteremia, can be an infection of the cerebral, pelvic, superficial or portal venous systems. When fibrin deposition and thrombus formation results from perivascular inflammation bacterial invasion of the clot can occur (Elvin-Lewis '77: 194).

Failure of clinical recognition of infective endocarditis in 43 per cent of the forty-seven patients is a major factor in the relatively high mortality of this disease (Robinson et al '70). In about 5 to 20% of all cases of endocarditis no organism can be isolated from the blood because of prior antibiotic therapy, because of difficulties in isolation of the offending agent, or because organisms become deeply embedded within the enlarging vegetation and are not released into the blood. Bacteremias emanate frequently from the gut, oral cavity and trivial injuries, seeding the blood with cardiotoxic species such as *Streptococcus viridans,* S. *faecalis, S. sanguis, Peptostreptococcus* or *Bactroides fragiles*. With antibiotic treatment the vegetations sometimes undergo progressive sterilization, organization and can eventually become recalcified, leaving

scars. With repeated blood samples, positive cultures can be obtained in 80 to 95% of cases. With early diagnosis and appropriate antibiotic treatment, the overall 5-year survival is in the range of 50 to 90%, being best for streptococcus induced subacute disease and worst for staphylococcal or fungal acute endocarditis (Schoen '94: 550-554). Staph infections are often resistant to all antibiotic treatment except doxycycline which is nearly always effective, but causes the permanent yellowing of developing teeth of children younger than 8. The lesions caused by staph are generally 1 to 2 cm in diameter and tend to grow in a cluster of similar lesions that can become colonized by Strep. Doxycycline, the once a day antibiotic, is not only cheap, it is effective against Staph and Strep, that responds better to penicillin.

Rheumatic Heart Disease on Autopsy



Rheumatic fever (RF) caused by *Streptococcus pyogenes* (Lancefiled type A) is characterized by painful swollen joints, fever, myocarditis, rash on the trunk and inner aspects of the thighs and upper arms (*erythema marginatum*) and rheumatic nodules over the elbows, knees, hands, and ankles. Salicylates (aspirin) and glycosteroids have been found to suppress the acute febrile and exudative manifestation of rheumatic fever but cannot prevent cardiac damage, for which penicillin is needed (Elvin'Lewis '77: 303). **Chronic rheumatic heart disease** (RHD) is characterized principally by deforming fibrotic valvular disease (particularly mitral stenosis), which produces permanent dysfunction and severe, sometimes fatal, cardiac failure decades later. The incidence of rheumatic fever and RHD has steadily declined in the United States and other developed countries. In 1940, the mortality rate from RHD in the United States was 20.6 per 100,000 population, in 1982, it was 2.2. This decline in morbidity and mortality has been related to improved diet, better control of streptococcal infections by penicillin and an apparent overall reduction nin the virulence of the causative organisms. Globally, there an estimated 15 to 20 million new cases a year, and there are occasional resurgences in localized areas of the United States. During the 1980s there were major outbreaks in Salt Lake City, Pittsburgh and other large U.S. cities, reemergence of virulent strains of group A streptococcus are the cause (Schoen '94: 549). Between 1990 and 2000 prescriptions for antibiotics declined by 40%. RH is no longer just of concern to the uninsured. Patients with chronic rheumatic heart disease may need to buy their own antibiotics online. Sporadic antibiotic prophylaxis to treat bacterial infections is fundamental to the recovery from any serious disease. With the consumption of probiotics there are not any side-effects (Huffnagle '05).

RF is a postinfectious, immunological hypersensitivity due to toxic shock syndrome from the combination of environmental Streptococcus and Staphylococcus infections. Initial attacks of RF follow some weeks after streptococcal infection (1 to 5 weeks). Around 3% of people get RF and RHD following streptococcal pharyngitis. During acute RF, widely disseminated, focal, inflammatory lesions are found in various sites. Most distinctive within the heart, they are called Aschoff bodies, and is a pancarditis as it can be found in any of the three layers of the heart – pericardium, myocardium or endocardium, that serve as the foci of fibrinoid necrosis in the form of small (1 to 2 mm) friable vegetations (verrucae). These acute valvular changes cause little dysfunction but subendocardial lesions, may induce irregular thickenings called MacCallum's plaques, usually in the left atrium. In chronic RHD, the mitral valve is virtually always deformed, but involvement of another valve, such as the aortic, may be clinically important. The RF is overwhelming the most frequent cause of mitral stenosis. The mitral valve alone is involved in 65 to 70% of cases, mitral and aortic in about 25%. The likelihood of acute arthritis increases with age at the time of the attack, appearing in about 90% of adults and less commonly in children. Lesions of the skin in the form of subcutaneous nodules or erythema marginatum are present in 10 to 60% of cases. Acute RF appears most often in children between the ages of 5 and 15 years. Both younger and older individuals, however, may be affected, and about 20% of first attacks occur in middle or later life. Typically, one joint after another becomes painful and swollen for a period of days and then subsides spontaneously, leaving no residual disability. Acute carditis develops in about 50 to 75% of children but only about 35% of adults, and comes with a 1% chance of sudden death, but untreated with antibiotics causes a 25% chance of dying from a heart attack over ten years and does not tend to heal of its own accord (Schoen '94: 550). Angina and rheumatism tend to clear up during or shortly after completing a course of antibiotics allowing an increase in physical activity and a chance for the injured myocardial muscle to heal. But in progressive disease the tissue is likely to become reinfected and the diarrheal and dental cavity side-effects of chronic antibiotic consumption (antibiotics require probiotic supplementation) and the proliferation of antibiotic resistant cultures are serious issues that must be dealt with. Doxycycline or clindamycin for pregnant women and children under age 8 may be necessary to treat Staph.

Antibiotics may be necessary to treat bacterial endocarditis, usually caused by β-hemolytic strains of pneumococcal bacteria, and the chronic heart patient will want to purchase them online. The bacteria can be found in most plaques and colonize "vegetations" on atherosclerotic arteries and necrotic heart muscle that even with treatment is prone to re-infection. Penicillin is generally the most effective treatment for *Streptococcus* spp. but some people have a life threatening allergy to penicillin, and any antibiotic will work. Most of the bacterial species that infect the heart and kidneys are easily treated with a five day course of any twice a day broad-spectrum antibiotic. This is good because most physicians these days are very poor at treating antiobiotic resistance and have fallen out of love with the best medicine of the 20th entirely, despite the ease with which probiotics taken within two hours of antibiotics consumption and for two weeks after completing the course. Between 1990 and 2000 prescription of antibiotics declined 40%. Doxycycline, the once a day antibiotic, that permanently yellows the teeth of children under 8, and metronidazole (Flagyl ER) are essential to solving the problem of **antibiotic resistance**. When pyogenic organisms such as *Staphylococcus aureus* and *Bactroides fragiles* are involved, acute bacterial endocarditis may result that does not respond to most antibiotic drugs. *Bactroides fragilis*, from as far away as the large intestine, can be involved, and there is definitely a connection between diet and the heart. *Staphylococcus aureus,* often transmitted by the meticulously washed hands of health care workers, tends to resistant to all antibiotics except doxycycline, and the lesions are painful and dangerous with 50% of acute

endocarditis from Staph infection resulting in death, according to some health care professionals who don't necessarily know to prescribe doxycycline or use effective and strong chlorine bleach preparations for institutional cleaning and HibiClens for the hands, nonetheless Staph is particularly painful and causes large lesions that are readily colonized by Strep. Epsom salt baths are highly recommended to treat Staph infection exposure.

The fecal coliform *Bactroides fragiles and Peptostreptococcus,* which may infect the heart, and *Clostridium difficile* which causes serious infectious diarrhea resist any antibiotic but metronidazole (Flagyl ER). To avoid idiopathic malabsortive disorders of the gut and kidneys it is probably more effective to treat *E. coli*, the most common cause of bladder and kidney infections, with metronidazole rather than Bactrim, which monopolizes the monograph for *E. coli* despite a long list of adverse drug reaction and nearly certain vitamin B_{12} deficiency, post-infectious auto-immune diarrhea and kidney disease due to malabsorption and antibiotic resistance of *Clostridium difficile* and the common streptococcus treated by all other antibiotics. Viruses and fungi are rare in the heart and many bacterial diseases are kind to the heart although they devastate other parts of the anatomy. Because Sporanox (itraconazole) is stongly contraindicated for the treatment of congestive heart failure due to interactions with Digitalis and hypertension drugs and fungal infections are not likely to compete with bacterial endocarditis, in the absence of profound immunosuppression with antibiotics. *Candida albicans* is the most common fungal pathogen to arise from antibiotic resistance, $1 hydrocortisone applied topically to the affected area should be effective although an oral anti-Candidal remedy might be purchased over-the-counter. Echovirus is an entero and respiratory infection that also attacks the heart treated with Human Immune Globulin IV (Elvin-Lewis ’77: 178, 28).

Bacterial infections may spread into and through the lymphatics to create acute inflammatory involvements in these channels. The most common etiologic agents are the group A beta-hemolytic streptococci, although any virulent pathogen may be responsible for an **acute lymphangitis**. The affected lymphatics are dilated and filled with exudate, chiefly of neutrophils and histiocytes, that usually extends through the wall into the perilymphatic tissues and may in severe cases produce cellulitis or focal abscesses. The most common cause of lymphatic blockage are (1) spread of malignant tumors with obstruction of either the lymphatic channels or the nodes of drainage, (2) radical surgical procedures with removal of regional groups of lymph nodes, (3) postirradiation fibrosis, (4) filariasis, and (5) postinflammatory thrombosis and scarring of lymphatic channels. Persistence of the edema leads to an increase of subcutaneous interstitial fibrous tissue, with consequent enlargement of the affected part, brawny induration, “peau d’orange” appearance of the skin and skin ulcers. Chylous ascites, chylothorax and chylopericardium are caused by rupture of obstructed, dilated lymphatics into the peritoneum, pleural cavity and pericardium. Almost invariably, this is due to obstruction of lymphatics by an infiltrating tumor mass (Schoen ’94: 506).

Myocarditis is best defined as an inflammatory involvement of the heart muscle characterized by a leukocytic infiltrate and resultant nonischemic necrosis or degeneration of myocytes. Of all patients with the recent onset of unexplained CHF, chest pain, or life-threatening arrhythmias, who have endomyocardial biopsy approximately 4 to 10% are demonstrated to have myocarditis. The causes of myocarditis include many microbiologic agents but most cases of well-documented myocarditis are **viral** in origin. The most frequently implicated agents are Coxsackievirus A and B, ECHO (treated with Human Immune Globulin IV), poliovirus (treated with metronidazole) and certain strains of influenza A and B viruses (treated with Tamiflu). In most instances, the cardiac involvement follows several days to a few weeks after a primary viral

infection elsewhere. Less commonly, myocarditis is cause by a non-viral microbiologic agent or its toxins. A direct cardiac infection is caused by the protozoa *Trypanosoma cruzi* producing **Chaga's disease**, which is uncommon in the northern hemisphere but affects up to one-half of the population in endemic areas of South America, and myocardial involvement is found in approximately 80% of infected individuals. About 10% of patients die during an acute attack, others may enter a chronic immune-mediated phase and develop progressive signs of cardiac insufficiency 10 to 20 years later. Metronidazole (Flagyl ER) seems to be called for. **Trichinosis** is the most common helminthic disease associated with cardiac involvement for which the antiprotozoal properties of metronidazole (Flagyl ER) are indicated. Injury to the myocardium by the potent exotoxin of the bacterium *Corynebacterium diphtheria* is characterized by patchy myocyte necrosis with only a sparse lymphocytic infiltrate. **Lyme disease** is a systemic illness caused by the bacterial spirochete *Borrelia burgdorferi* transmitted by the "deer tick" that has dermatologic, neurologic and rheumatologic manifestations that is effectively treated with any antibiotic. Myocarditis occurs in approximately two-thirds of patients with Lyme disease. Myocarditis occurs in many patients with acquired immunodeficiency syndrome (AIDS). Myocarditis can also be related to allergic reactions (**hypersensitivity**) to a particular drug, including some antibiotics, diuretics, and antihypertensive agents. Cardiac sarcoidosis and rejection of a transplanted heart may also be considered forms of myocarditis. **Giant cell myocarditis** is characterized by a widespread inflammatory cellular infiltrate containing multinucleate giant cells of macrophage origin. If the patient survives the acute phase of myocarditis, the inflammatory lesions heal with or without scarring (Schoen '94: 563, 564). Oral corticosteroids can be very useful for the treatment of myocarditis, particularly that of viral origin for which there is no better treatment short of Human Immune Globulin IV.

Nonsystemic arteritis is most frequently caused by the direct invasion of infectious agents, usually bacteria or fungi particularly aspergillosis and mucormycosis. Vascular lesions frequently accompany bacterial pneumonia, or occur adjacent to caseous tuberculous reactions, in the neighborhood of abscesses, or in the superficial cerebral vessels in cases of meningitis. Much less commonly they arise from the hematogenous spread of bacteria, in cases of septicemia or embolization from infective endocarditis. Vascular infections may weaken the arterial wall and result in the formation of a mycotic aneurysm. In **systemic lupus erythematosus**, mitral and tricuspid valvulitis is occasionally encountered and lead to the development of small, sterile vegetations from 1 to 4 mm in diameter, sterile, granular pink vegetations that may be single or multiple. Lesions are frequently located on the undersurfaces of the atrioventricular valves, but they may be scattered. **Nonbacterial thrombotic endocarditis** (NBTE) is a form of vegetative endocarditis most often encountered in debilitated patients, such as those with cancer or sepsis (Schoen '94: 554, 555) and is probably of fungal origin.

Candida species, which are part of the normal flora of the skin, mouth and GI tract are the ost frequent cause of human fungal infections . Severe disseminated candidiasis is associated with neutropenia secondary to chronic granulomatous disease, leukemia, anticancer therapy or immunosuppression after transplantation. Cadida can be directly introduced into the blood by intravenous lines, catheters, peritoneal dialysis, cardiac surgery or intravenous drug abuse. Although the course of candida sepsis is less rampant than that of bacterial sepsis, disseminated Candida eventually causes shock and disseminated intravascular coagulation. Candida has numerous molecules on its surface that mediate its adherence to host tissues and secretes aspartyl proteinase, which may be involved in tissue degradation and adenosine, which blocks neutrophil

oxygen radical production. Candida infections of the oral cavity (thrush) and vagina produce superficial, white patches or large, almost fluffy membranes that are easily detached, although this may be painful, leaving a reddened, irritated underlying surface. Spread of oral candidiasis, as by the nasogastric tube, may lead to similar lesions in the esophagus. Candida also causes cutaneous eczematoid lesions in moist areas of the skin. Severe invasive candidiasis associated with antibiotic consumption and immunosuppression, or with phagocyte depletion involves the kidney in 90% of cases, causing multiple micro-abscesses in both the cortex and the medulla. The fungus occupies the center of the lesion, with a surrounding area of necrosis and polymorphonuclear infiltrate. **Candida right-sided endocarditis** resulting from direct inoculation of the fungi into the bloodstream, most often in drug addicts, gives rise to large, friable vegetations that frequently break off into emboli. In the lungs lesions are extensive and polymorphoids and often are hemorrhagic and infarct-like owing to fungal invasion of vascular walls. Meningitis, multiple subcutaneous abscesses, arthritis and osteomyelitis are some of the other presentations of disseminated candidiasis. The fungus may evoke little or no inflammatory reaction, cause the usual suppurative response, or occasionally produce granulomas (Samuelson & Von Lichtenberg '94: 354, 355).

Antifungal drugs are available over-the-counter and online without prescription. Athlete's foot cream (clotrimazole), and hydrocortisone crème are quite effective. There are several oral antifungal drugs such as Lamisil and Grifulvin V available for the treatment of athlete's foot and toenail and fingernail onchymycosis but Sporanox (itraconazole) claims to be effective against all major known fungal pathogens, Candida, Aspergillis, Histoplasmosis, Cryptococcus, Mycormycosis and others and is prescribed -, 200 mg 3 times daily for 3 days, then 200 mg twice daily until no longer immune-compromised. The monograph reads; For primary prophylaxis of aspergillosis in immunocompromised individuals at high risk of invasive disease such as neutropenic patients with acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS) or hematopoietic stem cell transplant (HSCT) recipients with graft-versus-host disease (GVHD). IDSA considers posaconazole the drug of choice; alternatives are itraconazole or micafungin. The prophylaxis of invasive Aspergillus and Candida infections in patients, 13 years of age and older, who are at high risk due to being severely immunocompromised, such as hematopoietic stem cell transplant (HSCT) recipients with graft-versus-host disease (GVHD) or those with hematologic malignancies with prolonged neutropenia from chemotherapy and also fororopharyngeal candidiasis. Sporanox is hepatoxic and liver enzymes must be monitored on a monthly basis and is **highly contraindicated in heart failure**. IV amphotericin B is the preferred alternative to oral Sporonox (itraconazole). The effectiveness of oral antifungals is 60-80%. There is still a chance of re-infection after finishing the course of the medication. The re-infection rate is 15% but can be as high as 25% in diabetics. Serious adverse reactions are less than 0.5%. There are some interactions between these medication and other drugs such as cyclosporine, cimetidine, rifampin, terfenadine, and caffeine (Debrowolski ’04: 14-16). Sporanox is strongly contraindicated in cases of congestive heart failure due to adverse reaction with antihypertensive and *Digitalis* drugs.

Primary tumors of the heart are rare but metastatic tumors to the heart occur in about 5% of patients dying from cancer. The most common primary tumors, in descending order of frequency are myxomas, fibromas, lipomas, papillary fibroelastomas, rhabdomyomas, angiosarcomas and other sarcomas. The five most common all are benign and account collectively for 80 to 90% of primary tumors of the heart. **Myxomas** are the most common primary tumor of the heart in adults. About 90% are located in the atria. Surgical removal is usually curative, although rarely the neoplasm recurs months to years later. **Lipomas** are most

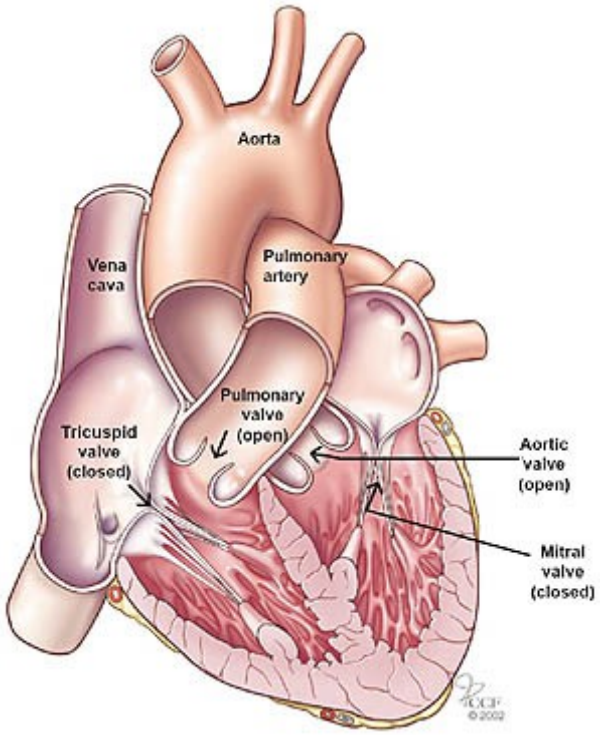
often located in the left ventricle, right atrium or atrial septum and are not necessarily neoplastic. In the atrial septum, the depositions are called "lipomatous hypertrophy". **Papillary fibroelastomas** cluster as hair-like projections up to 1 cm in diameter, covering up to several centimeters of the endocardial surface. **Rhabdomyomas** are the most frequent primary tumor of the heart in infants and children. **Cardiac angiosarcomas** and other sarcomas are not distinctive from their counterparts in other locations. Occasionally cardiac complications represent the dominant feature of the presentation of a noncardiac malignant tumor. Chemotherapy and radiation also manifest their own district cardiovascular side effects and toxicities (Schoen '94; 569-571). In patients with carcinoid tumors, cardiac involvement, is one of the **sequelae of the carcinoid syndrome**. The syndrome is characterized by distinctive episodic flushing of the skin and cramps, nausea, vomiting and diarrhea in almost all patients; bronchoconstrictive episodes resembling asthma in about one-third of patients, and cardiac lesions in about one-half. The carcinoid syndrome is encountered in about 1% of patients who have carcinoid tumors (argentaffinomas) whatever the primary site and in 10% of those with gastrointestinal carcinoid tumors with hepatic metastasis (Schoen '94: 555).

Bone pain, known either as **rheumatoid arthritis**, or myeloma, is an extremely common serious complication of endocarditis, because it is crippling and this comprimises cardiorespiratory exercise, and retreating or untreated infections can metastasize through the bloodstream or break through the bone to marrow causing leukemia or through soft tissue to the lymphatic system, causing lymphomas. Bone pain is the primary physical symptom of leukemia and very common in lymphoma. Oral Thalidomide, used in conjunction with dexamethsaome, a corticosteroid, are the first FDA approved chemotherapeutic drugs usually taken by people diagnosed with multiple myeloma and plasma cell dyscracias. Initial necrosis is usually caused by exposure to toxic chemicals, such as benzene, or physical trauma to the bone. Untreated with basic antibiotics and antifungals, the necrotic tissue becomes septic and doesn't heal and the diseases progresses and becomes worse, and the mycotic infection of the necrotic tissue breaks through the bone and induces mutations distorting the peripheral complete blood count and white blood cell differential, although there is no more exposure to the toxic substance.

III.B.4 Valvulitis

Disorders characterized by valvular involvement and dysfunction include calcific aortic valve stenosis, calcification of the mitral annulus, mitral valve prolapse, rheumatic heart disease, three forms of vegetative endocarditis (including infective endocarditis, nonbacterial thrombotic endocarditis and endocarditis of systemic lupus erythematosus and carcinoid heart disease. Endocarditis usually involves the heart valves. Major predisposing factors are congenital heart defects, rheumatic valvular disease, bicuspid or calcific aortic valves, mitral valve prolapse, and hypertrophic cardiomyopathy. Prosthetic valves are a particular risk. Occasionally, mural thrombi, ventricular-septal defects, and patent ductus arteriosus sites become infected. The actual nidus for infection is usually a sterile fibrin-platelet vegetation formed when damaged endothelial cells release tissue factor. Infective endocarditis occurs most often on the left side (eg, mitral or aortic valve). About 10 to 20% of cases are right-sided (tricuspid or pulmonic valve). IV drug abusers have a much higher incidence of right-sided endocarditis (about 30 to 70%).

Pulmonary, Tricuspid, Aortic and Mitral Valves



Credit: Cleveland Clinic

Functional disturbances of the valves are stenosis and insufficiency. **Stenosis** is the failure of a valve to open completely, thereby impeding forward flow. Insufficiency or regurgitation in contrast, results from failure of a valve to close completely, thereby allowing reversed flow. Abnormalities of flow often produce abnormal heart sounds (murmurs). Valvular dysfunction can vary in degree from slight and physiologically unimportant to severe and rapidly fatal. Sudden destruction of an aortic valve cusp by infection may cause rapidly fatal cardiac failure owing to massive regurgitation. Mitral stenosis is however remarkably well tolerated. **Valvular insufficiency** may result from either intrinsic disease of the valve cusps or damage to the supporting structures (e.g. the aorta, mitral annulus, chordae tendineae, papillary muscles, ventricular free wall) without primary changes in the cusps. Valvular stenosis almost always is due to a primary cuspal abnormality and is virtually always a chronic process. (Schoen ’94: 543). Audible events generated by the heart are classified as sounds if they are abrupt and murmurs if they consist of prolonged vibrations. Sounds result from an abrupt interruption of the momentum of local blood flow, whereas murmu**rs** occur when there is disturbved or turbulent high-velocity flow. If the distal mitral valve sleeve has been converted to a funnel and fails to open, resulting in an opening snap that is transmitted back toward the source of the moving column of blood. The opening snap is heard at the base (close to the left atrium), whereas the murmurs caused by disturbed inflow are heard only at the apex (Heger et al '04: 181).

Aortic valve incompetence can result from a number of pathologic processes that affect the valve leaflets and/or the aortic root. Congenital bicuspid valve deformity, with or without superimposed endocarditis, is the leading cause of aortic regurgitation in individuals younger than 30, whereas aortic root dilation from hypertension often causes valves to fail to coapt in older individuals. Rheumatic fever, Marfan disease, rheumatoid arthritis, aortitis, trauma and aortic dissection are additional etiologies. The primary pathophysiological finding is **backflow**

into the left ventricle, which leads to arterial diastolic collapse, lowering of the arterial diastolic pressure, and a decrescendo early diastolic murmur. Two secondary outcomes are an increase in the systolic stroke volume and turbulent mitral valve inflow. Increased stroke volume and outflow velocity are accompanied by a misystolic murmur emulating that aortic stenosis. Turubulent mitral inflow causes middiastolic and presystolic murmurs (Austin Flint murmur) that emulates mitral stenosis in patients with severe aortic regurgitation. Prominent sounds can be heard as well. The second sound may be tambour (like a kettle drum) if the aorta is dilated. The first sound may be perceived as "split" because of the loud ejection sound. The findings in aortic regurgitation can be quite different if the condition is acute rather than chronic. Aortic regurgitation is usually well tolerated for many years because of compensatory mechanisms that can counterbalance the impact of the leaky ventricle (Heger '04: 182-184).

Aortic stenosis is the most frequent valve abnormality; it can be congenital or acquired. The definition of congenital aortic stenosis excludes congenital bicuspid and the rare uni-cuspid valves that do not cause functional stenosis at birth but have enhanced susceptibility to superimposed damage that later can cause stenosis. Acquired aortic stenosis is usually the consequence of calcification induced by the “wear and tear” of aging. With the decline in the incidence of rheumatic fever, rheumatic aortic stenosis now accounts for less than 10% of cases of acquired aortic stenosis. Therefore the overwhelming majority of cases represent age-related degenerative calcification and come to clinical attention primarily in the sixth to seventh decades of life with pre-existing bicuspid valves but not until the eighth and ninth decades with previously normal valves (Schoen ’94: 544). In approximately 1 to 2% of the population, the aortic valve is **congenitally bicuspid**. Bicuspid aortic valves are generally neither stenotic nor symptomatic at birth or throughout early life, but they are predisposed to progressive calcification. Incomplete commissures are frequently a major site of calcific deposits. With or without calcification, bicuspid aortic valves may also become incompetent or be complicated by infective endocarditis. As the stenosis worsens, angina or syncope, and risk of sudden death, may appear. The myocardial oxygen supply/demand balance is difficult to maintain when the ventricle must create more than 200 mg Hg pressure to deliver 100 mm Hg to the aorta, coronary perfusion is compromised when the ratio of capillaries to the myocardial mass is reduced by ventricular hypertrophy and passage of capillary blood through the myofibers is obstructed by the prolonged systolic compressions (Heger et al '04: 189). The onset of symptoms such as angina, syncope of congestive heart failure, in aortic stenosis carries a poor prognosis if not treated by surgery (death in more than 50% within 3 years). There is no effective medical therapy for for aortic stenosis. Congestive failure can be treated with digoxin. Patients with aortic stenosis are often drastically improved by surgical aortic valve repair or replacement. Doppler echocardiography, which measures the flow velocities a well as structure, can be used repetitively to examine the progression of disease with time (Schoen ’94: 545).

Aortic valve replacement is required when the left ventricle is not tolerating the volume overload or that the systolic function of the left ventricle is declining. When endocarditis destroys the valve's ability to close competently, urgent surgery is required. The surgeon may be able to debride the infected tissue, including perivalvar abscesses and affect a bacteriologic cure more effectively than with antibiotics alone. The choice of prosthetic valve should take into account the patient's age, life expectancy and ability to maintain and tolerate life-long anticoagulation. **Tissue valves**, fashioned from porcine aortic valves or bovine pericardium, permit freedom from anticoagulation, have a functional longevity of approximately 10 years and should be used for women who may consider future pregnancies. Although modern **mechanical valves** are unlikely to undergo component failure and should last indefinitely in the absence of

infection, thrombosis or fibrous growth they require frequent assessment of prothrombin time and maintenance of therapeutic anticoagulation. Homograft cryopreserved (freeze-dried) aortic valves from human cadavers do not enjoy superior durability over xenograft (animal) tissue valves. The **Ross procedure** in which the patient donates his or her own pulmonic valve to the aortic position and has the explanted pulmonic valve replaced with a homograft, requires considerably more surgical complexity but in the hands of experience surgeons shows promise of durability as well as growth of the living tissue valve. **Valvuloplasty**, or valve repair without replacement, is only applicable to a small percentage of cases (Heger '04: 187, 188).

In elderly people, especially women, degenerative calcific deposits can develop in the ring of the mitral valve. They can often be visualized as irregular, stony hard nodules (2 to 5 mm in thickness) that lie behind the leaflets. Rheumatic fever causes retraction of the leaflets and dilation of the mitral annulus. **Rheumatic mitral regurgitation** is three times more common in men than women. However in the United States rheumatic fever is overlooked as a cause of mitral valve prolapse, endocarditis, hypertension, ischemic disease and cardiomyopathy are more common. Mitral valve stenosis almost always results from rheumatic fever (Heger et al '04: 191, 192, 197). The process generally does not affect valvular function. Occasionally the calcium deposits may penetrate sufficiently deeply to impinge on the atrioventricular conduction system and produce arrhythmias (and occasionally sudden death). Because calcific nodules may provide a site for thrombi that can embolize, patients with mitral annular calcification have an increased risk of stroke. The calcific nodules can also be the nidus for infective endocarditis. Heavy calcific deposits are sometimes visualized on echocardiography or seen as a distinctive, ring-like opacity on chest radiographs.

Mitral valve prolapse (myxomatous degeneration of the mitral valve) is a valvular abnormality, where one or both mitral leaflets are enlarged, redundant, or “floppy” and prolapse, or balloon back, into the left atrium during systole. The mitral valve often becomes incompetent, and the mitral regurgitation induces an accompanying late systolic or sometimes holosystolic murmur. This is an extremely common condition, thought to be present in about 5 to 10% of the population of the United States, most often young women, but is of serious import to only a small fraction of those affected. Mitral valve prolapse is a common feature of Marfan syndrome and occasionally occurs with other hereditary disorders of connective tissues. Most patients with mitral valve prolapse are asymptomatic, and the condition is discovered only on routine examination by the presence of a midsystolic click. Echocardiography reveals mitral valve prolapse. Although the great majority of patients with mitral valve prolapse have no untoward effects, approximately 3% develop one of four serious complications (1) infective endocarditis is manifold more frequent in these patients than in the general population, (2) mitral insufficiency, from either slow onset attributed to cuspal deformity, dilatation of the mitral annulus or chordal lengthening, or sudden death owing to chordal rupture, (3) stroke or other systemic infarct resulting from embolism of leaflet thrombi and (4) arrhythmias, both ventricular and atrial can develop, although sudden death is uncommon (Schoen ’94: 547). Significant mitral stenosis is associated with pulmonary hypertension and inability of the right ventricle to overcome downstream resistance prevents an increase in flow that might magnify further left atrial pressure in reactive pulmonary hypertension (Heger et a '04: 201).

Treatment of mitral valve prolapse with beta-adrenergic blocking agents often ameliorate symptoms and **antibiotic prophylaxis** should be used. Transient acute mitral regurgitation can sometimes be reversed within five minutes by sublingual nitrate administration. Digoxin and treatment of hypertension with arterial dilators or ACE inhibitors may be used chronically or to

prepare patients for valve surgery. Lessening the symptoms of mitral stenosis can be achieved medically by preventing heart rate increases or treating existing sinus tachycardias or rapid response to atrial fibrillation with beta-adrenergic blocking agents. Beta blockers may be given in the presence of pulmonary edema if the heart rate is elevate and can bring rapid relief by allowing the left atrium time to decompress. Arterial dilator drugs should be discouraged because they might cause reflex tachycardia and increased flow rate through the stenotic valve. Unless there is a strong contraindication, anticoagulation with warfarin (Coumadin) is recommended in patients with mitral stenosis, especially if intermittent or chronic atrial fibrillation is present. (Heger et al '04: 202).

Significant mitral stenosis should be relieved by mechanical means, either catheter-based ballon or direct surgical commissurotomy. Heavily calcified or immobile valves require replacement. A good-quality transthoracic echocardiogram combined with Doppler interrogation can provide data regarding the functional anatomy of the valve, the degree of stenosis and the presence of mural thrombus. **Transesophageal echocardiography** is a prerequisite for performance of either commissurotomy procedure because of the enhanced ability to screen the atrium for thrombus and the better images of the valve leaflets. **Valve repair**, rather than replacement, is often possible when mitral regurgitation warrants operative intervention because of progressive left atrial and ventricular enlargement. When the atrium achieves a diameter of more than 5 cm, (by echocardiographic measurement) the onset of atrial fibrillation is almost invariably predictable, if not already present. The leaflets are usually sufficiently redundant to tolerate resection of one-fourth of the leaflet area combined with reinforcement of the annulus (annuloplasty) to render the valve competent (Heger et al '04: 202, 203).

Replacement of damaged cardiac valves with prostheses has become a common and often lifesaving mode of therapy. **Tissue valves**, fashioned from porcine aortic valves or bovine pericardium, permit freedom from anticoagulation, have a functional longevity of approximately 10 years and should be used for women who may consider future pregnancies. Although modern mechanical valves are unlikely to undergo component failure and should last indefinitely in the absence of infection, thrombosis or fibrous growth they require frequent assessment of prothrombin time and maintenance of therapeutic anticoagulation. Homograft cryopreserved (freeze-dried) aortic valves from human cadavers do not enjoy superior durability over xenograft (animal) tissue valves. **Artificial valves** fall primarily into two categories – mechanical prostheses using different types of occluders, such as caged balls, tilting disks, or hinged flaps and tissue valves usually bio-prostheses consisting of chemically treated animal tissue, especially porcine aortic valve tissue, which has been preserved in a dilute glutaraldehyde solution and subsequently mounted on a prosthetic frame (called a “stent”). Mechanical valves are composed of nonphysiologic biomaterials that employ one to two rigid mobile poppet occlude(s), whereas tissue valves are flexible, trileaflet valves that function somewhat like natural valves. Approximately 60% of substitute valve recipients have a serious prosthesis-related problem within 10 years postoperatively (Schoen ’94: 556).

The most frequent valve-related complications include (1) thromboembolism (local occlusion of the prosthesis by thrombus or distant thromboemboli), (2) partial dehiscence (separation) of the suture line anchoring the valve leading to a paravalvular leak, (3) infective endocarditis, (4) durability problems caused by structural deterioration, and (5) intrinsic (design-related) obstruction to forward flow. Thromboembolic complications constitute the major problem with mechanical valves. This necessitates long-term anticoagulation. Hemorrhagic side-effects, such as stroke or gastrointestinal bleeding, may arise. Infective endocarditis is an infrequent but

serious potential complication developing in about 6% of patients within 5 years of valve replacement. Bioprosthetic valves may develop vegetations that directly involve the prosthetic valvular cusps and can embolize. The major contaminating organisms are staphylococcal skin contaminants (e.g. *S. aureus, S. epidermidis*) early (less than 1 month) postoperatively and streptococci later. Within 10 years postoperatively, at least 30% of tissue valves require replacement for calcification, often with tearing. Other complications, such as hemolysis induced by high blood shear, mechanical obstruction to flow and dysfunction due to ingrowth of fibrous tissue, may be serious (Schoen '94: 557).

III.B.5 Arrhythmia

Sudden cardiac arrest is the condition in which a patient collapses suddenly due to a heart rhythm abnormality. A blockage in the left anterior descending artery is called "the widowmaker". Sudden coronary death frequently involves a rapidly progressing coronary lesion, in which plaque disruption and often partial thrombus (and possibly embolization) lead to regional myocardial ischemia that induce a **fatal ventricular arrhythmia** (Schoen '94: 528). Sudden cardiac arrest victims have a 93 percent fatality rate. In the United States, sudden cardiac arrest takes a life every two minutes, nearly 1,000 individuals each day. The event is most often associated with rapid rhythms from the lower chamber, called ventricular tachycardia or ventricular fibrillation. The heart rhythm problems that cause sudden cardiac arrest most often affect people who have heart disease (an abnormal heart) caused by a heart attack, blockages of the coronary arteries, a weak heart muscle, thick heart muscles or other problems. Reversible causes of sudden cardiac arrest are neutralizing toxic drugs, correct electrolyte abnormalities, and remove blockage (stent) or bypass blockade (surgery). Someone in the household should be trained in cardiopulmonary resuscitation (CPR) (Cohen '10: 49, 45, 47).

By counting the number of pulsations over a fifteen-second interval and multiplying that number by four, you can calculate the heart rate (in beats per minute). A **normal heart rate** is between 60 and 100 beats per minute. A slower than normal rhythm in which the heart rate is below 60 beats per minute indicates sinus bradycardia. If the rhythm exceeds 100 beats per minute, a sinus tachycardia would be present. Heart rates slower than 60 beats per minute can be normal if there are no symptoms such as fatigue, shortness of breath, light-headedness or dizziness. Rapid heart rates (greater than 100 beats per minute) may be normal or abnormal, depending on circumstances. Conditions that weaken the heart muscle may cause rapid heart rhythms, called **tachycardias**, with rates greater than 100 beats per minute and possibly much faster. The faster the heart rate, the great the chance that delivery of oxygen and other nutrients to the brain and other organs will be impaired. With very fast beats (over 200 a minute) the person will likely become light-headed and dizzy and even pass out.

An irregular heart rate might indicate early beats, called premature contractions (coming from either the atria or the ventricles) or may be an indicator of a rhythm problem called **atrial fibrillation**, in which the atria beats at rates greater than 400 beats per minute. The heart may also beat too slowly (called **bradycardia**) with heart rates below 60 beat per minute. Reversible causes of bradycardia are nonessential medicines such as beta blockers, calcium channel blockers, digitalis, antiarrhythmic drugs such as sotalol and amiodarone, Lyme disease, hypothyroidism, electrolyte abnormality and drug toxicity. **Sinus bradycardia** is commonly caused by second-degree heart block, Mobitz type I (block typically occurs in the AV node), second-degree heart block, Mobitz type II (block typically occurs in the His bundle or below), third-degree heart block or complete heart block, Asystole (Cohen '10: 12, 61, 13, 22, 23, 14).

Several forms of **inherited arrhythmic diseases** have common associated gene subtypes (1) Arrhythmogenic right ventricular dysplasia (fat deposits in right ventricular wall) exhibit gene subtypes PKP2, DSP, GSG2, (2) Hypertrophic cardiomyopathy (thickened heart muscle exhibiting gene subtypes MYH7, MYBPC3, (3) Long QT syndrome (has specific ECG patterns) exhibit gene subtypes KCNQ1 (long QT1); KCNH2 (long QT2); SCN5A (long QT3) and (4) Brugada syndrome (has specific ECG pattern) exhibits gene subtypes SCN5A (Cohen '10: 143).

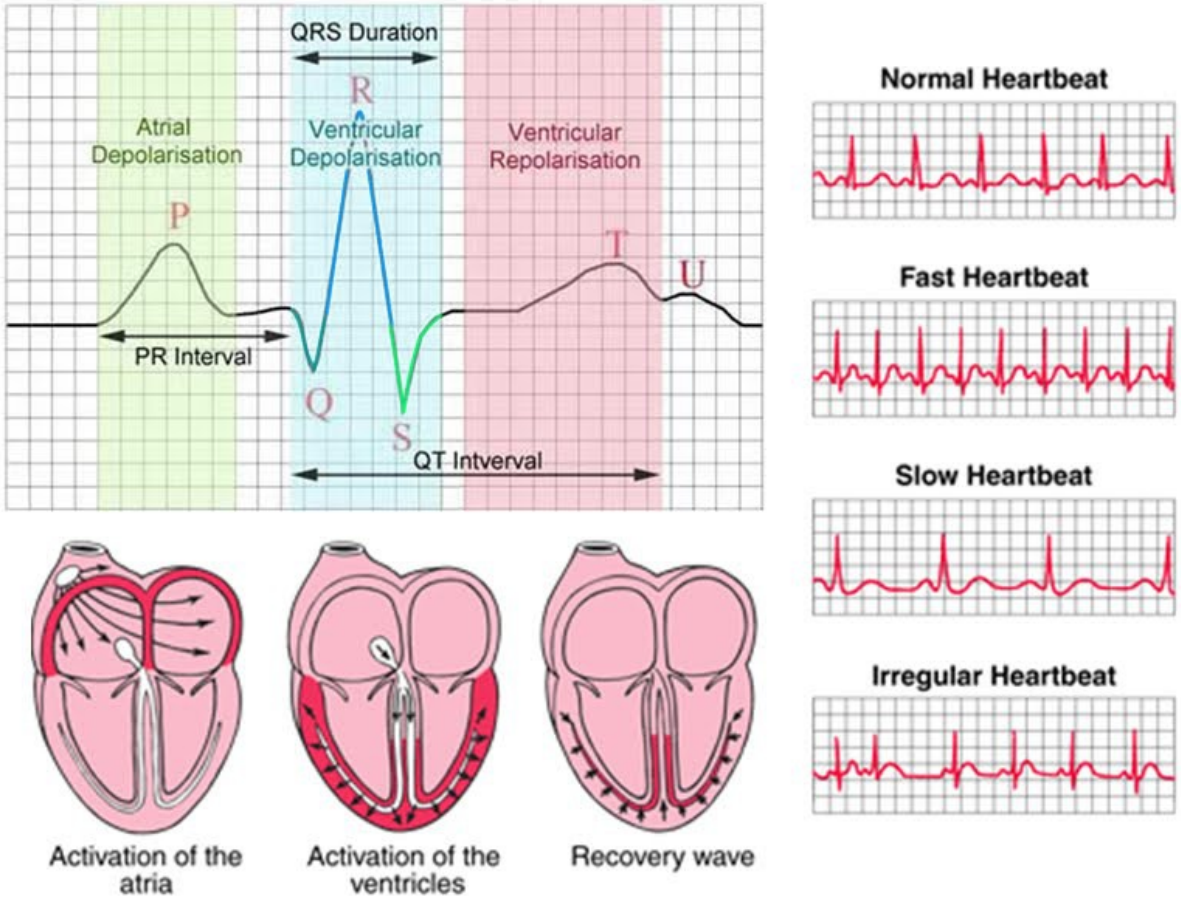
The U.S. Food and Drug Administration is proposing new rules aimed at improving the reliability of emergency defibrillators following some 45,000 reports of device failures over seven years. The defibrillators, found in hundreds of airports, shopping malls and restaurants across the country, are designed to jump-start the heart after it has suddenly stopped. When the heart rhythm is too rapid and chaotic (as it is with ventricular fibrillation) and time is of the essence (as with unstable ventricular tachycardia) defibrillation is performed. Paddles are placed directly on the chest may be used as well as patches or pads to deliver electrical energy from the defibrillator to the chest. Electrical cardioversion and defibrillation are useful for breaking fast rhythms and terminate atrial fibrillation, atrial flutter, ventricular fibrillation, ventricular flutter and any rapid rhythm that does not respond to standard drugs and is not stable, such as when the patient is semiconscious or unconscious or has a low blood pressure (Cohen '10: 87, 89, 91).

Blood flow through the heart chamber should be smooth and rhythmic. The **electrical system** (which is also called the conduction system) tells the heart (and its chambers) when and in what sequence it should contract and relax to pump blood to the rest of the body. The electrical impulses begin high up in the right atrium, in a structure called the sinus, or **sinoatrial node** (SA node). A node is defined as a beginning structure or a point for electrical signals to come together and then be redirected to another region in the heart. There are two nodes in the heart: the SA node and the **atrial ventricular node** (AV node). Impulses move from the SA node across the atrial structures to the AV node (located in the middle of the heart, between the atria and ventricles). A small delay in the electrical signal typically occurs in the AV node before the impulse travels to the **His bundle** it then moves down through the right and left bundles to **specialized Purkinje fibers** before activating the ventricles. The presence of disease in any of the specialized electrical conducting tissues may disrupt the flow of electricity through the heart, slowing or pausing the heart rate.

A single electrocardiogram (ECG) recording of a heartbeat shows the electrical sequence of the heart. The electrical signal may be broken into different waves. The P wave represents atrial electrical activity; the QRS complex represents ventricular electrical activity; and the QT interval (from the beginning of the Q wave to the end of the T wave) represents the ventricles returning to a resting state. Sometimes a test is performed through the esophagus (called a **transesophageal echocardiogram**) where it is particularly useful in looking for the presence of blood clots in the left atrium. Blood clots may form in the left atrial appendage (a site that is not well visualized by standard echocardiogram) (Cohen ’10: 60, 68). An electrocardiogram, or ECG, is an electrical recording from the limbs and the surface of the chest that shows the pattern of electrical activity in the heart. The ECG can detect rhythm disturbances such as atrial fibrillation, may detect the presence of an old myocardial infarction, and in some circumstances, particularly when repeated daily for several days, can detect a recent heart attack (myocardial infarction). The accuracy of this diagnosis by ECG is greatly aided by measuring enzymes or other markers from the heart released into the bloodstream when the heart muscle breaks down, such as CK (creatine phosphokinase) and troponin. An electrocardiogram requires sticking

electrodes to the limbs and the chest, and then making a recording. It is completely safe and painless (except for the pulling of chest hair when the electrodes are removed) (Spence '06: 43).

Electrocardiogram (ECG) Reading



Credit: IVLine May 2010

Atrial fibrillation is a very common heart rhythm problem. It is known as an "irregular rhythm". The chance of developing atrial fibrillation increases with age. According to recent statistics from the American Heart Association, atrial fibrillation may be found in 3 to 5 percent of people over the age of 65. Atrial fibrillation begets atrial fibrillation (i.e. the longer you are in atrial fibrillation the longer you stay in atrial fibrillation). Early treatment may help to slow down the progression to persistent atrial fibrillation. Blood thinners (anticoagulants) are recommended in patients with congestive heart failure, hypertension, age greater than 75 years, diabetes, or history of stroke. First-line treatment is medication, including antiarrhythmic drugs. If antiarrhythmic drug therapy fails, catheter ablation should be considered. Inciting causes should also be treated; excess alcohol consumption, ischemia, hypertension, stimulant use, and thyroid disorders. **Atrial flutter** is more organized that atrial fibrillation. Atrial flutter should be treated like atrial fibrillation with respect to medications, including blood thinners (anticoagulants). Atrial flutter is much easier to cure with catheter ablation than atrial fibrillation. **Catheter ablation** can be considered a first-line therapy for symptomatic atrial flutter. Catheter ablation success rates for the typical forms of atrial flutter are higher than those achieved with atrial fibrillation. A long thin medical device called an ablation catheter is inserted by hand through a blood vessel and then is guided into the heart using x-ray or mapping

equipment to find and treat abnormal rhythms. The success rate of catheter ablation is 90 percent or greater for superventricular tachycardia, such as atrial flutter, atrial tachycardia, AV node, AV node reentrant tachycardia, Wolff-Parkinson-White syndrome, 50 to 85 percent for atrial fibrillation, 50 to 75 percent for ventricular tachycardia from coronary artery disease and 90 percent or greater for focal ventricular tachycardia (Cohen '10: 35, 39, 87, 89).

Loss of consciousness, passing out or fainting, is called **syncope**. Fainting is one of the most common reasons people are brought to the emergency room or admitted to the hospital. Common causes of syncope are neurocardiogenic syncope or vasovagal syncope, dehydration, heart rhythm problems, valve problems (aortic stenosis or mitral stenosis), seizure disorder or stroke. Syncope is one of the most common reasons a person visit the emergency room. Syncope from heart problems is often more serious (there is a higher chance of dying) than syncope from non-heart related problems if the heart problems are not successfully treated. Heart-related syncope is often readily treatable. A **tilt table test** can be used to assess syncope, especially if the history, physical exam, and ECG fail to elucidate any significant cardiac findings. An electrophysiology study (**invasive heart rhythm test**) is useful, especially when heart rhythm-related abnormalities are discovered in the history, physical exam, or ECG. External or implantable cardiac monitors are often helpful in finding a heart rhythm problem related to syncope. Extensive neurological evaluations may not be necessary and should not be routine for each syncope episode, but they may be performed on a case-by-case basis (Cohen '10: 55).

Age and disease can lead to problems such as the heart pumping too fast or too slow - and it can even stop completely, in what is known as a cardiac arrest. The **electrophysiology study** (EP study) is a crucial procedure for identifying heart rhythm problems. During the EP study catheters are guided through blood vessels into the heart using an x-ray technique called fluoroscopy imaging. The catheters are placed through the veins, arteries, or both up into the chambers of the heart. The doctor is able to pace (stimulate) the heart at a faster rate than normal and take readings of the signals. Electrical signals are recorded directly from the heart. This test can reveal if a pacemaker or a defibrillator is needed. **Ejection fraction** (EF) measures the percentage of blood that is ejected from the heart. The EF can be calculated through various tests by determining the difference between the volume of blood in the left ventricle at the end of a full relaxation. If EF is less than 35 percent, an implantable cardioverter defibrillator, may be indicated. If the EF is greater than 50 percent, it is less likely an implantable defibrillator would be needed. An exception is **hypertrophic cardiomyopathy**, a condition in which the heart muscle is thickened and its contraction is very strong (hyperdynamic). The EF in this condition may be greater than 70 percent but there is a heightened risk for sudden death from **ventricular arrhythmias**, especially if the heart muscle is very thick or there is a family history of sudden death, ventricular tachycardia, or syncope (sudden loss of consciousness). The cardiac MRI is particularly useful at looking for an inherited condition called **arrhythmogenic right ventricular dysplasia** (in which fat deposits are seen within the wall of the right ventricle) who should be considered candidates for implantable cardioverter defibrillator (ICD) (Cohen '10: 71-72). **T-wave alternans** (TWA) is a test that can be performed in a doctors office. The patient is attached by electrodes to computerized equipment and undergo a stress test. An intravenous line is inserted and continuous ECG monitoring is performed. The computer analyzes the heart rhythm for a scientific phenomenon called microvolt T-wave alternans (TWA). TWA helps to determine the risk for **ventricular tachycardia**. It is not useful if the patient is in atrial fibrillation (Cohen '10: 78, 77).

The solution for dysrhythmia is often an implanted battery-powered pacemaker which will jolt the heart to keep it in line. An **implantable cardioverter defibrillator** (ICD) is connected to at least one wire, which is typically inserted through a blood vessel into the heart. A doctor may prescribe an ICD if there might be a high risk for sudden cardiac death without one. An ICD helps to treat lethal arrhythmias such as ventricular tachycardia and ventricular fibrillation (Cohen '10: 16, 28). When the heart rate is too slow, a person may develop symptoms and may need to have a **pacemaker** surgically implanted to correct the problem. Disease inside or outside the specialized cardiac conduction tissue can also result in fast heart rhythm problems that might require treatment with medications, catheter ablation (a procedure that identifies the heart rhythm abnormality and destroys specific tissue to cure the rhythm problem) or an implantable device such as a defibrillator (Cohen '10). A **pacemaker pulse generator** is used to treat slow heart rhythms. One, two or three leads may be attached to the device depending on the number of heart chambers that are required to receive pacing therapy. **ICDs** were developed in the early 1980s and are very similar to pacemakers. ICDs help regulate both fast rhythms (tachycardias) and slow rhythms (bradycardias). Simply put, ICDs monitor the heart rate, and if it is greater than a predetermined (or programmed) value, the ICD may deliver therapy to treat the arrhythmia. Ventricular tachycardia or ventricular fibrillation may be treated by the delivery of a shock (defibrillation) or rapid pacing (also called antitachycardia pacing). This ability to deliver a shock to the heart to terminate tachycardias is one important difference between and ICD and a simple pacemaker. **Implantable cardiac monitors** are useful in identifying very rare or infrequent abnormal cardiac rhythms that may result in light-headedness, dizziness, or loss of consciousness. The term **pacemaker dependent** is used when a patient is completely dependent on the pacing function from the device and has little or no underlying heart rhythm. (Cohen '10: 106, 109, 117, 126). In 2012 a team of researchers at the Cedars-Sinai Heart Institute tried to restore the heart's own ability to dictate the beat by creating new pacemaker cells. They used a virus to infect heart muscle cells with a gene, called Tbx18, which is normally active when pacemaker cells are formed during normal development in an embryo. When heart cells were infected with the virus they became smaller, thin and tapered as they acquired the "distinctive features of **pacemaker cells**. When the virus was injected into a region of the hearts of seven guinea pigs, five later had heartbeats which originated from their new pacemaker. More animal testing would be needed before the technique would ever be considered in people (Gallagher '12).

Common heart rhythm (antiarrhythmic) medication and their effects

Medicine	Effects	Comments
Beta-blocker	PO Slows pulse (treats SVT, and atrial fibrillation or flutter) lowers blood pressure, helps treat heart failure and coronary artery disease.	Avoid in patients with asthma; can cause impotence, depression, bradycardia and congestive heart failure
Calcium channel blocker	PO Slows pulse (treats SVT and atrial fibrillation or flutter); lowers blood pressure	Not as good as a beta-blocker with coronary artery disease
Adenosine	IV for atrioventriuclar nodal reentrant supraventricular arrhythmia.	Commonly causes brief ventricular escape rhythms
Amiodarone	IV Best drug treatment for ventricular tachycardia and atrial fibrillation or flutter	Many potential side effects; can affect thyroid, liver, lungs; requires follow up every three months; ventricular

		tachycardia (proarrhythmia) is a rare complication
Diltiazem	IV for urgent ventricular rate control	
Dofetilide	Can treat atrial fibrillation or flutter	Can bring on or worsen ventricular tachycardia (proarrhythmia)
Dronedarone	Can treat atrial fibrillation or flutter	Amiodarone-like drug with fewer side effects
Flecainide	Can treat SVT and atrial fibrillation	Can bring on ventricular tachycardia (proarrhythmia)
Mexiletine	Even less effective than sotalol for ventricular tachycardia	Does not worsen ventricular tachycardia; can cause confusion, dizziness, numbness and tingling
Procainamide	IV Sustained ventricular tachycardia	Hypotension may occur with IV loading
Propafenone	PO Can treat SVT and atrial fibrillation	Can bring on ventricular tachycardia (proarrhythmia)
Sotalol	PO Less effective than amiodarone for ventricular tachycardia and atrial fibrillation or flutter	Can bring on or worsen ventricular tachycardia (proarrhythmia)
Verapimil	IV or PO for atrial fibrillation or flutter or atrioventricular nodal reentrant supraventricular	Hypotension resulting from vasodilation; consider pretreatment with calcium

Source: Table 25.1 Cohen ’10: 95; Table 18.2 Heger, Nieman & Criley '04: 271

To perform **chemical cardioversion** the doctor may use medications known as antiarrhythmic drugs to help convert certain arrhythmias (such as atrial fibrillation and atrial flutter) into normal rhythms (Cohen ’10: 87, 89, 91, 92, 94). Anti-arrhythmia drugs have a number of adverse cardiac side-effects. Beta-blockers seem to be the most highly recommended for slowing the ventricular response rate in atrial fibrillation, converting reentrant supraventricular tachyarrhythmias, and suppressing ventricular arrhythmias, but chronic treatment with propranolol, metoprolol or timolol following myocardial infarction decreases 1 year mortality, but bradychardia and congestive heart failure, could result from decompensation. Drugs that slow the upstroke, such as quinidine, procainamide, diopyramide, lidocaine, mexiletine, tocainide, moricizine, propafenone and flecainide, have been found worsen outcomes when compared to no treatment in patients with ventricular arrhythmias at risk for sudden coronary death (Heger et al '04: 269-270). In general cardiac drugs are the second leading cause of fatal drug overdose and antiarrhythmia drugs are no exception (Bronstein '11). Hawthorne (*Crataegus laevigata*) is outstanding both to prevent heart problems and to treat high or low blood pressure, heart disease, edema, angina and heart arrhythmia. Hawthorne doesn’t store in the body and isn’t accumulative in action. Unlike prescription antiarrhythmia medicine Hawthorne does not have any adverse cardiac effects called decompensation in congestive heart failure, for instance when the treatment for tachycardia causes brachycardia, that is why Hawthorne is called the "supreme herb for the heart". It’s important to take Hawthorne on a regular basis if using as a heart tonic (Glastar '12).

III.B.6 Congestive Heart Failure

Heart failure is defined as the pathophysiologic condition in which the heart is unable to generate an adequate cardiac output such that there is inadequate perfusion of tissues or increased diastolic filing pressure of the left ventricle, or both, so that pulmonary capillary pressures are increased. It is estimated that nearly 10% of Americans older than age 65 have symptomatic heart failure and approximately 20% of asymptomatic individuals older than age 40 have some evidence of myocardial dysfunction. Ischemic heart disease and hypertension are the most important predisposing factors. Other risk factors include age, obesity, diabetes, renal failure, vascular heart disease, cardiomyopathies, myocarditis, congenital heart disease, and excessive alcohol use. Genes have been discovered for cardomyopathies, myocyte contractility and neurohumoral receptors. Most causes of heart failure result in dysfunction of the left ventricle (systolic and diastolic heart failure). The right ventricle also may be dysfunctional, especially in pulmonary disease (right ventricular failure). Left heart failure, commonly called congestive heart failure is categorized as heart failure with reduced ejection fraction (systolic heart failure) or heart failure with preserved ejection fraction (diastolic heart failure). These two types of heart failure can occur together or singly. Heart failure with reduced ejection (systolic heart failure) is defined as an ejection fraction of <40% and an inability of the heart to generate an adequate cardiac output to perfuse vital tissues. Some conditions cause inadequate perfusion despite normal or elevated cardiac output (high-output failure). Nearly 75% of heart failure cases have an antecedent in hypertension (McCance '14: 1175).

Cardiac output is the volume of blood flowing through either the systemic or the pulmonary circuit and is expressed in liters per minute. Cardiac output is calculated by multiplying heart rate in bats per minute by stroke volume in liters per beat. Normal adult cardiac output at rest is about 5L/mi. The ventricles do not eject all of the blood they contain with each heartbeat and the amount ejected is called the **ejection fraction**. The ejection fraction is calculated by dividing the stroke volume by the end-diastolic volume. The end-diastolic volume (EDV) of the normal ventricle is about 70 to 80 ml/m^2 and the normal ejection fraction of the resting heart is 55% or higher. Four factors affect cardiac output directly: preload, afterload, myocardial contractility and heart rate. Preload pressure generated at the end of diastole and afterload resistance to ejection during systole, depend on the heart as well as the vascular system. Contractility and heart rate are characteristic of the cardiac tissue per se and are influenced by neural and humoral mechanisms, understood by Frank-Starling and Laplace laws of the heart. According to the Frank-Starling law, the longer the initial resting length of the cardiac muscle fiber (optimal length is between 2.2 and 2.4 mm), the greater the strength of contraction. At 2.2 mm an optimal number of active cross-bridges exist between actin and myosin. However, if the fibers are stretched beyond 2.2 to 2.4 mm, the force of contraction decreases because actin and myosin become partially disengaged, disrupting may of the cross-bridges. Excessive stretching, to about 3.65 mm, causes actin and myosin to become completely disengaged so that tension (force of contraction) drops to zero. Laplace's law states that wall tension is related directly to the product of intraventricular pressure and internal radius and inversely related to the wall thickness as shown in the Laplace equation: $T = (p \times r)/\mu m$. Where T = wall tension, p = intravascular pressure, r = internal radius of the sphere, and μm = wall thickness. Essentially, the amount of tension generated in the ventricular wall (or any chamber or vessel) to produce a given intraventricular pressure depends on the size (radius and wall thickness) of the ventricle. Laplace's law is useful for understanding aneurysm formation distensibility in blood vessels and the effects of ventricular dilation on myocardial contraction (McCance et al '14: 1101-1102).

Cardiac output (CO) = stroke volume (SV) x heart rate (HR). Heart failure occurs when the heart weakens and cannot effectively pump blood to the rest of the body. Blood may back up

from the left side of the heart into the lungs, causing congestion and shortness of breath, this is called **left heart failure**. Or blood may back up on the right side of the heart, resulting in leg swelling and swelling of other tissues and organs. This is called right heart failure. A person may have either right or left heart failure, or both (Cohen '10: 131). The effects of pure left-sided heart failure are largely due to pulmonary congestion and edema. **Right-sided heart failure** induces essentially a systemic venous congestive syndrome with hepatic and splenic enlargement peripheral edema, pleural and pericardial effusions and ascites. In contrast to left-sided failure, respiratory symptoms may be absent or quite insignificant in right-sided failure. In many cases of frank chronic cardiac decompensation, however, the patients presents with both right and left sided heart failure. To some extent the right and left sides of the heart act as two distinct anatomic and functional units. Under various pathologic stresses, one side or even one chamber may fail, so from the clinical standpoint, left-sided and right sided failure can occur separately. Nevertheless, because the vascular system is a closed circuit, failure of one side cannot exist for long without eventually producing excessive strain on the other, terminating in total heart failure (Schoen '94: 523, 522).

Another classification of heart failure is related to an impaired ability of the heart to pump blood (systolic dysfunction) or to an increased stiffness of the ventricles, which impairs blood filling (diastolic dysfunction). In heart failure, the heart's contraction, relaxation, or both may be affected. Remodeling is a process in which the heart actually reshapes itself due to some injury or insult, such as long-standing fluid accumulation in the hart, which causes the heart muscle to stretch until it can no longer pump efficiently. In long standing or chronic heart failure, many of the heart's repair mechanisms, which were initially compensating and allowing the heart to pump effectively, turn maladaptive and actually make the situation worse. Cardiac hypertrophy is the compensatory response of the myocardium to increased work. Myocardial hyperfunction induces increased myocyte size (cellular hypertrophy) through addition of sarcomeres, the contractile elements that causes an increase in the overall mass and size of the heart. The diameter of cardiac myocytes can increase from the normal 15 μm to 25 μm or more in hypertrophy. Because adult myocytes cannot divide, augmentation of myocyte number (hyperplasia) cannot occur in the adult heart. The pattern of hypertrophy reflects the stimulus. Pressure-overloaded ventricles develop concentric hypertrophy, with an increased ratio of wall thickness to cavity radius. In contrast, volume-overloaded ventricles (e.g. mitral regurgitation) develop hypertrophy with dilatation (eccentric hypertrophy) with proportionate increase in ventricular radius and wall thickness. Left ventricular hypertrophy is an independent risk factor for cardiac mortality and morbidity, especially for sudden death and ischemic heart disease. Interestingly, an in contrast to pathologic hypertrophy, hypertrophy that is induced by exercise (physiologic hypertrophy) seems to have minimal or no deleterious effect (Schoen '94: 521).

Congestive heart failure (CHF) is a constellation of problems rather than a specific disease. It means that the heart is not functioning properly, so that blood is not being pumped around the body efficiently. The end result is that tissues are not receiving adequate blood supply to meet their needs. People with heart failure frequently suffer from **fatigue** and tire easily when exerting themselves, because decreased pumping action form the heart does not deliver enough blood to the leg muscle during walking or other exercise. As blood pressure rises, it provides higher and higher resistance to the blood flowing out of the heart into the aorta. The higher the resistance in the "pipes" the harder the pump has to squeeze to get the blood out into the system to feed the organs and muscles. The lungs become congested with blood. This causes some of the water in the blood to squeeze through the very thin walls of the blood vessels into the air sacs of the lungs. That makes it harder to breathe, because oxygen can't pass through the air sacs into

the blood vessels when the air sacs are flood with water. Eventually this backup causes **edema**, or swelling, in the rest of the body, especially the ankles. When the heart can't pump adequately, people get fatigued and develop shortness of breath when they try to exert themselves. Hypertension was the most common cause of congestive heart failure until the middle of the last century (Wilson & Childre '06: 33-35). CHF is a common clinical entity affecting nearly 5 million people in the United States, approximately 1 million will be hospitalized this year. Of CHF cases 75% have antecedent hypertension. Approximately one-fourth of male and one-half of female myocardial infarction cases will develop CHF in 5 years. The 5-year mortality for CHF in general is about 50%. For severe class 4 CHF, there is 50% mortality in 1 year (Heger et al '04: 165).

The New York Heart Association classification of congestive heart failure

Class I: Patients with no limitation of activities; they suffer no symptoms from ordinary activities
Class II: Patients with a slight limitation of activity; they are comfortable at rest and with mild exertion
Class III: Patients with marked limitation of activity; they are comfortable only at rest
Class IV: Patients are symptomatic even at rest, and physical activity brings on discomfort

Source: Table 33.2 Cohen '10: 132

Symptoms of heart failure are shortness of breath, leg swelling, decreased exercise tolerance, fatigue, light-headedness, dizziness, confusion, coughing or wheezing, weight gain and palpitation. Causes of heart failure are: (1) lack of blood flow to the heart (ischemia) (2) presence of a heart attack (myocardial infarction (3) weak heart muscle (cardiomyopathy) (4) thickened heart muscle (such as occurs in hypertrophic cardiomyopathy (5) leaky heart valves (valvular regurgitation) (6) tight heart valves (stenosis) (7) inherited conditions (8) drug toxicity (9) heart rhythm problems (arrhythmias) that weaken the heart muscle (tachycardia-induced cardiomyopathy) and (10) infection (such as virus) (Cohen '10: 131, 133). With age changes occur in the myocardium, chamber cavities, valves, coronary arteries, conduction system, pericardium and aorta. **Brown atrophy** is a term used to describe a small, brown heart with extensive lipofuscin deposits in the muscle cells. **Basophilic degeneration** describes the accumulation within cardiac myocytes of a gray bluish material, likely glucan, a probably byproduct of glycogen metabolism. With advances age, the amount of s**ubpicardial fat** increases, particularly over the anterior surface of the right ventricle. Elderly myocardium also has fewer myocytes, increased collagenized connective tissue and a variable deposition of **amyloid**. Moreover, associated with increasing age is a reduction in the size of the left ventricular cavity, particularly in the base-to-apex dimension, in part owing to a generally lower cardiac output. This chamber alteration, accompanied by a rightward shift and tortuosity of a dilated ascending aorta, causes the basal ventricular septum to bend leftward, bulging into the left ventricular outflow tract. The configuration, termed a **sigmoid septum**, can simulate the obstruction to blood leaving the left ventricle. Several changes of the valves are noted, including **calcification of the mitral annulus**, that is not usually of clinical significance, and aortic valve, frequently leading to aortic stenosis. In addition, the valves develop fibrous thickening, and the mitral leaflets tend to buckle back toward the left atrium during ventricular systole, simulating a **prolapsing (myxomatous) mital valve**. Moreover, small filiform processes (Lambl's excrescences) are on the closure lines of aortic and mitral valves in nearly all subjects older than 60 years of age. **Lambl's excrescences** are wear-and-tear lesions that arise from small thrombi on the valve contact margins. Although these morphologic changes are common in elderly

patients at necropsy and may mimic disease, only in a minority are they associated with clinical cardiac dysfunction (Schoen ’94: 519).

Dysfunction of the heart or the overall cardiovascular system can only occur by one of the following mechanisms. (1) Disruption of the continuity of the circulatory system (e.g. gunshot wound through the thoracic aorta) that permits the blood to escape; in such cases the heart cannot fill, and the resistance against which it pumps is lost. (2) Disorders of cardiac conduction (e.g heart block) or arrhythmias owing to generation of impulses in an uncoordinated manner (e.g. ventricular fibrillation) which leads to contractions of the muscular walls that are not uniform and efficient. (3) A lesion preventing valve opening or one narrowing the lumen of a vessel (e.g. aortic valvular stenosis or coarctation), which obstructs blood flow and overworks the pump behind the obstruction. (4) Regurgitants flow (e.g., mitral or aortic valvular regurgitation) that causes some of the output form each contraction to efflux backward; this necessarily forces portions of the pump to expel the same blood several times and thereby induces substantial myocardial stress. (5) Failure of the pump itself. In the most frequent circumstances, damaged muscle itself contracts weakly or inadequately and the chambers cannot empty properly. In some conditions, however, the muscle cannot relax sufficiently, the left ventricular chamber cannot dilate during diastole, and the heart cannot properly fill (Schoen ’94: 520). Any one of the causes mentioned above, when sufficiently severe or advanced, may ultimately impair cardiac function and render the heart unable to maintain an output sufficient for the metabolic requirements of the tissues and organs of the body producing congestive heart failure (CHF) (Schoen ’94: 520).

Pericardial lesions are almost always associated with disease in other portions of the heart, surrounding structures or secondary to a systemic disorder; isolated pericardial disease is unusual. Normally there is about 30 to 50 ml of thin, clear, straw-colored, translucent fluid in the pericardial space. Under a variety of circumstances, **pericardial effusions** may appear; because they accumulate slowly and are rarely larger than 500 ml, they are usually without clinical significance. **Serous effusion** in heart failure are common. The fluid is completely clear, or straw colored, and sterile. **Caseous pericarditis** creating caseation within the pericardial sac is, until presumed to be tuberculous in origin; infrequently mycotic infections evoke a similar pattern. **Chronic or healed pericarditis**, although frequently observed on autopsy is rarely of clinical importance, except in the form of adhesive mediastinopericarditis or constrictive pericarditis. **Adhesive mediastinopericarditis** occurs when the pericardial sac is obliterated, and adherence of the external aspect of the parietal layer to surrounding structures produces a great strain on cardiac function. With each systolic contraction the heart is pulling not only against the parietal pericardium, but also against the attacked surrounding structures, causing hypertrophy. **Constrictive pericarditis** encases the heart in a dense, fibrous, scar that limits diastolic expansion and seriously restrict cardiac output. Cardiac hypertrophy and dilatation cannot occur because of the dense enclosing scar, and the heart is consequently quiet with reduced output. The major therapy is surgical removal of the shell of constricting fibrous tissue (pericardiectomy). **Hemopericardium** is the accumulation of pure blood in the pericardial sac, distinct from **hemorrhagic pericarditis**, a condition in which there is an inflammatory exudate containing blood mixed with pus. Hemopericardiuim is almost invariably due to rupture of the heart wall secondary to myocardial infarction, traumatic perforation or rupture of the intrapericardial aorta. In such cases, blood rapidly fills the sac, under greatly increased pressure, producing **cardiac tamponade**. As little as 200 to 300 ml of pericardial fluid (blood) may be sufficient to cause death when it accumulates rapidly (Schoen ’94: 566-568).

The World Health Organization (WHO) defines **cardiomyopathy**, as "heart muscle disease of unknown cause", generally referred to as primary or idiopathic cardiomyopathy and (2) specific heart muscle disease, defined as "heart muscle disease of known cause of associated with disorders of other systems". **Idiopathic dilated cardiomyopathy** (DCM) is characterized by the gradual development of cardiac failure associated with four-chamber hypertrophy and dilatation of the heart, that often weighs two to three times normal, of unknown cause, although a familial occurrence has been found in 20% of cases. The primary abnormality is impairment of left ventricular myocardial contractility (systolic failure; in the end stage, patients may have ejection fractions of less than 25% (normal, approximately 50 to 65%). DCM may occur at any age but usually affects those 20 to 60. It is progressive and unremitting in most cases, fifty percent of patients die within 2 years and only 25% of patients survive longer than 5 years. Death is usually attributable to progressive cardiac failure or arrhythmia. Embolism from dislodgement of an intracardiac thrombus may occur. Cardiac transplantation is frequently recommended.

Hypertrophic cardiomyopathy (HCM) is characterized by a heavy muscular hypercontracting heart, in striking contrast to the flabby hypocontracting heart of DCM. It is a diastolic rather than systolic disorder. The differential diagnosis must distinguish HCM from amyloidosis, HHD and age-related subaortic septal hypertrophy. The frequency of sudden death is 2 to 3% per year for adults and 4 to 6% per year for children. **Restrictive cardiomyopathy** (RCM) is a form of primary myocardial disease, with diastolic relaxation and impeded left ventricular chamber filling that must be distinguished from HCM and **Endomyocardial fibrosis**, a valvular disease primarily of children and young adults in Africa and other tropical areas. **Loeffler's endomyocarditis** marked by endomyocardial fibrosis typically with large mural thrombi similar to those seen in the tropical disease. The release of toxic products of eosinophils, especially major basic protein, is postulated to initiate endocardial damage, with subsequent foci of endomyocardial necrosis accompanied by an eosinophilic infiltrate, followed by scarring of the necrotic area and layering of the endocardium by thrombus, and finally organization of the thrombus. Untreated or medically treated eosinophilic endomyocardial disease has a poor prognosis, so surgical endomyocardial stripping (decortication) is often recommended. **Endocardial fibroelastosis** is an uncommon heart disease of obscure etiology characterized by cartilage-like fibroelastic thickening, most common in the first two years of life, it is often accompanied by some form of congenital cardiac anomaly, most often aortic valve obstruction in about one-third of all cases. When focal it can be of no functional important, when diffuse, it may be responsible for rapid and progressive cardiac decompensation and death, particularly in children. **Endomyocardial biopsy** involves inserting a device (called a bioptome) into the right internal jugular vein, advancing it under fluoroscopic or echocardiographic guidance through the tricuspid valve toward the right side of the ventricular septum, and snipping a small piece of myocardium in its jaws. Each biopsy specimen is a 1 to 3 mm fragment of myocardium most frequently derived from the apical half of the right side of the ventricular septum (Schoen '94: 562).

Peripartum cardiomyopathy is the designation given to a globally dilated heart when it is discovered within several months before or after delivery. In about half of these patients, proper function is restored, and dilatation of the heart disappears within months after delivery, in contrast to the classic course of dilated cardiomyopathy. **Cardiac amyloidosis** may appear along with systemic amyloidosis or may affect only the heart. The heart in cardiac amyloidosis varies from normal to firm, rubbery and noncompliant with thickened walls. In the cardiovascular senile form of amyloidosis the deposited proteins are known as senile amyloid (Asc) proteins. Clinically important amyloid deposits can occur in the hearts of patients with

multiple myeloma. **Iron overload** can occur in hereditary hemochromatosis and hemosiderosis owing to multiple blood transfusions. Patients with iron storage disease present most commonly with a dilated pattern. Iron deposition is more prominent in ventricles than atria. Other than a rust-brown color the heart is indistinguishable from DCM. It is thought that iron causes dysfunction by interfering with metal-dependent enzyme systems. Cardiac manifestations are among the earliest and most consistent features of hyperthyroidism and hypothyroidism. In hyperthyroidism tachycardia, palpitations and cardiomegaly are common; supraventricular arrhythmias occasionally appear. In **hypothyroidism** cardiac output is decreased, with reduced stroke volume and heart rate (Schoen ’94: 566).

Alcohol or its metabolites, especially acetaldehyde, have a direct toxic effect on the myocardium, and **alcoholic cardiovascular disease** is not an idiopathic disorders. Chronic alcoholism may be associated with thiamin deficiency. The **anthracycline chemotherapeutic agent** doxorubicin (Adriamycin and daunorubicin are well recognized causes of toxic myocardial injury. The hazard is dose dependent (usually greater than 500 mb/m^2) and attributed primarily to lipid peroxidation of myofiber membranes. Many other **agents**, such as lithium, phenothiazines, and cocaine have been implicated in myocardial injury and sudden coronary death. Common themes in cardiotoxicity of many chemicals and drugs are myofiber swelling and vacuolization, fatty change, individual cell lysis (myocytolysis) and sometimes patchy foci of necrosis. Electron microscopy usually reveals cytoplasmic vacuolization and lysis of myofibrils, typified by Adriamycin cardiotoxicity. With **discontinuance** of the toxic agent, these changes may resolve completely, leaving no apparent sequelae. **Catecholamine** effect is evident in drugs, such as cocaine, and appears as a foci of myocardial necrosis with contraction bands (Schoen ’94: 566).

In general cardiac drugs are the second leading cause of fatal drug overdose and antiarrhythmia and antihypertension drugs are no exception (Bronstein '11). Because 75% of cases of heart failure involve antecedent high blood pressure it is important to review hypertension medicines both for the treatment of malignant hypertension and as possible cause of cardiac failure. Drugs that block activation of angiotensin by blocking angiotensin-converting enzyme, **ACE inhibitors** such as captopril, enalapril, lisinopril or any drug with a proper name ending in –pril), or by blocking angiotensin II at its receptor angiotensin receptor blockers (ARBs) (losartan irbesartan, candesartan, or other drug ending in –sartan) will reduce urinary losses of potassium, magnesium and probably the other ions that are depleted by diuretics. Because potassium loss from the kidney is driven by exchange of potassium for sodium as regulated by aldosterone, salt intake is an important concern. The more salt eaten, the more potassium lost. Every sodium ion reabsorbed from the renal tubule leads to excretion of a potassium ion; high sodium intake aggravates potassium losses, and when potassium is depleted, potassium ions are exchanged for hydrogen ions, leading to acid urine with alkaline blood. Blocking the effect of high renin – potassium and magnesium depletion – by blocking the effect of angiotensin II with **angiotensin receptor blockers** (ARBs) prevent secondary hyperaldosteronism. This may be the best approach for people who have either congestive heart failure or secondary hyperaldosteronism from renal artery stenosis or other high-renin states. ACE inhibitors, also block formation of angiotensin II, but this effect wears off after a few weeks because there are other pathways for the formation of angiotensin II (Spence '05: 147, 148, 152). Beta-blockers seem to be the most highly recommended for slowing the ventiruclar response rate in atrial fibrillation, converting reentrant supraventricular tachyarrhythmias, and suppressing ventricular arrhythmias, but chronic treatment with propranolol, metoprolol or timolol following myocardial infarction decreases 1 year mortality, but bradychardia and congestive heart failure, could result from decompensation. Drugs that slow the upstroke, such as quinidine, procainamide, diopyramide,

lidocaine, mexiletine, tocainide, moricizine, propafenone and flecainide, have been found worsen outcomes when compared to no treatment in patients with ventricular arrhythmias at risk for sudden coronary death (Heger et al '04: 269-270).

Heart failure drugs
Angiotensin-converting enzyme (ACE) inhibitors: Used to help improve the heart's function. May vasodilate the blood vessels and lower blood pressure, making it easier for the failing heart to pump blood. It may adversely affect the kidneys and cause a cough in some people. Note: ACE inhibitors or ARBs plus a beta blocker fulfill the AHA's Get with the Guidelines heart failure program for treating congestive heart failure.
Angiotensin II receptor blockers (ARBs): Used to help improve the heart's function. May vasodilate the blood vessels and lower blood pressure, making it easier for the failing heart to pump blood. May adversely affect the kidneys.
Beta blockers: Can improve heart function in patients with heart failure. Note that some medications act by blocking both alpha and beta receptors. One such drug, carvedilol, blocks the alpha-1 receptor as well as beta receptors.
Digitalis: May make a weak heart pump stronger. May be useful if heart failure does not improve with ACE inhibitors or ARBs. Side effects include worsening heart rhythm problems and yellow vision. Dosage should be reduced in people with heart failure and kidney failure.
Hawthorne: Supreme herb for the heart. Treats high or low blood pressure, heart disease, edema, angina and heart arrhythmia. Hawthorne doesn't store in the body and isn't accumulative in action. Unlike prescription antiarrhythmia medicine Hawthorne does not have any adverse cardiac effects.

Source Table 25.2 Cohen '10: pg. 97-98

Digitalis purpurea, or **foxglove** had been used by illiterate farmers and housewives in England and on the Continent for centuries to treat congestive heart failure and arrhythmia. *Digitalis* slows the wildly beating ventricles to a normal level by blocking or delaying the conduction of the electric impulse through the atrioventricular node. By increasing the heart stoke, *Digitalis* increases the amount of blood being oxygenated by the lungs, as well as the blood in general circulation, by as much as 30% with each beat. Because of this improved action of the heart and circulation, the drug tends to improve renal secretion to relieve edema, and to aid the cardiac muscle to compensate for mechanical defects or structural lesions. More than 3 million heart patients in the United States routinely use the glycoside digoxin from *D. lanata*, and this is but one of six glycosides from *Digitalis* prescribed today. *Digitalis* whole leaf, digitoxin, digoxin, lanatoside C, acetyldigitoxin and deslanoside. Since the effective dose may be as high as 70% of the toxic dose, administration must be done carefully on an individual basis. Recently it has been recommended the use of whole leaf preparations over isolated glycosides. Cardiac glycosides bring only temporary relief and must be administered orally during the whole course of the disease. Adverse reactions are found in about 20% of hospitalized patients receiving *Digitalis* preparations (Elvin-Lewis '77: 184, 186). The FDA required warning for Digitalis and related cardiotonic drugs for human use in oral dosage forms, states "Digitalis alone or with other drugs has been used in the treatment of obesity. This use of digoxin or other digitalis glycosides is unwarranted. Moreover, since they may cause potentially fatal arrhythmias or other adverse effects, the use of these drugs in the treatment of obesity is dangerous" 21CFR§201.317 to which could be appended, "Hawthorne is the supreme herb for the heart".

Hawthorne (*Crataegus laevigata*) may be better for the treatment of congestive heart failure than both *Digitalis* and modern antihypertensive drugs used in the treatment of congestive heart

failure, and is likely to cure more people than nitrates or nitrites. Patients leaving the emergency room would be much more likely to benefit with a recommendation for Hawthorne than for Aspirin, which does help to prevent platelet aggregation and thrombosis that occur in the only most advanced stages of atherosclerosis, and taken in excess the analgesic affect can leave the heart muscle feeling dead complicating the accurate diagnosis of infarction and estimate of myocardial damage, although not harmful, Aspirin is not worth the trip to the hospital. Hawthorne (*Crataegus laevigata*) is outstanding both to prevent heart problems and to treat high or low blood pressure, heart disease, edema, angina and heart arrhythmia. Hawthorne doesn't store in the body and isn't accumulative in action. Unlike prescription cardiovascular and antihypertensive medicine Hawthorne does not have any adverse cardiac effects that might cause decompensation in congestive heart failure, for instance when the treatment for tachycardia causes brachycardia, that is why Hawthorne is known as the "supreme herb for the heart". It is important to take Hawthorne on a regular basis if using as a heart tonic. One drinks four cups of strong herbal tea infusion or cups of water mixed with 2 droppers of tincture, 40 drops, a day, for as many months as the number of years the chronic disease has progressed untreated (Gladstar '12) or for one week to treat a simple infarction.

Surgery for patients with end-stage congestive heart failure currently is limited to **heart transplantation**, frequently after a period of left ventricular assistance with a mechanical device. The number of heart transplants performed in the United States each year is limited to approximately 2,000 because of the shortage of donor organs. Patients older than age 60 have been shown to have similar early mortality ad length of hospitalization as younger groups. Five year survival ranges from 71% in older patients to 82% in younger patients. Hypercholesteremia affects 60-80% of recipients and may contribute to coronary vasculopathy. Transplant atherosclerosis is responsible for many later deaths. Statins reduce the level of cholesterol and appear to have the added advantage of decreasing the incidence of cardiac rejection (Heger et al '04: 264).

III.B.7 Hypertension

High blood pressure is reported to be the most common problem for which people go to doctors in the United States. Hypertension is one of the leading causes of heart attack and stroke. According to the National Institutes of Health, the number of adults with high blood pressure has risen dramatically over the last ten years from fifty million to sixty-five million. In 1990, approximately one in four adults in the United States had hypertension. In 2000, it was about one in three Americans, or sixty-five million people over the age of eighteen, with elevated blood pressure. High blood pressure is a major risk factor for the development of heart disease, including coronary artery disease (the number one killer of Americans) and congestive heart failure (the number one cause for hospital admission in people over the age of sixty-five). It is also a major risk factor for stroke and kidney damage. 30 to 50 percent of individuals with hypertension will be "salt sensitive" (Willson '06: 15, x, 1).

High blood pressure is a major risk factor for the development of heart disease, including coronary artery disease (the number one killer of Americans) and congestive heart failure (the number one cause for hospital admission in people over the age of sixty-five). It is also a major risk factor for stroke and kidney damage. In large populations, the prevalence of hypertension rises with the levels of sodium intake. Most groups with very low sodium intake have no hypertension. When higher levels of salt are introduced, hypertension develops. Only about 5 to 10 percent of high blood pressure has a known cause. Despite the fact that less than half of

people are salt sensitive, dietary salt restriction will lower blood pressure in most people. To be effective dietary restrictions extend to salt, fat and sugar. One problem with high blood pressure is that most people can't feel it. That means that a person could have elevated blood pressure for a long period of time and be completely unaware of it (Wilson & Childre'06: x, 1, 22, 23, 28, 30). Hypotension is characterized by an abnormally low tension of muscle cells in peripheral blood vessels, which are marked by capillary permeability and fragility and is treated as congestive heart failure.

In the 1950s it was discovered that Reserpine and other **Rauvolfia alkaloids**, used in Ayurvedic medicine for the treatment of schizophremia, act on the sympathetic nervous system by depleting almost all the neurotransmitter substance, norepinephrine, from sympathetic nerve tissue. This neural blocking results in relaxation of the vessels and output of the heart, with subsequent reduction in blood pressure. Drug therapy can now control about 80% of all cases of hypertension (Elvin-Lewis '77). 12.5 mg hydrochlorothiazide (HCTZ) is the commonest and cheapest drug for treating high blood pressure, is enough (Spence '05). The ABC of adrenergenic blockers have however been abused in the treatment of congestive heart failure to the neglect of statins (Spence '05)(Heger '05)(Moore '98) and **Hawthorne**, the supreme herb for the heart, that amongst its many cartdiotonic properties, moderates both high and low blood pressure (Gladstar '12).

Blood pressure is the force of the blood pushing out against the walls of the blood vessels. As blood is pumped out of the heart into the arteries that lead away from it, there is a certain pressure in the system created by this pumping actin of the heart. Blood pressure is measured in a few different ways, but the most common method is called **sphygmomanometry** that refers to inflating a blood pressure cuff on the arm (or leg, in some cases). Air is slowly let out of the cuff while the person taking your blood pressure listens with a stethoscope below the cuff to hear the pulse. When the person first hearts the pulse as the cuff deflates, the pressure is recorded as the systolic pressure. The bottom number is called the diastolic pressure. It reflects the pressure in the arteries when it normalizes. The circulatory system is a closed system. There are no valves anywhere in the pipes to let blood out. In addition to the pumping and filling of the heart, pressure is maintained in this closed system by the tension in the walls of the arteries. Arteries have a layer of muscle in their walls. This muscle layer can contract or relax and have a great impact on the pressure in the overall system. Arteries that supply blood to muscles and organs have the ability to dilate (enlarge) under conditions when more blood is required lowering blood pressure. Muscles help to squeeze the arteries and veins to raise pressure to normal. The blood pressure is therefore maintained by the constriction and relaxation of the arteries as well as the pumping of the heart (Wilson & Childre '06: 11-13).

High blood pressure is a blood pressure reading of 140/90 mmHg or higher. Both numbers are important. Once high blood pressure develops, it usually lasts a lifetime. Blood pressure changes during the day. It is lowest as you sleep and rises when you get up. It also can rise when you are excited, nervous, or active. Still, for most of your waking hours, your blood pressure stays pretty much the same when you are sitting or standing still. That level should be lower than 120/80 mmHg. When the level stays high, 140/90 mmHg or higher, it implies high blood pressure. For example, 160/80 mmHg would be stage 2 high blood pressure. With high blood pressure, the heart works harder, your arteries take a beating, and your chances of a stroke, heart attack, and kidney problems are greater. Normal blood pressure is a reading of less than 120/80 mmHg (mmHg = millimeters of mercury, a unit for measuring pressure). Drops in blood pressure that don't threaten life are called **hypotension**. Some people do just fine with blood pressures of

85/50 and doctors treat some people with conditions such as congestive heart failure to reduce their pressures down to these levels. Other people feel terrible when their systolic pressure drops from 150 down to 130 (Wilson & Childre '06: 16). Hypotension is abnormally low blood pressure. Hypotension is blood pressure that is lower than 90/60 mmHg. In a healthy person, hypotension without signs or symptoms is usually not a problem and requires no treatment. Doctors will want to identify and treat any underlying condition that is causing the hypotension, if one can be found. Hypotension can be dangerous if a person falls because of dizziness or fainting. **Shock**, a severe form of hypotension, is a life-threatening condition that is often fatal if not treated immediately. Shock can be successfully treated if the cause can be found and the right treatment provided in time (Sanders '08: 24).

Blood Pressure Sphygmomanometry Reading

Normal (optimal): less than 120 systolic and less than 80 diastolic
Prehypertension: 120-139 systolic or 80-89 diastolic, or both
Stage 1 Hypertension: 140-159 systolic or 90-99 diastolic, or both
Stage 2 Hypertension: greater than 160 systolic or greater than 100 diastolic, or both.

High blood pressure is common and has been identified as one of the most important risk factors in both coronary heart disease and cerebrovascular accidents, it may also lead to congestive heart failure (hypertensive heart disease), aortic dissection, and renal failure. The detrimental effects of blood pressure increase continuously as the pressure increases. A sustained diastolic pressure greater than 90 mm Hg or a sustained systolic pressure in excess of 140 mm Hg are generally considered to constitute hypertension. By this criteria, screening programs reveal that 25 percent of the population is hypertensive. The prevalence increases with age, but in older groups the disease is likely to be mild, but in young adults tends to be more severe. Blacks are affected by hypertension about twice as often as whites and seem more vulnerable to its complications. About 90 to 95 percent of hypertension is idiopathic and apparently primary (**essential hypertension**). Of the remaining 5 to 10 percent most is secondary to renal disease or, less often, to narrowing of the renal artery, usually by an atheromatous plaque (renovascular hypertension). Infrequently, **secondary hypertension** is the result is the result of adrenal disorders, such as primary aldosteronism, Cushing's syndrome, or pheochromocytoma. Both essential and secondary hypertension may be either benign or malignant, according to the clinical course. About 5 percent of hypertensive persons show a rapidly rising blood pressure, which, if untreated, leads to death within a year or two from accelerated or **malignant hypertension** Malignant hypertension usually develops in the fourth decade of life (Schoen '94: 484, 485).

One problem with high blood pressure is that most people can't feel it. That means that a person could have elevated blood pressure for a long period of time and be completely unaware of it. The brain is very sensitive to high blood pressure, both acutely (moment to moment) and chronically (over the long term). 10% of strokes are **hemorrhagic strokes**, caused by a rupture of a blood vessel in the brain. Although much less common than ischemic strokes there is a 50% mortality rate and normal stroke treatment tissue plasminogen activator (tPA) which reduces disability by 30% would exacerbate the hemorrhage and increase the already extremely high risk of death. other type of stroke is caused by rupture of one of the blood vessels in the brain. The most common reason for this is high blood pressure. When pressure gets too high one of these vessels may burst, causing bleeding or hemorrhage in the brain. Hemorrhagic stroke is usually more serious and harder to recover form than embolic stroke. **Aneurysm**, or weakening in the

wall of the arteries (in the brain) can be the source of hemorrhagic stroke. An aneurysm looks a little like a bulge on the inner tube of a tire. This segment of the artery wall is thinner and weaker, and can rupture. Dementia is a term used to describe decreased cognitive mental function. The term **hypertensive encephalopathy** describes a syndrome of severe hypertension accompanied by brain dysfunction and neurologic impairment. Complete resolution can be achieved if the blood pressure is quickly lowered, usually with intravenous medication in an intensive care environment (Wilson and Childre '06: 34, 36, 37).

In the vast majority of cases, doctors have no idea what causes hypertension. They know the predictors that can contribute to it, such as stress, obesity, and diabetes. In medicine when doctors don't know the cause of something, it's usually referred to as idiopathic, meaning "we're idiots when it comes to knowing the cause". When doctors don't know the cause of high blood pressure, a special term is used called **essential hypertension** (also called primary hypertension). Unfortunately, essential hypertension is the diagnosis in 90 to 95 percent of people who have high blood pressure. Some people have "**white coat hypertension'** which means that their pressure is only high when they are at the doctor's office. Therefore doctors perform **repeated tests**. Real hypertension is very common and leads to many other illnesses and complications if not detected and treated in some way to bring the pressure back to the normal or optimal range. African-Americans have an increased incidence and prevalence of hypertension, and higher complication rates, including death, than whites and other ethnic groups. They also have a higher incidence of kidney damage as a result of high blood pressure, and more patients progress to the point of kidney failure and dialysis. Some researchers think African-Americans might be more susceptible to "sodium overload". **Obesity** is a strong contributor to hypertension. Obesity contributes to other diseases as well. Type 2 diabetes is usually seen in middle age as a direct consequence of obesity. Type 2 diabetes contributes to coronary artery disease, eye disease, and many other conditions including premature death. Obesity is also a strong risk factor for the development of high cholesterol and heart disease. Sleep apnea, a disease of disordered breathing during sleep causing many other medical complications, is also predominantly a disease of the overweight (Wilson & Childre '06: 19-21).

More than 50 percent of senior citizens in the United States develop high blood pressure although the incidence of high blood pressure among senior citizens in countries eating traditional low-fat plant based diets is virtually none. Ideal blood pressure 110/70 or less (without medication). Average blood pressure of vegetarians 112/69. Average blood pressure of non-vegetarians 121/77. High blood pressure is defined when the top number (systolic) is consistently over 140, or the bottom number (diastolic) is consistently over 90, while the person is at rest. Meat eaters have nearly triple the incidence of high blood pressure as vegans and very high blood pressure is thirteen times more common in meat eaters. 30-75 percent of patients with high blood pressure achieve substantial improvement by switching to a vegetarian diet and are able to discontinue high blood pressure medicine they were expected to have to take for the rest of their life (Robbins '01: 28, 29).

Regular **exercise**, especially aerobic exercise (sustained exercise that raises the heart rate but doesn't put sudden strain on your system like heavy weight lifting), lowers blood pressure, strengthens the heart and cardiovascular system, helps your muscles to utilize the oxygen delivered by the blood more efficiently, improve energy levels and endurance, improve muscle strength, strengthen bones, increase flexibility and balance, reduce body fat, help to reduce tension, stress and depression, improve sleep, and increase self-esteem. Too much **salt** in the diet can be harmful. The chemical name for salt is sodium chloride. Nutrition labels on foods

now list how much sodium is contained. Sodium is present in high amounts in certain types of foods. Ketchup and pickles are great examples of high-sodium foods. Many canned soups and most snack-food items (potato chips, corn chips, and the like are very high in salt also. Any type of meat that has preservatives to such as sausage, hot dots, or bacon, will contain high levels of sodium. Some people seem to be more sensitive to salt than others, meaning they will develop hypertension in response to excess sodium in their diet. There is no way to predict who might be salt sensitive. Evidence for a causative role of salt follows: In large populations, the prevalence of hypertension rises with the levels of sodium intake. Most groups with very low sodium intake have no hypertension. When higher levels of salt are introduced, hypertension develops. Certain animals seem predisposed to high blood pressure when fed high-sodium diets. Despite the fact that less than half of people are salt sensitive, dietary salt restriction will lower blood pressure in most people (Wilson & Childre '06: 22-23). There is an increased risk of having hypertension if you: are over the age of thirty-five, are overweight, eat foods that are high in salt or fat, or both, are not active, smoke, drink excess alcohol (more than two drinks per day), have family members with high blood pressure, are African-American, are pregnant, take oral contraceptives (birth control pills) or are under stress (Wilson and Childre '06: 24).

Secondary hypertension is the name given to high blood pressure with a known etiology. Only about 5 to 10 percent of high blood pressure has a known cause. The kidneys are frequently the cause of hypertension for many reasons. This is because the kidneys help to regulate blood pressure. As blood is pumped out of the heart in to the main artery, the aorta, it travels throughout the body. The aorta gives off many arteries that feed all of the organs, muscles and other structures. When blood goes through the kidneys, it passes through the renal (kidney) arteries. The kidney are very complex filtering machines that filter out toxins that will then leave the body via the urine. Blood passes from the aorta through the renal artery and into the kidney, where it is pushed through a fine mesh of very small blood vessels that act like a sieve. After going through this filter, the blood travels through a loop of blood vessels that control salt and water balance. This allows water to be reabsorbed back into your circulation to keep everything in balance. Ultimately, toxins and whatever salt and water you don't need pass from the kidneys down pipes called ureters into the bladder, which you empty periodically when the urge hits you As kidney function deteriorates, doctors use the term **renal insufficiency**. When kidney function is extremely poor, and eventually absent, it's called renal failure. The patient generally does not produce any urine At this point, the patient will die in the course of a couple of weeks if he or she does not undergo kidney dialysis, a complicated but routine procedure whereby the blood is withdrawn from a vein, sent through a series of external filters to remove toxins and water, and returned to circulation. People can live for years while undergoing dialysis, although their quality of life is usually significantly diminished. The other option for a patient with end-stage kidney disease is to undergo a kidney transplant operation (Wilson and Childre '06: 24, 28, 25, 37, 38).

The magnitude of arterial pressure depends on two fundamental **hemodynamic variables**: cardiac output and total peripheral resistance. Vasoconstricting agents are angiotensin II, catecholamines, thromboxane, leukotienes, and endothelin. Vasodilators include kinins, prostaglandins and nitric oxide. Arterial hypertension can best be considered a disease dependent on factors that may alter the relationship between blood volume and total arteriolar resistance. The **kidneys** play an important role in blood pressure regulation by at least three mechanisms (1) renin-angiotensin system (2) sodium homeostasis and (3) renal vasodepressor substances. **Environmental factors** implicated in the causation of hypertension include stress, obesity, smoking, inactivity, and heavy consumption of salt. Hypertension is associated with

two forms of small blood vessel disease: hyaline ateriolosclerosis and hyperplastic arteriolosclerosis (Schoen '94: 485, 486, 488). The body is very sensitive to changes in blood pressure. Special cells in the arteries, called **baroreceptors**, can sense if blood pressure begins to rise or drop. When the baroreceptors sense a rise or drop in blood pressure, they cause certain responses to occur throughout the body in an attempt to bring the blood pressure back to normal. For example, if you stand up quickly, the baroreceptors will sense a drop in your blood pressure. They quickly take action to make sure that blood continues to flow to the brain, kidneys, and other important organs. The baroreceptors cause the heart to beat faster and harder. They also cause the small arteries (arterioles) and veins (the vessels that carry blood back to the heart) to narrow (Wilson & Childre '06: 14).

When the kidney senses low blood pressure it produces a hormone called **renin**. This hormone is spilled from the kidney into the circulation and acts on another chemical, which then acts on a another, and in the long run the message goes to the arteries in the body to squeeze down, thus raising the overall pressure in the system. This phenomenon of contracting arteries in the body is known as **vasoconstriction**. The arteries have muscles in their wall for exactly this reason. Another consequence of renin production by the kidneys is the triggering and the production and release of hormones and chemicals form the adrenal glands, which sit on top of the kidneys. These substances not only contribute to the constriction of the arteries, but also pass through the kidneys and cause them to reabsorb salt and water back into the circulatory system, thus helping to raise blood pressure by maintaining the fluid volume in your blood vessels. Many diseases, including hypertension, can create damage to the kidney. Tumors, infection, diabetes, autoimmune diseases (lupus, for example) or kidney stones can also cause **kidney problems** resulting in higher blood pressure. Buildup of cholesterol in the renal artery can create a partial blockage and thereby decrease blood flow to the kidney, triggering renin production and raising pressure. Each **adrenal gland** looks like a little triangular hat sitting atop the kidney below it. It is made up of two parts: the middle core, known as the medulla, and the outer layer, known as the cortex (cover). The medulla makes and stores adrenaline and couple closely related compounds, which quickly raise blood pressure in a crisis situation. The outer cortex of each adrenal gland makes a hormone called aldosterone. **Aldosterone** is a very powerful compound that travels by way of the blood to the kidney, where it tells the kidney to reabsorb sodium (salt) before it goes out in the urine. Nerve signals and hormones from the brain serve as messenger to raise blood pressure often through many steps. Pain or cold temperatures can do this too (Wilson & Childre '06: 25-29).

The minimal criteria for the diagnosis of **Systemic (Left-sided) Hypertensive Heart Disease** (HHD) are: (1) left ventricular hypertrophy in the absence of other cardiovascular pathology and (2) a history of hypertension. The Framingham Heart Study established unequivocally that even mild hypertension (levels only slightly above 140/90 mm Hg), if sufficiently prolonged, induces **left ventricular hypertrophy**. The left ventricular wall thickness may exceed 2 cm and the heart weight 500 gm. Hypertrophy can lead to myocardial dysfunction, cardiac dilatation and ultimately congestive heart failure (CHF). Approximately 25% of the population of the United States suffers from hypertension of this degree, that could be detected on an ECG or echocardiograph, making systemic HHD the second most common form of cardiovascular disease. Depending on the severity of the hypertension, its duration, the adequacy of therapeutic control, and the underlying basis for the hypertension, the patient may enjoy normal longevity and die of unrelated causes, may develop progressive ischemic heart disease, may suffer progressive renal damage or cerebrovascular hemorrhagic stroke, particularly of the 10% hemorrhagic kind that is more than 50% fatal, or may experience progressive heart failure. The

risk of sudden cardiac death is also increased. There is substantial evidence that effective control of hypertension can lead to regression of cardiac hypertrophy (Schoen '94: 541, 542).

Cor Pulmonale, also known as Pulmonary (Right Sided) Hypertensive Heart Disease, constitutes the right ventricular enlargement secondary to pulmonary hypertension caused by disorders that affect the lungs or pulmonary vasculature. **Acute cor pulmonale** refers to the right ventricular dilatation that follows massive pulmonary embolism. **Chronic cor pulmonale** usually implies right ventricular hypertrophy (and later dilatation) secondary to prolonged pressure overload owing to obstruction of the pulmonary arteries or arterioles or compression or obliteration of septal capillaries (e.g. owing to emphysema). Chronic cor pulmonale is a surprisingly common condition because of its association with such widespread disorders as chronic bronchitis and emphysema (COPD), which affect perhaps 40 million or more Americans. Disorders which predispose the patient to cor pulmonale are such diseases of the lung as, chronic obstructive pulmonary disease (COPD), diffuse pulmonary interstitial fibrosis, extensive persistent atelectasis and cystic fibrosis; diseases of the pulmonary vessels such as pulmonary embolism, primary pulmonary vascular sclerosis, extensive pulmonary arteritis (e.g. Wegener's granulmonatosis), drug, toxin or radiation induced vascular sclerosis, or extensive pulmonary tumor micrometastases; disorders affecting chest movement such as, kyphoscoiosis, marked obesity (pickwicckian syndrome) or neuromuscular diseases and disorders inducing pulmonary arteriolar constriction such as, metabolic acidosis or hypoxemia, chronic altitude sickness, obstruction to major airways or idiopathic alveolar hypoventilation. In most instances, clinical effects of the pulmonary impairment overshadow those of the heart (Schoen '84: 542, 543).

Malignant hypertension is relatively rare occurring in 1 to 5% of people with high blood pressure. Before introduction of the new antihypertensive drugs, malignant hypertension was associated with a 50% mortality rate within 3 months of onset, progressing to 90% within a year. At present, however, about 75% of patients will survive 5 years, and 50% survive with pre-crisis renal function. The full blown syndrome of malignant hypertension is characterized by diastolic pressures greater than 130 mm Hg, papilledema retinopathy, encephalitis, cardiovascular abnormalities and renal failure sometimes encountered in "hypertensive crisis". At the onset of rapidly mounting blood pressure, there is marked proteinuria and microscopic or sometimes macroscopic hematuria, but no significant alteration in renal function. Soon, however, renal failure makes its appearance and the patient is unable to urinate. The syndrome is a true medical emergency requiring the institution of aggressive and prompt antihypertensive therapy before the development of irreversible renal lesions (Saunders '94: 978).

It wasn't until the 1940s and 50s that big changes in the **treatment** of hypertension took place, partly due to the fact that President Franklin Delano Roosevelt eventually died of a stroke, but also suffered from congestive heart failure and kidney failure, all complications of his long-standing hypertension. In the 1950s it was discovered that Reserpine and other Rauvolfia alkaloids, used in Ayurvedic medicine for the treatment of schizophremia, act on the sympathetic nervous system by depleting almost all the neurotransmitter substance, norepinephrine, from sympathetic nerve tissue. This neural blocking results in relaxation of the vessels and output of the heart, with subsequent reduction in blood pressure. Drug therapy can now control about 80% of all cases of hypertension. Drugs however do not cure, salt and meat elimination diets are necessary, but drug control of this disease marks a tremendous change in the outlook for patients who developed malignant hypertension whose inflexible fate until 1950 was a stroke, heart failure, or kidney failure (Elvin-Lewis '77). Although many drugs were tried in the early days of treatment, compounds began to be developed in the 1950s through the l970s that evolved into the

new drugs classes currently in use. In the 1980s and 90s a couple more families of medications hit the scene. Today there are **four basic classes** of antihypertensive medications used in the treatment of high blood pressure – diuretics, beta-blockers, angiotensin converting enzyme (ACE) inhibitors and calcium channel blockers; aldosterone blockers are for certain patients. Patients must be willing to persevere and deal with the "art" of medicine, often known as "trial and error" (Wilson and Childre '06: 41, 42). Modern cardiac drugs, including all hypertension medication are however the **second leading cause of fatal drug overdose** (Bronstein '11) and their prescription is rife with abuse (Moore '98). Doctors and nurses come out of medical school, able to rattle off these dangerous medicines, cardiologists are generally much more reluctant to prescribe these medicines than primary care doctors and these two offices, despite their disparate cardiac and hypertensive population, probably prescribe an equal amount of ACE inhibitors, beta-blockers, and calcium channel blockers. Among the many cardiotonic properties of Hawthorne *Crataegus laevigata* is the treatment of both high and low blood pressure (Gladstar '12)(Elvin-Lewis '77).

Prescription Medicine for the Treatment of Hypertension

Diuretics Generic Name	**Diuretics Trade Name**	**Beta-blockers Generic Name**	**Beta-blockers Trade Name**
Bumetanide	Bumex	Acebutolol	Sectral
Chlorthalidone	Hygroton	Atenolol	Tenormin
Ethacrynic acid	Edecrin	Carvedilol	Coreg
Furosemide	Lasix	Labetalol	Normodyne, Trandate
Hydrochlorothiazide (HCTZ)	HydroDIURIL, Microzide	Metoprolol	Lopressor, Troprol
Indapamide	Lozol	Nadolol	Corgard
Metolazone	Zaroxolyn, Mykrox	Pindolol	Visken
Torsemide	Demadex	Propranolol	Inderal
ACE Inhibitors Generic Name	**ACE Inhibitors Trade Name**	**ARBs Generic Name**	**ARBs Trade Name**
Benazepril	Lotensin	Candesartan	Atacand
Captopril	Capoten	Eprosartan	Teveten
Enalapril	Vasotec	Irbesartan	Avapro
Fosinopril	Monopril	Losarten	Cozaar
Moexipril	Univasc	Olmesartan	Benicar
Perindopril	Aceon	Telmisartan	Micardis
Quinapril	Accupril	Valsartan	Diovan
Ramipril	Altace	**Aldosterone Blockers Generic Name**	**Aldosterone Blockers Trade Name**
Trandolaril	Mavik	Eplerenone	Inspra
Calcium Channel Blockers Generic Name	**Calcium Channel Blockers Trade Name**	Spironolactone	Aldactone
Amlodipine	Norvasc	**Alpha Blockers Generic Name**	**Alpha Blocker Trade Name**
Diltiazem	Cardizem, Tiazac	Doxazosin	Cardura
Felodipine	Plendil	Prazosin	Minipress

Nicardipine	Cardene	Terazosin	Hytrin
Nifedipine	Procardia, Adalat	**Sympatholytic Drugs Generic Name**	**Sympatholytic Drugs Trade Name**
Verapamil	Calan, Isoptin, Verelan	Clonidine	Catapres
Direct Vasodilators Generic Name	Direct Vasodilators Trade Name	Guanabenz	Wytensin
Hydralazine	Apresoline	Methyldopa	Aldomet
Minoxidil	Loniten		
Rauwolfia alkaloids Generic Name	**Rauwolfia alkaloids Trade Name**		
Rauwolfia serpentine			
Rauwolfemms			
Reserpidine Oral	Serpasil, Serpalan, Harmonyl, Novoreserpine, Raudixin, Rauval, Rauverid, Reserfia, Serpalan, Wolfina		
Deserpidine and Hydrochlorothiazide or Methyclothiazide	Demi-Regroton, Diupres, Diurigen with Reserpine, Diutensen-R, Dureticyl, Enduronyl, Enduronyl Forte, Hydropres, Oreticyl, Oreticyl Forte, Rauzide, Regroton		

Source: Wilson & Childre '06: Appendix Table I-VII pgs. 136-139

Arterial **hypertension** is the medical term for high blood pressure. Effective measures to improve blood pressure without drugs include weight loss, exercise, and avoidance of substance that aggravate blood pressure. The most important substance to avoid is salt but also aggravating are alcohol, licorice, decongestants, amphetamines, birth control and NSAIDs.
With rare exceptions high blood pressure is related to the powerful hormone systems we need to survive that controls salt and water. The exceptions include tumors of the inner part of the adrenal gland (the adrenal medulla) called pheochromocytomas, and a congenital narrowing of the aorta called aortic coarctation. Much commoner is high blood pressure due to kidney problems or to enlargement of the outer part of the adrenal gland (the adrenal cortex). To control high blood pressure that is difficult the best way to sort out the cause is to measure the **renin** (a kidney enzyme) and aldosterone (an adrenal gland hormone) in the blood plasma (28, 29); this is most informative after the individual take a dose of diuretic to stimulate the production of renin and aldosterone. The kidney and adrenal gland have a central role in the long-term regulation of body salt and water. When it goes wrong, it causes high blood pressure. If the kidney senses that the body is too dry or the blood pressure is too low it puts out renin, the enzyme that activates a precursor to angiotensin I, a short chain of amino acids. Angiotensin I is converted to angiotensin II by an enzyme called angiotensin converting enzyme (ACE). Angiotensin II can raise blood pressure by itself because if constricts arteries by causing thickening of the arteries

and heart muscle but it also goes to the outer part of the adrenal gland (the adrenal cortex) and causes the adrenal gland to release aldosterone. Aldosterone goes to the kidney, where it causes salt and water retention and excretion of potassium, magnesium and other ions (Spence '05: 120, 121, 132).

Thiazine diuretics are the commonest and cheapest drug for treating high blood pressure is hydrochlorothizide, a drug that is particularly effective in the elderly and people with African ancestors, it acts first as a diuretic; after six weeks or so, iuts main effect is to relax the small artery branches, the arterioles. The main issue with this drug is determining the correct dose: for most indiviuals a dose of 12.5 mg daily is enough, and for others 12.5 mg every other day. Hydrochlorothizide is usually available in tablets of 25 mg or more, so half of the smallest tablet is the optimal dose (Spence '05: 127). Drug therapy can now control about 80% of all cases of hypertension. Drugs do not cure, but their control of this disease marks a tremendous change in the outlook for patients whose inflexible fate until 1950 was a stroke, heart failure, or kidney failure (Elvin-Lewis '77: 189). There are other categories of drugs that may be necessary in specific high blood pressure patients. **Aldosterone blockers** – aldosterone is made in the adrenal gland and travels to the kidney to save sodium (salt) and water. It also acts as a **constrictor of blood vessels**. Blocking aldosterone may lower blood pressure by both mechanisms. These drugs are most often **used in conjunction** with other drugs, or may be used alone. **High potassium** is the most common side effect. **Sympatholytic drugs** are older drugs that decrease the outpouring of nervous system hormone with numerous side effects that are therefore rarely used. **Direct vasodilators** directly dilate the blood vessels and are used only in special situations (Wilson and Childre ’06: 48-49).

People taking long term diuretic therapy to rid their body of salt and water, often experience adverse effects related to the depletion of the number of ions. Often the rubric **hypokalemia** (low blood level of potassium) is used to characterize the problem. The problem is however not a low eve of potassium in the blood, it is potassium depletion in the cells throughout the body, including muscles, heart, brain, and elsewhere. Potassium supplements do not restore intracellular potassium unless magnesium is taken at the same time. Maintaining adequate intracellular potassium helps prevent toxicity of digoxin (a heart medication that can cause serious problems if the blood level is too high, or the potassium level in the cells is too low) and minimizes the adverse effects on diabetes and cholesterol. Taking diuretic causes the body to react by turning on hormone systems designed to retain salt and water. **Aldosterone** causes the kidney to retain sodium and excrete potassium and other ions; when potassium is eventually depleted, there is excretion of hydrogen ions, leading to an alkaline state in the blood (alkalosis). Most individuals with depleted potassium have a normal serum potassium. If taking a diuretic and feel tired, achy, have cramps in extremities, are impotent, and feel faint when standing up, presume depleted potassium. Usually when there is potassium depletion there is also depletion of magnesium, zinc, selenium, rubidium and other ions (Spence '05: 146).

Drugs that reduce production of aldosterone by the adrenal gland also are magnesium and potassium sparing. Drugs that block activation of angiotensin by **blocking angiotensin-converting enzyme**, ACE inhibitors such as captopril, enalapril, lisinopril or any drug with a proper name ending in –pril), or by blocking angiotensin II at its receptor (losartan irbesartan, candesartan, or other drug ending in –sartan) will reduce urinary losses of potassium, magnesium and probably the other ions that are depleted by diuretics. Because potassium loss from the kidney is driven by exchange of potassium for sodium as regulated by aldosterone, salt intake is an important concern. The more salt eaten, the more potassium lost. Every sodium ion

reabsorbed from the renal tubule leads to excretion of a potassium ion; high sodium intake aggravates potassium losses, and when potassium is depleted, potassium ions are exchanged for hydrogen ions, leading to acid urine with alkaline blood. Blocking the effect of high renin – potassium and magnesiu depletion – by blocking the effect of angiotensin II with angiotensin receptor blockers (ARBs) will prevent **secondary hyperaldosteronism**. This may be the best approach for people who have either congestive heart failure or secondary hyperaldosteronism from renal artery stenosis or other high-renin states. ACE inhibitors, also block formation of angiotensin II, but this effect wears off after a few weeks because there are other pathways for the formation of angiotensin II (Spence '05: 147, 148, 152).

If potassium-sparing diuretics and ARBs or ACE inhibitors are used together, there is a real risk of seriously increased levels of potassium in the blood (hyperkalemia). For primary hyperaldosteronism the specific treatment is blockers of aldosterone such as spironolactone and eplerenone; amiloride can also be used and is the specific treatment for hypertension due to abnormalities of the renal tubule such as Liddle's syndrome. The problem is not low levels of potassium in the blood (hypokalemia) but **potassium/magnesium depletion**; potassium supplements do not solve the problem because magnesium is required to restore intracellular potassium. A recommended approach is to: (1) reduce salt intake below 2-3 grams per day; (2) reduce the dose of diuretic, (3) use potassium/magnesium sparing diuretics to prevent losses or (4) use angiotensin blockers to reduce secondary hyper-adlosteronism and thus prevent depletion of potassium and magnesium (Spence '05: 152). To **minimize potassium losses**, one can reduce salt intake; use angiotensin-receptor blockers (ARBs) to prevent angiotensin II from causing the adrenal cortex to release aldosterone; or block the effects of aldosterone on the kidney tubule by using potassium-magnesium sparing diuretics. A minority of patients with difficult to treat high blood pressure will require potassium and magnesium supplementation. Potassium depletion is usually managed by a combination of reducing salt intake, reducing the dose of diuretic and using either potassium/magnesium sparing diuretics or drugs that prevent excess aldosterone production such as angiotensin receptor blockers. For most individuals, particularly the elderly, a daily dose of 12.5 mg hydrochlorothiazide (HCTZ) is the commonest and cheapest drug for treating high blood pressure, is enough. Among that do not deplete the body's potassium and magnesium, amiloride is generally preferred for men, because men who take spironolactone often have sore nipples and sometimes breast enlargement. This does not appear to be a problem with eplerenone, a new aldosterone antagonist. Avoid triamterene, because half the people who take it develop an abnormality in the urine (triamterene casts) and it is implicated in kidney inflammation (interstitial mephritis) and kidney stones. If a small does of one of the thiazide family of diuretics if required, a common ratio might be HCTZ 12.5 mg to amiloride 10-20 mg, or spironolactone 100 mg. For people with secondary hyperaldosteronism, overproduction of aldosterone because of high levels of renin and angiotensin - angiotensin receptor blockers are more effective (Spence '05: 149, 150).

Any **ACE inhibitor** will cause a cough in about 8 percent of people and swelling of the face and tongue (angiodedema) in about one in one thousand. One can avoid these adverse effects by switching to angiotensin blockers, which have benefits similar to those of ACE inhibitors. The first dose of any ACE inhibitor or angiotensin blocker can cause a severe drop in blood pressure, particularly in people taking diuretics. They can also cause acute kidney failure in people that have severe narrowing of both kidney arteries. This problem is rare except in very severe high blood pressure or heart failure. Among ACE inhibitors the main difference is due to the presence of a sulfhydryl group in captropril, which is responsible for the loss of taste and a characteristic generalized rash that looks like measles. Both of these problems will disappear if

you switch to another ACE inhibitor or to an angiotensin blocker. Captopril is very short acting and must be taken two or three times per day to achieve desired effects in all but the least severe cases. Lisinopril, quinapril, and some of the other ACE inhibitors are long acting enough to work well when taken once a day. Captopril is also the most expensive of ACE inhibitors (Spence '05: 145).

Beta-blockers block one of the two kinds of adrenaline receptor (a structure on the surface of cells that responds to adrenaline), the beta receptors. Beta receptors are of two types, beta-1 and bta-2. Stimulating beta-1 receptors causes the heart to speed up and beat more forcefully. Stimulating the beta-2 receptors causes the bronchi to dilate and the arteries that got to the muscles to dilate. **Alpha-blockers** block the second of the two kinds of adrenaline receptor, the alpha receptors: the alpha-1 receptor when stimulated causes the arteries to constrict, and the alpha-2 receptor when stimulated inhibits the sympathetic nervous system. Alpha-blockers are used selectively to block the alpha-1 receptors by preventing the arteries from constricting, they tend to lower blood pressure. They also have beneficial effects on cholesterol and diabetes, and are now commonly used for bladder symptoms from prostate gland enlargement. The main ones in use are prazosin, doxazosin, and terazosin. Compared with prazosin, the latter two are longer acting so can be taken less often, and they tend to cause less trouble with a faint feeling on standing. Doxazosin is the longest acting, and probably the best choice for that reason (Spence '05: 128, 129, 130).

Beta-blockers have issues in the different ways individual bodies handle the drugs (pharmacokinetics) and the way the drugs interact with adrenaline receptors (pharmacodynamics). Concerns include how drugs metabolize, how long the drug action lasts, how the drugs are absorbed into various body tissues, and how tightly the drug binds to receptors. Propranolol undergoes extensive metabolism during its first pass through the liver (first-pass metabolism); about 70 percent of an oral dose is broken down in the liver and never makes to the rest of the body. Both propranolol and metoprolol have a twenty-fold range in the blood levels achieved with a given dose that in different people can lead to blood levels that range from five to one hundred units. If propranolol and metoprolol don't work well at the dose prescribed hypertension can be controlled, at a much lower cost, with a beta-blocker that is excreted by the kidney or metabolized in a different way. Nadolol and atenolol are two beta-blockers that are excreted by the kidney, creating special problems for the elderly and for people with impaired kidney function. They can build up in the blood-stream, causing relatively slow heart action (bradycardia), and aggravate heart failure, which in turn aggravates the kidney function. If the heart rate has been getting slower and slower switch to a beta-blocker that is not excreted by the kidney, but metabolized by the liver (Spence '05: 140, 141).

The best and most convenient beta-blocker is **pindolol**, it has the most potent ISA, so it does not cause the adverse effects due to blockade of beta-2 receptors. (ISA, intrinsic sympathomimetic activity of drugs that block beta-1 receptors and stimulate beta-2 receptors.) Pindolol is also the best beta-blocker for people with diabetes, high cholesterol, or blocked arteries in the legs; it is less likely to aggravate cholesterol and diabetes, and less likely to cause fatigue and is the least likely to cause rebound hypertension if doses are missed. The downside of pindolol is that small proportion of people (about 5 percent) experience vivid dreams, tremor or anxiety because of the drug's greater penetration into the brain. Beta-blockers penetrate brain tissue to markedly varied extents because of difference in how well they dissolve in fat. These differences explain why pindolol, with its extreme penetration into brain tissue, is the most likely beta-blocker to cause anxiety, tremors and vivid dreams, and why propranolol, which is also concentrated in the brain,

is the most likely to cause subjective tiredness and hallucinations. Selective blockade of beta-1 receptors that speed up the heart and cause it to beat harder and stimulation of beta-2 receptors that cause dilation of the large air tubes in the lung and of the arteries that go to muscles. Nonselective drugs such as propranolol, nadolol and timolol are more likely to cause adverse effects due to beta-2 blockade. Drugs that stimulate beta-2 receptors will have a different profile again; pindolol, a relatively potent beta-2 stimulator, had beneficial effects on cholesterol, may benefit diabetes, and is least likely to cause problems with cold extremities and asthma (Spence '05: 141, 142, 144).

Calcium-channel antagonists, or **calcium-channel blocker**s, dilate arteries by interfering with the channels that permit calcium to enter cells; they are useful for both hypertension and angina. Calcium-channel antagonists, or calcium-channel blockers, dilate arteries by interfering with the channels that permit calcium to enter cells. Trouble with constipation or shortness of breath or other symptoms of heart failure, is often helped by changing from verapamil or diltiazem to another type of drug, or changing to a dihydropyridine (the largest class of CCBs) such as nifedipine, felodipine, or amlodipine. If the problem is a slow heart rate from diltiazem, changing to a dihydropyridine or another class of drug should help; if it doesn't, check out a pacemaker. Consumers of both diltiazem and a beta-blocker, may need to reduce the dose of beta-blocker. Those having a lot of angina on a dihydropyridine such as felopidipine, are helped by adding a beta-blocker (or switching to diltiazem for those who can't take a beta-blocker). If it doesn't help, find out about endartectomy, angioplasty or bypass surgery, and make sure that all the risk factors are optimally controlled. If the problem is ankle swelling, flushing, or headache, switching from nifedipine or felodipine to amlodipine or another class of drug should help. Diltiazem and verapamil are not very strong and are extremely expensive, so are not advised for treating high blood pressure: the main reason to use them. Verapamil is good for heat-rhythm disturbances such as atrial fibrillation and diltiazem is good for angina (chest pain brought on by exertion, due to narrowing of the coronary arteries) (Spence '05: 139, 140). There are other categories of drugs that may be necessary in specific high blood pressure patients. **Aldosterone blockers** – aldosterone is made in the adrenal gland and travels to the kidney to save sodium (salt) and water. It also acts as a constrictor of blood vessels. Blocking aldosterone may lower blood pressure by both mechanisms. These drugs are most often used in conjunction with other drugs, or may be used alone. High potassium is the most common side effect. **Sympatholytic drugs** are older drugs that decrease the outpouring of nervous system hormone with numerous side effects that are therefore rarely used. **Direct vasodilators** directly dilate the blood vessels and are used only in special situations (Wilson and Childre '06: 48-49).

Drugs in the class called **dihydropyridines**, the largest group, tend to be the best at lowering blood pressure. Diltiazem is a somewhat weaker vasodilator in the peripheral arteries throughout the body, but it affects the coronary arteries and so may be better for angina. Verapamil is another relatively weak drug that may aggravate heart failure. The main dihydrpyrinidines are nifedipine, felodipine, amlodipine, nisodipine, and nicardipine. Nifedipine and felodipine are quite short acting, and the slow-release pills that have been developed are only partially effective in correcting the problem of peaks and troughs in blood pressure. Nifedipine is relatively expensive, but the best value is felodipine, and if it is causing too many side effects, amlodipine may be better. Nicardipine is very expensive and usually has to be taken several time a day, so it has little advantage. A special problem occurs when dihydropyridines are taken with **grapefruit juice** that reduce the metabolism of a number of drugs. Felodipine blood levels go up on average about 300 percent with grapefruit juice, nisodipine levels about 500 percent. A number of important interactions occur between grapefruit and other drugs such as cyclosporine,

terfenadine (an antihistamine), and propafenone; based on the known metabolism of warfarin and the cholesterol-lowering drugs such as lovastatin and simvastatin, can be anticipated to be affected by grapefruit juice. As a rule of thumb any drug that should not be taken with erythromycin, ketoconazole or itraconazole, should not be taken with grapefruit juice (Spence '05: 162).

Grapefruit juice inhibits the metabolism of a number of drugs, whereby a large proportion of the drug is metabolized by oxidation to form another chemical, in the wall of the intestine. This oxidation is performed by a specific form of the family of oxidative enzymes (Cytochrome P450) called CYP3A4. Drugs that are largely metabolized during oxidation are said to have low bioavailability, because a low proportion of the drug is available to the body. When the metabolism of these drugs in the intestinal wall is inhibited, a much larger proportion of the drug is absorbed unchanged, and the blood levels of the drug are much higher. Dihydropyridine calcium-channel antagonists) drugs with high bioavailability such as amlodipine are not much affected by grapefruit juice; nifedipine, which is 60 percent bioavailable, ahs a 30 percent rise in blood levels when taken with grapefruit juice, and nisoldipine, which is 8 percent bioavailable, goes up on average fivefold up to ninefold. Interesting Florida orange juice has no such effect, although Seville orange juice and lime juice have some effect (though less powerful than grapefruit juice). Other drugs for which the grapefruit juice effect is important include the transplant anti-rejection drug cyclosporine (a tripling of blood levels); the AIDS drug squinovir (large effects); the sleeping pills midazolam and triazolam; and most importantly, the anti-histamine terfenadine. Both terfenadine and the gut-motility drug cisapride can cause serious heart-rhythm disturbances when their metabolism is inhibited, wherefore they are no longer on the market. Other drugs affected importantly by grapefruit include the anticoagulant warfarin and the heart-rhythm drug propafenone in some individuals, and the cholesterol-lowering drugs lovastatin and simvastatin. Blood levels of both lovastatin and simvastatin can be increased fifteen-fold by a glass of grapefruit juice. Atorvastatin is also affected by grapefruit, although to a much lesser degree, but pravastatin and rosuvastatin are not. A simple rule of thumb is that if a drug should not be taken with erythromycin, ketoconazole or itraconazole, it should not be taken with grapefruit juice. To be safe, don't drink grapefruit juice if taking one of the affected drugs (Spence '05: 162).

III.B.8 Kidney Disease

Human **kidneys** serves to convert more than 1700 liters of blood per day into about 1 liter of a highly specialized concentrated fluid called urine. In so doing the kidney excretes the waste products of metabolism, precisely regulates the body's concentration of water and salt, maintains the appropriate acid balance of plasma, and serves as an endocrine organ, secreting such hormones as erythropoietin, renin and prostaglandins. Renal disease is responsible for a great deal of morbidity and some mortality. Approximately 45,000 deaths are attributed yearly to renal disease in the United States, in contrast to about 650,000 to heart disease, 560,000 to cancer, and 145,000 to stroke. Millions of people are affected annually by nonfatal kidney diseases, most notably infections of the kidney or lower urinary tract, kidney stones and urinary obstruction. Twenty percent of all women suffer from infections of the urinary tract or kidney at some time in their lives, and as many as 5% of the U.S. population develops renal stones, cured with Stonebreaker (Chanca piedra). Modern treatment, notably dialysis and transplantation, keep many patients alive who earlier would have died of renal failure. People with even mild chronic kidney disease have a greatly enhanced risk for cardiovascular disease. The study of kidney

disease is facilitated by dividing them up in those that affect the four basic morphologic components: glomeruli, tubules, interstitium and blood vessels. Most glomerular disease are immunologically mediated, whereas tubular and interstitial disorders are frequently caued by toxic or infectious agents. Damage to one kidney invariably affects the other. Disease primarily in the blood vessels, for example, inevitably affects all the structures that depend on this blood supply. Severe glomerular damage impairs the flow through the peritubular vascular system and also delivers potentially toxic products to tubules; conversely, tubular destruction, by increasing intraglomerular pressure, may induce glomerular injury. Whatever its origin there is a tendency for all forms of chronic kidney disease ultimately to destroy all four components of the kidney, culminating in chronic renal failure and what has been called end-stage kidneys. The functional reserve of the kidney is large and much damage may occur before there is evident functional impairment (Saunders-Elsevier; Alpers '10: 906).

Pyelonephritis is a renal disorder affecting the tubules, interstitium and renal pelvis and is one of the most common diseases of the kidney. It can be acute renal lesion caused by bacterial infection. Chronic pyelonephritis is more complex, bacterial infection plays a dominant role, but other factors such vesicoureteral reflux, where the reflux of urine allows bacteria to ascend the ureter and obstruction by a tumor or enlarged prostate are involved. Pyelonephritis is a serious commplication of urinary tract infections that affect the bladder (cystitis). The dominant **etiologic agents**, accounting for more than 85% of cases of urinary tract infection are the gram-negative bacilli that are normal inhabitants of the intestinal tract, most commonly *Escherichia coli*, followed by *Proteus*, *Klebsiella* and *Enterobacter*. *Streptococcus feacalis*, also of enteric origin, *staphylocooci* and virtually every other bacterial and fungal agent, (e.g. *Candida*) can also cause lower urinary tract and renal infection that destroys the glomeruli (Alper '10: 939). Bactrim monopolizes the drug monograph for *E. coli* although it may be the drug and not the disease that so often causes malabsorption, that manifests as a post-infectious auto-immune disease in the kidneys or intestines, particularly in vegans without adequate vitamin B_{12} and probiotic supplementation. **Metronidazole** (Flagyl ER) is preferred for the treatments of all fecal coliform and although it is contraindicated with alcohol causes such minimal vitamin B_{12} deficiency exhibited by chronic consumption of all other antibiotics more research is needed for the FDA to verify in the impressive metronidazole monograph, that it is effective against *E. coli*. Because the effective oral antifungal Sporanox (itraconazole) is highly contraindicated for congestive heart failure patients due to adverse reactions with almost all hypertension medicine natural anticandidal remedies and vigilance with **athletes foot crème** (clotrimazole), rather than the antifungal foot powder (prescribed for elders) spray (Toftate) that causes diffuse pain and chest pain, are all available over-the-counter.

The **glomerular filtration barrier** allows discrimination among various protein molecules, depending on their size (the large, the less permeable) and charge (the more cationic, the more permeable). Most cases of human glomerulonephritis are a consequence of deposits of discrete immune complexes. **Microbial antigens** that have been implicated are bacterial products (streptococci), appearing 1 to 4 weeks post-streptococcal infection of the pharynx or skin, but only certain strains of groups A β-hemolytic streptococci are nephritogenic, as well as the surface antigen of hepatitis B and C virus antigens, and antigens of *Treponema pallidum*, *Plasmodium falciparum* and several other viruses. More than 95% of children and 60% of adults recover but fewer than 1% of children and 40% of adults become severely oliguric, and develop a rapidly progressive glomerulonephritis; prolonged and persistent heavy proteinuria and abnormal GFR mark patients with an unfavorable prognosis (Alpers '10: 940, 941, 907, 910, 914, 919). In **chronic interstitial nephritis** there is infiltration with predominantly mononuclear

leukocytes present interstitial fibrosis and widespread tubular atrophy. Defects in tubular function may cause impaired ability to concentrate urine, evidenced by polyuria or nocturia, salt wasting, diminished ability to excrete acids (metabolic acidosis), and isolated defects in tubular reabsorption or secretion. In immunocompromised persons, particularly those with transplanted organs, viruses such as Polyomavirus, cytomegalovirus and adenovirus can also cause renal infection. In most patients with **urinary tract infections**, the infecting organisms are derived from the patient's own fecal flora that has reached the kidney through the bloodstream (hematogenous infections) or from the lower urinary tract (ascending infection) the most common cause of clinical pyelonephritis. **Chronic pyelonephritis** at one time accounted for 10-20% of patients in renal transplant or dialysis units, until predisposing conditions such as reflux became better recognized.

The clinical manifestations of renal disease can be grouped into well defined syndromes. **Azotemia** is a biochemical abnormality that refers to an elevation of the blood urea nitrogen (BUN) and creatinine levels, and is related largely to a decreased glomerular filtration rate (GFR). Azotemia is a consequence of many renal disorders, but also arises from extra-renal disorders. **Prerenal azotemia** is encountered when there is hyperfusion of the kidneys (e.g. hemorrhage, shock, volume depletion and congestive heart failure that impairs renal function in the absence of parenchymal damage. **Postrenal azotemia** is seen whenever urine flow is obstructed beyond the level of the kidneys. Relief of the obstruction is followed by correction of the azotemia. **Uremia** is characterized by a host of metabolic and endocrine alterations resulting from renal damage. **Nephritic syndrome** onset present grossly visible hematuria (red blood cells in urine), mild to moderate proteinuria (>3.5 gm/day), hypoalbuminemia (plasma albumin <3 gm/dL), severe edema, hyperlipidemia and lipiduria (lipid in the urine) is due to glomerular disease classically acute poststreptococcal glomerulonephritis. **Glomerular disease** is often associated with such systemic disorders as diabetes mellitus, SLE, vasculitis, amyloidosis and endocarditis. **Rapidly progressive glomerulonephritis** includes a rapid decline (hours to days) in GFR) (Alpers '10: 906-907).

Acute renal failure is dominated by oliguria or anuria (reduced or no urine flow), and recent onset of azotemia that can result from glomerular, interstitial or vacular injury or acute tubular injury. **Chronic renal failure** is characterized by prolonged symptoms and signs of uremia, it is the end result of all chronic renal parenchymal diseases. **Renal tubular defects** are dominated by polyuria (excessive urine formation), noctuira and electrolyte disorders (e.g. metabolic acidosis). Defects in specific tubular functions can be inherited (e.g., familial nephrogenic diabetes, cystinuria, renal tubular acidosis) or acquired (e.g. lead nephropathy). **Urinary tract infection** is characterized as bacteriuria and pyuria (bacteria and leukocytes in the urine). The infection may be symptomatic or asymptomatic and may affect the kidney (pyelonephritis) or the bladder (cystitis). **Nephrolithiasis** (renal stones) manifest as severe spasma of pain (renal colic) and hematuria, often with recurrent stone formation. **Urinary tract obstruction** and renal tumors have varied clinical manifestations based on the specific anatomic location and nature of the lesion. Nephrotic patients are particularly vulnerable to **infection** especially staphylococcal and pneumococcal. Thrombotic and thromboembolic complications are also common due in part to loss of endogenous anticoagulants (e.g. antithrombin III) and antiplasmins in the urine. Renal vein **thrombosis** may result (Alpers '10: 907-908, 922).

Chronic renal failure progresses through four stages that merge into one another. In stage 1 there is a **diminished renal reserve** the GFR is about 50% of normal. Serum BUN and creatinine values are normal, and the patient is asymptomatic. However, they are more susceptible to

developing azotemia with an additional renal insult. Stage 2 is known as **renal insufficiency** the GFR is 20-50% of normal. Azotemia appears, usually associated with anemia and hypertension. Polyuria and nocturia can occur as a result of decreased concentrating ability. Stage 3 **chronic renal failure**, GFR is less than 20-25% of normal. The kidneys cannot regulate volume and solute composition, and patients develop edemia, metabolic acidosis, and hyperkalemia. Overt uremia may ensue, with neurologic, gastrointestinal and cardiovascular complications. Stage 4 **end-stage renal disease** GFR is less than 5% of normal; this is the terminal stage of uremia. The major characteristic of normal glomerular filtration are an extraordinarily high permeability to water and small solutes, and impermeability to proteins, such as molecules of the size of albumin (~3.6 nm radius; 70 kilodaltons [kD] molecular weight or larger (Alpers '10: 907, 910).

A century ago, two French investigators reported that small amounts of plasma from anemic rabbits injected into normal animals caused an increase in red blood cell production (**erythropoiesis**) within a few hours. They referred to this activity as **hemopoietine.** Over time, as investigators became more convinced that this red-blood-cell stimulating activity was caused by a single protein in the blood plasma, they gave it a variety of names – erythropoietic-stimulating activity, erythropoietic-stimulating factor, and, ultimately, "erythropoietin." Refining the work of the French scientists in the 1950s and 60s, American investigators conclusively showed that a hormone stimulated red cell production, and that the kidneys were the primary source of erythropoietin, and that low oxygen was the main driver of erythropoietin production. Soon, researchers found that patients with anemia responded by increasing their levels of erythropoietin to stimulate increased red blood cell production. Patients who required an increase in red blood cells in order to make up for low oxygen levels in the blood (such as patients with lung disease living at high altitudes, or smoking more than a pack of cigarettes a day) also had elevated erythropoietin levels. In the early 1960s came the development of **hemodialysis**, a method of removing waste products from the blood when the kidneys are unable to perform this function, to sustain the lives of patients with end-stage kidney disease. As a result of this treatment advance, these patients were able to survive the underlying disease, but their damaged kidneys could no longer make erythropoietin, leaving them severely anemic and in desperate need of Epo therapy. In 1983, scientists discovered a method for mass producing a synthetic version of the hormone. Experiments were conducted to test the safety and effectiveness of the new drug, **Epo**, for treating anemia in patients with kidney failure. The results of these early clinical trials were dramatic. Patients who had been dependent on frequent blood transfusions were able to increase their red blood cell levels to near-normal within just a few weeks of starting therapy. Patients' appetites returned, and they resumed their active lives. It was the convergence of two technologies – long-term dialysis and molecular biology – that set the stage for anemia management in this group of patients. Since then, millions of patients worldwide have benefited from Epo therapy (Adamsom '08).

In some patients with **rapidly progressive (crescentic) glomerulonephritis**, exhibiting hematuria with red blood cell casts in the urine, variable hypertension and edema, antibodies produce the clinical picture of pulmonary hemorrhage associated with renal failure known as **Goodpasture syndrome** treated with plasmapheresis to remove the pathogenic circulating antibodies and immunosuppression. Exposure to viruses and hydrocarbon solvents has been implicated. Crescentic glomuleronephritis can also be caused by immune complex deposition or pauci-immune type with circulating anti-neutrophil cytoplasmic antibodies (ANCAs). 1 to 7% of patients treated for rheumathoid arthritis with drugs such as penicillamine, captopril, gold, develop **membranous glomerulopathy**. Underlying malignant tumors are present in as many as 5-10% of adults with membranous glomerulopathy that can be caused by chronic hepatitis B or

C, syphilis, schistosomiasis, malaria, Systemic Lupus Erythomatous (SLE), or autoimmune disorders such as thyroiditis but in 85% of patients no associated condition is discovered and the condition is considered idiopathic. Although proteinuria persists in more than 60% of patients, only about 10% die or progress to renal failure within 10 years. **Minimal-change disease** can be caused by non-steroidal anti-inflammatory drugs (NSAIDs), and although there are no immune deposits, tends to respond well to corticosteroids and other immunosuppressive therapies.

Focal segmental glomerulonephrosis is characterized by sclerosis of some but not all, glomeruli and can be a primary disease or secondary disease due to HIV infection, sickle-cell disease, massive obesity, scarring and accounts for 10-35% of cases of neophrotic syndrome in children and adults in the United States particularly in Hispanic and African-American patients, there is a poor response to corticosteroid therapy, and 50% develop end-state renal disease in 10 years. 20% of patients follow an unusually rapid course, with intractable massive proteinuria ending in renal failure within 2 years. Recurrences are seen in 25% to 50% of patients receiving allografts. **Membranoproliterative glomerulonephritis** (MPGN) accounts for 10-20% of cases of nephrotic syndrome in children and young adults. Glomerular immune deposits are thought to derive from infections by hepatitis B and C viruses. About 50% develop chronic renal failure within 10 years. Treatment with steroids, immunosuppressive agents and antiplatelet drugs have not proved to be effective, There is a high incidence of recurrence in transplant recipients, particularly in dense deposit disease recurrence happens in 90% of patients although renal failure in the allograft is much less common. Secondary MPGN can result from SLE, hepatitis B and C, cryoglobulinemia, endocarditis, infected ventriculoatrial shunts, chronic visceral abscesses, HIV infection, schostosomiasis, α_1-Antitrypsin deficiency, malignant diseases such as chornic lymphocytic leukemia and lymphoma and hereditary deficiencies of complement regulatory proteins (Alpers '10: 920, 922, 925).

IgA Nephropathy (**Berger Disease**) has prominent IgA deposits that occur with increased frequency with Henoch-Schönlein purpura, gluten enteropathy (celiac disease) and liver disease. The disease affects people of any age, but older children and young adults are most commonly affected. The hematuria typically lasts for several days and then subsides, only to return every few months. Many patients maintain normal renal function for decades. Slow progression to chronic renal failure occurs in 15-40% of cases over a period of 20 years. Recurrence of IgA deposits in transplanted kidneys is frequent and 15% develop another progressive disease. **Alport Syndrome** is a hereditary nephritis that is manifest by hematuria with progression to chronic renal failure, accompanies by nerve deafness and various eye disorders, including lens dislocation, posterior cataracts and corneal dystrophy. The disease is inherited as an X-linked trait in 85% of cases with males expressing the full syndrome and females as carriers limited to hematuria although autosomal recessive and autosomal dominant pedigrees exist. Symptoms appear at ages 5 to 20 years, and the onset of overt renal failure is between the ages of 20 and 50 years in men. **Thin basement membrane lesion** (Benign Familial Hematuria) is a fairly common hereditary entity manifested clinically by familial asymptomatic hematuria and diffuse thinning of the GBM to between 150 and 250 nm (compared with 300-400 nm in normal adults) renal function is normal and prognosis is excellent but most patients are heterozygous for the defective gene and may be carriers, homozygotes or compound heterozygotes may progress to renal failure (Alpers '10: 929-933).

Chronic glomerulonephritis is best considered a pool of end-stage glomerular disease fed by several streams of specific types of glomerulonephritis. Patients with crescentic glomerulonephritis, if they survive the acute episode, usually progress to chronic

glomerulonephritis, membranous nephropathy, MPGN, IgA nephropathy and FSDS all may progress to chronic renal failure, but there are unexplained cases of obliteration of the glomeruli. Because hypertension is an accompaniment of chronic glomerulonephritis, arterial and arteriolar sclerosis may be conspicuous. Kidneys from patients with end-stage disease on long-term dialysis show a variety of changes that are unrelated to the primary disease, including arterial intimal thickening, extensive deposition of calcium oxalate crystals, acquired cystic disease and uremic complications such as uremic pericarditis, uremic gastroenteritis, secondary hyperparathyroidism and left ventricular hypertrophy due to hypertension. Patients often present with such nonspecific complaints as loss of appetite, anemia, vomiting or weakness. In some, renal disease is suspected with the discovery of proteinuria, hypertension or azotemia on routine medical examination. In others, the underlying renal disorder is discovered in the course of investigating edema. Most patients are hypertensive and sometimes the dominant clinical manifestations are cerebral or cardiovascular. Advanced or end-stage kidney disease occurs in as many as 40% of both insulin-dependent type 1 diabetics and type 2 diabetics. The term **diabetic nephropathy** describes the conglomerate of lesions that occur on the glomeruli. Deposits of amyloid, typically light-chain (AL) or AA type, Congo red-positive, eventually obliterate the glomerulus completely and the kidney may increase in size. Goodpasture syndrome, microscopic polyangiitis, Wegener granulomatosis, essential mixed cryoglobulinemia, plasma cell dyscrasias and multiple myeloma are commonly associated with glomerular lesions (Alper '10: 933-935) treated as neoplasms, probably of fungal origin.

Acute kidney injury (AKI) is a reversible renal lesion that causes 50% of case of acute renal failure in hospitalized patients and can be caused by ischemic or toxic tubular injury and acute renal failure or inflammatory reaction of the tubules and interstitium (tubulo-interstitial nephritis). In AKI there is a rapid reduction of renal function and urine flow, falling within 24 hours to less than 400 mL per day. It can be caused by ischemia, direct toxic injury by drugs, such as gentamicin and other antibiotics, poisons (heavy metals such as mercury), organic solvents (e.g. carbon tetrachloride), pancreatitis, radiocontrast dyes, myoglobin, hemoglobin, radiation or urinary obstruction by tumors, prostatic hypertrophy or blood clots. The clinical course of AKI is variable but he classic case may be divided into (1) initiation phase lasting about 36 hours dominated by the inciting medical, surgical or obstetric event with a slight decline in urine output and rise in BUN, declining GFR and blood flow explaining oliguria; (2) maintenance phase with sustained decreases in urine output to between 40 to 400 mL/day (oliguria), salt and water overload, rising BUN concentrations, hyperkalemia, metabolic acidosis and other manifestations of uremia. With appropriate attention to the balance of water and blood electrolytes, including dialysis, the patint can be supported through this oliguric crisis; and (3) the recovery phase has a steady increase in urine volume that may reach up to 3 L/day. The tubules are still damaged, so large amounts of water, sodium and potassium are lost in the flood of urine. Hypokalemia, rather than hyperkalemia becomes a clinical problem and there is a peculiar increased vulnerability to infection at this stage. Eventually, renal tubular function is restored and concentrating ability improves, BUN and creatinine levels return to normal. Tubular functional impairment may persist for months, but most patients who reach this phase recover completely. The prognosis of AKI depends on the clinical setting, recovery is expected with nephrotoxic AKI when the toxin has not caused serious damage to other organs, such as the liver or heart. With current supportive care, 95% recover but with shock related to sepsis, extensive burns, or other causes of multi-organ failure, the mortality rate can rise to more than 50%. Up to 50% of patients with AKI do not have oliguria and instead have increased urine volumes and tend to follow a more benign clinical course. (Alper '10: 935-938).

An increasing number of drugs are known to be **nephrotoxic**. First reported after the use of sulfonamides, acute tubulointerstitial nephritis and renal papillary necrosis most frequently occurs with synthetic penicillins (methicillin, ampicillin) other synthetic antibiotics (rifampin), diuretics (thiazides), allopurinol, cimetidine, aristolochic acid found in some herbal remedies, NSAIDs, analgesics mixtures including phenacetin, aspirin, caffeine, acetaminophen and codeine. Selective COX-2 inhibitors, while sparing the gastrointestinal tract, affect the kidneys. Acute uric acid nephropathy can be caused by the precipitation of uric acid crystals in the renal tubes particularly in individuals with leukemias and lymphomas who are undergoing chemotherapy whereas the drugs induce death of tumor cels and uric acid is produced as relased nucleic acids are broken down. Gouty nephropathy is often precipitated by the consumption of moonshine whiskey contaminated with lead. Papillary necrosis is readily induced experimentally by a mixture of aspirin and phenacetin, usually combined with water depletion. The disease begins about 15 days (2-40) after exposure to the drug and characterized by fever, eosinophilia, a rash in 25% of patients and renal abnormalities in the form of hematuria, mild proteinuria and lukocyturia (often including eosinophils). A rising serum creatinine level or acute renal failure with oliguria develops in about 50% of cases, particularly older patients. Withdrawal from the offending drug is followed by recovery, although it may take several month, and irreversible damage occurs occasionally in older subjects. While drugs are the leading cause of acute interstitial nephritis in 30-40% of patients no offending drug or mechanism can be found. Urinary tract infections complicate 50% of cases (Alper '10: 944-946).

Disorders associated with **hypercalcemia**, such as hyperparathyroidism, multiple myeloma, vitamin D intoxication, metastatic cancer, or excess calcium intake (milk-alkali syndrome) may induce the formation of calcium stones and deposition of calcium in the kidney (nephrocalcinosis) which can lead to chronic tubulointerstitial disease and renal insufficiency. The earliest functional defect is an inability to concentrate the urine. Other tubular defects, such as tubular acidosis and salt-losing nephritis, may also occur. Extensive accumulations of calcium phosphate crystals can occur in patients consuming high doses of oral phosphate solutions in preparation for colonoscopy, presenting as renal insufficiency several weeks after exposure. Nonrenal malignant tumors, particularly those of hematopoietic origin, affect ht ekidneyas in several ways. The most common involvements are tubulo-interstitial, caused by complications of the tumor (hypercalcemia, hyperuricemia, obstruction of ureters) or therapy (irradiation, hyperuricemia, chemotherapy, injections in immunosuppressed patients). As the survival rate of persons with malignant neoplasms increases, so do these renal complications. Overt renal insufficiency occurs in half of those with multiple myeloma and related lymphoplasmacytic disorders. The main cause of renal dysfunction is related to the Bence Jones (light-chain) proteinuria. Amyloidosis formed from free light chains occur in 6-24% of individuals with myeloma. Light-chain deposition disease can cause glomerulopathy or tubulointerstitial nephritis. Hypercalcemia and hyperuricemia are often present in these patients. In the most common form, chronic renal failure develops insidiously and usually progresses slowly during a period of several months to years. Another form occurs suddenly and is manifested by acute renal failure with oliguria. Precipitating factors in these patients include dehydration, hypercalcemia, acute infection and treatment with nephrotoxic antibiotics, mistakenly used to treat myeloma of fungal origin (Alper '10: 947, 948).

Nearly all diseases of the kidney involve the renal blood vessels secondarily. **Hypertension** is intimately linked to the kidneys because kidney disease can be both the cause and consequence of increased blood pressure. There are benign and malignant nephrosclerosis and renal artery stenosis, lesions associated with hypertension and sundry lesions involving mostly smaller

vessels of the kidney. **Benign nephrosclerosis** is associated with the sclerosis of renal arterioles and small arteries causing focal ischemia of parenchyuma supplied by vessels with thickened walls and narrowed lumens. Nephrosclerosis at autopsy is associated with increasing age, more frequent in blacks than whites, and may be seen in the absence of hypertension. Kidneys are often moderately reduced in size, with average weights of 110 to 130 gm. It is unusual for uncomplicated benign nephrosclerosis to cause renal insuffiiecy or uremia. Although there is usually a moderate reduction in renal bood fow, the GFR is normal or only slightly reduced and occasionally there is mild proteinuria. Hypertension and diabetes mellitus, however, increase the incidence and severity of the lesions. **Malignant nephrosclerosis** is the form of renal disease associated with the malignant or accelerated phase of hypertension. It is relatively uncommon, occurring in 1-5% of all people with elevated blood pressure. In its pure form is usually affects younger individuals and occurs more often in men and in blacks. The turn for the worse seems to result from some sort of vascular damage to the kidneys. Fibrinoid necrosis of the arterioles and small arteies cause the kidneys to become markedly ischemic, and patients with malignant hypertension nhave markedly elevated levels of plasma renin which causes angiotensin II to cause intrarenal vasoconstriction. Aldosterone levels are also elevated, and salt retention contributes to the elevation of blood pressure. The consequences of the markedly elevated blood pressure on the blood vessels throughouth the body are known as malignant arteriosclerosis and the renal disorder is malignant nephrosclerosis. The full blown syndrome is characterized by a systolic pressure greater than 200 mm Hg and diastolic pressures greater than 120 mm Hg, papilledema, retinal hemorrhages, encephalopathy, cardiovascular abnormalities and renal failure. Early symptoms are related to increased intracranial pressure and include headaches, nausea, vomiting and visual impairment, particularly scotomas or spots before the eyes. Hypertensive criss are sometime encountered, characterized by loss of consciousness or convulsions. Soon however, renal failure makes its appearance. The syndrome is a true medical emergency requiring the institution of aggressive and prompt antihypertensive therapy to prevent the development of irreversible renal lesions. Before the introduction of current antihypertensive drugs, malignant hypertension was associated with a 50% mortality rate within 3 months of onset, progressing to 90% within a year. At present, however, 75% of patients survive 5 years, and 50% survive with restoration of pre-crisis renal function (Alper '10: 949-950).

Unilateral renal artery stenosis is a relatively uncommon cause of hypertension, responsible for 2-5% of cases, but it is important because it represents a potentially curable form of hypertension with surgical treatment. 70% of cases of renal artery stenosis involve an occlusion by an atheromatous plaque at the origin of the renal artery, that are more common in men, the remaining 30% are caused by fibromuscular dysplasia of the renal artery, which are more common in women. The hypertensive effect is, at least initially, due to stimulation of renin secreting cells of the juxtaglomerular apparatus and the subsequent production of vasoconstrictor angiotensin II. Many patients with reno-vascular hypertension have elevated plasma or renal vein renin levels, and almost all show a reduction of blood pressure when given drugs that block the activity of angiotensin II. Unilateral renal renin hypersecretion can be normalized after renal revascularization, usually resulting in a decrease of blood pressure. Other factors, however, may contribute to the maintenance of renovascular hypertension after the renin-angiotensin system has initiated it, including sodium retention and possibly endothelin and loss of nitric oxide. **Bilateral renal artery disease**, usually diagnosed definitively by arteriography, seems to be a fairly common cause of chronic ischemia with renal insufficiency in older individuals, sometimes in the absence of hypertension, that is reversible with surgical revascularization. **Atheroembolic renal disease** involving embolization of fragments of atheromatous plaques from the aorta or renal artery into intraparenchymal renal vessels occurs in elderly patients with

severe atherosclerosis, especially after surgery on the abdominal aorta, aortography, or intra-aortic cannulization. These emboli can be recognized in the lumens and walls of arcuate and interlobular arteries by their content of cholesterol crystals, which appear as rhomboid clefts. Frequently they have no clinical significance, however, acute renal failure may develop in elderly patients in whom renal function is already compromised, principally after abdominal surgery or atherosclerotic aneurysms. **Sickle cell nephropathy** can occur in homozygous people with the disease or heterozygous people with the trait. The most common clinical abnormalities are hematuria and diminished concentrating ability (hyposthenuria). Patchy papillary necrosis may occur associated with cortical scarring. Mild to moderate proteinuria is also common, occurring in about 30% of patients.

Diffuse cortical necrosis is an uncommon condition that occurs most frequently after obstetric emergency, such as abrupti placentae (premature separation of the acenta), septic shock, or extensive surgery, giving rise to sudden anuria, terminating rapidly in uremic death. When bilateral and symmetric, it is fatal in the absence of supportive therapy, unilateral or patchy involvement is compatible with survival. Renal infarcts are predisposed by the extensive blood flow to the kidneys (one fourth of the cardiac output), and end-organ nature of the arterial blood supply. Most infarcts are due to embolism. A major source of such emboli is mural thrombosis of the left atrium and ventricle as a result of myocardial infarction. Vegetative endocarditis, aortic aneurysms and aortic atherosclerosis are less frequent sources of emboli. Most renal infarcts are of the white anemic variety. They may be solitary lesions or may be multiple and bilateral. Within 24 hours infarcts become pale, yellow-white areas tat may contain small irregular foci of hemorrhagic discoloration, usually ringed by a zone of intense hyperemia. Many renal infarcts are clinically silent. Sometimes pain with tenderness occurs. Large infarcts of one kidney are probably associated with narrowing of the renal artery or one of its major branches, which in turn may be a cause of hypertension (Alper '10: 953-955).

About 10% of all people are born with potentially significant malformations of the urinary system. Renal dysplasias and hypoplasias account for 20% of chornic renal failure in children. Congenital renal disease can be hereditary but is most often the result of an acquired developmental defect that arises during gestation. Genetic abnormalities may also cause enzymatic or metabolic defets in tubular transport, such as syctinuria and renal tubular acidosis. All except horseshoe kidney are uncommon. **Horseshoe kidney** is caused by fusion of the upper or lower poles of the kidneys produces a horsehoe-shaped structure that is found in 1 in 500 to 1,000 autopsies. Ninety percent tof such kidneys are fused atht hlower pole and 10% are fused ath the upper pole. Agenesis of the kidney can be bilateral, which is incompatible with life, usually encountered in stillborn infants, and is often associated with other congential disorders and leads to early death. Unilatera agenesis is compatible with normal life if no other abnormalities exist. The opposite kidney is usually enlarged as a result of compensatory hypertrophy. Some patients eventualy develop progressive glomerular sclerosis in the remaining kidney. **Hypoplasia** refers to a failure o fhte kidneys to develop to a normal size. This anomaly may occur bilaterally, resulting in renal failure in early childhood, but it is more commonly encountered as a unilateral defect. Most cases probably represent acquired scarring but a truly hypoplastic kidney shows no scars and has a reduced number of renal lobes and pyramids, usually six or fewer. In one form of hypoplastic kidney, oligomeganephronia, the kidney is small with fewer nephrons that are markedly hypertrophied. **Ectopic kidneys** lie either just above the pelvic brim or within the pelvis. They are usualy normal or slightly small in size but otherwise not remarkable, because of their abnormal position, kinking or tortuosity of the ureters may cause some obstruction to urinary flow, which predisposes to bacterial infection.

Multicystic renal dysplasia is characterized by the persistence in the kidney of abnormal structures-cartilage, undifferentiated mesenchyme and immature collecting ductures, and by abnormal lobar organization. Most cases are associated with ureteropelvic obstruction, ureteral agenesis or atresis and other anomalies of the lower urinary tract. Dysplasia, enlargement of the kidney, can be unilateral or bilateral and is almost always cystic. When unilateral surgical nephrectomy is performed, when bilateral renal failure may ultimately result (Alper '10: 954-956).

Cystic diseases of the kidney may be hereditary, developmental or acquired disorders. Besides Multicystic renal dysplasia, explained above, polycystic kidney disease is a hereditary disorder. **Polycystic kidney disease** can be autosomal-dominant (adult) polycystic disease (ADPKD) or autosomal-recessive (childhood) polycystic disease (ARPKD). **ADPKD** is characacterized by multiple expanding cysts of both kidneys that ultimately destroy the renal parenchyma and cause renal failure. It is a common condition affecting roughly 1 of every 400 to 1000 live births and accounting for 5-10% of cases of chronic renal failure requiring transplantation or dialysis. The likelihood of developing renal failure with a PKD1 mutation is less than 5% by 40 years of age, rising to more than 35% by 50, more than 70% at 60 and m ore than 95% by 70. With a PKD2 mutation the odds of renal failure are less than 5% by 50, 15% at 60, and about 45% at 70. Progression is accelereated in blacks (largely correlated with the sickle cell trait), in males, and in the presence of hypertension. Individuals with PKD tend to have external congenital anomalies and about 40% have one to several cysts in the liver (polycystic liver disease) that are usually asymptomatic. Cysts are derived from biliary epithelium. Cysts occur much less frequently in the spleen, pancreas, and lungs. Intracranial berry aneurysms arise in the circle of Willis, and subarachnoid hemorrhages from these account for death in about 4-10% of individuals. Mitral valve prolapse and other cardiac valvular anomalies occur in 20-25% of patients, but most are asymptomatic. Patients may survive for many years with azotemia slowly progressing to uremia. Ultimately, about 40% of adult patients die of coronary or hypertensive heart disease, 25% of infection, 15% of a ruptured berry aneurysm or hypertensive intracerebral hemorrhage, and the rest of other causes. ARPKD is genetically distinct. Patients who survive infancy may develop a peculiar type of congenital hepatic fibrosis. In older children the hepatic disease is the predominant clinical concern. Such patients may develop portal hypertension with splenomegaly (Alper '10: 956- 959).

The three major types of medullary cystic disease are medullary sponge kidney, a relatively common and unusually innocuous structural change, and nephronophthisis and adult-onst medullary cystic disease, which are almost always associated with renal dysfunction. **Medullary sponge kidney** is restricted to lesions consisting of multiple cystic dilations of the collecting ducts in the medulla. The condition occurs in adults and is usually discovered radiographically. The papillary ducts in the medulla are dilated, and small cysts may be present. The cysts are lined by cuboidal epithelium or occasionally by transitional epithelium. **Nephronophthisis and Adult-onset medullary cystic disease** is a group of progressive renal disorders. The common characteristic is the presence of a variable number of cysts in the medulla, usually concentrated at the corticomedullary junction, cortical tubulointerstitial damage is the cause of the eventual renal insufficiency. Some forms are inherited as autosomal recessive traits and usually become manifest in childhood or adolescence. As a group, the nephronophthisis complex is now thought to be the most common genetic cause of end-stage renal disease in children and young adults. Adult-onset medullary cystic disease has an autosomal dominant pattern of transmission and is now considered a distinct entity. Affected children present first with polyuria and polydipsia, reflecting a defect in the concentrating ability

of the renal tubules. Sodium wasting and tubular acidosis are also prominent. The kidneys are small and show cysts in the medulla and small cysts in the cortex. The expected course is progression to terminal renal failure during a period of 5 to 10 years (Alper '10: 959, 960).

The kidneys from patients with end-stage renal disease who have undergone prolonged dialysis sometimes show numerous cortical and medullary cysts, a condition known as **acquired (dialysis associated) cystic disease**. The cysts measure 0.5 to 2 cm in diameter, contain clear fluid, are lined by either hyperplastic or flattened tubular epithelium, and often contain calcium oxalate crystals. The probably form as a result of obstruction of tubules by interstitial fibrosis or by oxalate crystals. Most are asymptomatic, but sometimes the cysts bleed, causing hematuria. The most ominous complication is the development of renal cell carcinoma in the walls of these cysts occuring in 7% of dialyzed patients observed for 10 years. Simple cysts may occur as multiple or single, usually cortical, cystic spaces that vary widely in diameter. They are commonly 1 to 5 cm but may reach 10 cm or more in size. They are translucent, lined by a gray, glistening, smooth membrane, and filed with clear fluid. Simple cysts are a common postmortem finding without clinical significance. The main importance of cysts lies in their differentiation from kidney tumors when they are discovered either incidentally or because of hemorrhage and pain. Radiologic studies show that in contrast to renal tumors, renal cysts have smooth contours, are almost always avascular, and give fluid rather htan solid signals on ultrasonography (Alper '10: 960).

Urinary tract obstruction increases susceptibility to infection and to stone formation, and unrelieved obstruction almost always leads to permanent renal atrophy, termed hydronephrosis or obstructive uropathy. Fortunately many causes of obstruction are surgically correctable or medically treatable. Congenital anomalies can cause posterior urethral valves and urethral strictures, meatal stenosis, bladder neck obstruction, ureteropelvic junction narrowing or obstruction or severe vesicouretera reflux. Urinary calculi, benign prostatic hypertrophy, tumors, carcinoma of the prostate, bladder tumors, retroperitoneal lymphoma and carcinoma of the cervix or uterus, inflammation, prostatitis, ureteritis, urethritis, retroperitoneal fibrosis, sloughed papillae or blood cots, pregnancy, uterine prolapse and cystocele and functional disorders such as spinal cord damage or diabetic nephropathy and other functional abnormalities of the ureter or bladder can all cause obstructive uropathy. Hydronephrosis is the term used to describe dilation of the renal pelvis and clayces associated with progressive atrophy of the kidney due to obstruction of the outflow of urine. Even with complete obstruction, glomerular filtration persists for some time because the filtrate subsequently diffuses back into the renal interstitium and perirenal spaces, where it ultimately returns to the lymphatic and venous systems. Affected calyces and pelvis become dilated. The high pressure in the pelvis transmitted back through the collecting ducts into the cortex, causing renal atrophy, and diminution in inner medullary blood flow. Obstruction also triggers an interstitial inflammatory reaction leading eventually to interstitial fibrosis. In far advanced cases the kidey may become transformed into a thin-walled cystic structure having a diameter of up to 15 to 20 cm. Acute obstruction may provoke pain. Unilateral complete or partial hydronephrosis may remain silent for long periods, since the unaffected kidney can maintain adequate renal function. In bilateral partial obstruction the earliest manifestation is inability to concentrate urine, reflected by polyuria and nocturia. Hypertension is common in such patients. Complete bilateral obstruction results in oliguria or anuria and is incompatible with survival unless the obstruction is relieved. After relief of complete urinary tract obstruction, postobstructive diuresis occurs, this can be massive, with the kidney excreting large amounts of urine that is rich in sodium chloride (Alper '10: 961, 962).

Stones may form at any level in the urinary tract, but most arisein the kidney. **Urolithiasis** is a frequent clinical problem affecting 5-10% of Americans in their lifetime. Men are affected more often than women, and the peak age at onset is between 20 and 30 years. Familial and hereditary predisposition has long been known. Many inborn errors of metabolism, such as gout, cystinuria and primary hyperoxaluria, provide examples of hereditary disease characterized by excessive production and excretion of stone-forming substances. There are four main types of calculi (1) calcium stones (about 70%), composed largely of calcium oxalate or calcium oxalate mixed with calcium phosphate, (2) another 15% are triple stones or struvite stones, composed of magnesium ammonium phosphate formed largely after infections by bacteria (e.g. Proteus and stone staphylococci) and can get huge (3) 5 to 10% are uric acid stones, common in people with hyperurecemia, like gout, and radioluscent (4) 1 to 2% are made up of cystine caused by genetic defects it eh renal reabsorption of amino acids, including cysteine, leading to cystinuria. An organic mucoprotein matrix, making up 1 to 5% of the stone by weight, is present in all calculi. Although there are many causes for the formation of stones the most important is an increased urinary concentration of the stones' constituents, such that it exceeds their solubility (supersaturation). Stones are of importance when they obstruct urinary glow or produce ulceration and bleeding and may cause significant renal damage. In general smaller stones are most hazardous, because they may pass into the ureters, producing colic, one of the most intense forms of pain. Larger stones cannot enter the ureters and are more likely to remain silent within the renal pelvis first manifesting by hematuria. Stones also predispose to superimposed infection (Alper '10: 962, 963). Stonebreaker (Chanca piedra) is a tincture that cures kidney, urinary and gallstones overnight.

Most kidney stones won't require invasive treatment. A small stone may be passed by: **Drinking water.** Drinking as much as 2 to 3 quarts (1.9 to 2.8 liters) a day may help flush out the urinary system. **Large and symptomatic kidney stones** that aren't treated with Stonebreaker — either because they're too large to pass on their own or because they cause bleeding, kidney damage or ongoing urinary tract infections — may require more invasive treatment. Procedures may include: **Using sound waves to break up stones.** For certain kidney stones — depending on size and location — a doctor may recommend a procedure called extracorporeal shock wave lithotripsy (SWL). SWL uses sound waves to create strong vibrations (shock waves) that break the stones into tiny pieces that can be passed in your urine. The procedure lasts about 45 to 60 minutes and can cause moderate pain, so sedation or light anesthesia is administered to make the patient comfortable. SWL can cause blood in the urine, bruising on the back or abdomen, bleeding around the kidney and other adjacent organs, and discomfort as the stone fragments pass through the urinary tract.

A procedure called **percutaneous nephrolithotomy** (nef-row-lih-THOT-uh-me) involves surgically removing extremely large kidney stone(s) using small telescopes and instruments inserted through a small incision in your back. General anesthesia is administered during the surgery and the patient is hospitalized for one to two days to recover. A doctor may recommend this surgery if SWL was unsuccessful or if the stone is very large. **Using a scope to remove stones** is done **t**o remove a smaller stone in the ureter or kidney. A doctor may pass a thin lighted tube (ureteroscope) equipped with a camera through the urethra and bladder to the ureter. Once the stone is located, special tools can snare the stone or break it into pieces that will pass in your urine. The doctor may then place a small tube (stent) in the ureter to relieve swelling and promote healing. The patient may need general or local anesthesia during this procedure. **Parathyroid gland surgery** is performed if **s**ome calcium stones are caused by overactive parathyroid glands, which are located on the four corners of your thyroid gland, just below your

Adam's apple. When these glands produce too much parathyroid hormone (hyperparathyroidism), calcium levels can become too high and kidney stones may form as a result. Hyperparathyroidism sometimes occurs when a small, benign tumor forms in one of the parathyroid glands or another condition leads these glands to produce more parathyroid hormone. Removing the growth from the gland stops the formation of kidney stones. Or a doctor may recommend treatment of the condition that's causing your parathyroid gland to overproduce the hormone. Surgery is the most common treatment for primary hyperparathyroidism and provides a cure in at least 90 percent of all cases. A surgeon will remove only those glands that are enlarged or have a tumor (adenoma). If all four glands are affected, a surgeon will likely remove only three glands and perhaps a portion of the fourth — leaving some functioning parathyroid tissue. Surgery may be done as an outpatient procedure.

Medications to treat hyperparathyroidism include: **Calcimimetics,** a drug that mimics calcium circulating in the blood. Therefore, the drug may trick the parathyroid glands into releasing less parathyroid hormone. This drug is sold as cinacalcet (Sensipar). The Food and Drug Administration approved cinacalcet to treat hyperparathyroidism caused by chronic kidney disease or parathyroid cancer. Some doctors may prescribe it to treat primary hyperparathyroidism, particularly if surgery hasn't successfully cured the disorder or a person isn't a good candidate for surgery. **Hormone replacement therapy**, for women who have gone through menopause and have signs of osteoporosis, hormone replacement therapy may help bones retain calcium and is also reported to reduce the risk of heart disease, but five to ten years of regular use are apparently needed to gain these benefits. This treatment, usually a combination estrogen and progestin, doesn't address the underlying problems with the parathyroid glands. Prolonged use of hormone replacement therapy can increase the risk of cardiovascular disease and some cancers. **Bisphosphonates.** Bisphosphonates also prevent the loss of calcium from bones and may lessen osteoporosis caused by hyperparathyroidism.

Both benign and malignant tumors occur in the kidney. With the exception of oncocytoma, the benign tumors rarely cause clinical problems. **Renal papillary adenoma** are small, discrete adenomas arising from the renal tubular epithelium and are found commonly in 7 to 22% at autopsy. **Angiomyolipoma** consists of vessels, smooth muscle and fat and are present in 25 to 50% of patients with tuberous sclerosis, a disease caused by loss-of-function mutations in the TSC1 or TSC2 tumor suppressor genes. It is characterized by lesions of the cerebral cortex that produce epilepsy and mental retardation, a variety of skin abnormalities and unusual benign tumors at other sites, such as the heart and kidneys. They are susceptible to spontaneous hemorrhage. **Oncocytoma** is an epithelial tumor composed of large eosinophilic cells having small, round, benign-appearing nuclei that have large nucleoli. It is not an uncommon tumor, accounting for approximately 5 to 15% of surgically resected renal neoplasms. The tumors are tan or mahogany brown, and well encapsulated, however, they may achieve a large size (up to 12 cm in diameter). Malignant tumors on the other hand, are of great significance. The most common of these malignant tumors is renal cell carcinoma, followed by Wilms tumor, which is found in children and urothelial tumors of the calyces and pelves.

Renal cell carcinoma (adenocarcinoma of the kidney) represent about 3% of all newly diagnosed visceral cancers in the United States and account for 85% of renal cancers in adults. There are approximately 30,000 new cases per year and 12,000 deaths. The tumors occur most often in older individuals, usually in the sixth and seventh decades of life and show a 2:1 male preponderance. Tobacco is the most significant risk factor and cigarette smokers have double the incidence of renal cell carcinoma. Additional risk factors include obesity (particularly in

women), hypertension, unopposed estrogen therapy and exposure to asbestos, petroleum products, and heavy metals. There is an increased incidence in patients with chronic renal failure and acquired cystic disease and in tuberous sclerosis. Although they account for only 4% of renal cancers, familial variants are instructive and include: (1) Von Hippel-Lindau (VHL) syndrome with half to two thirds developing renal cysts and bilateral, often multiple renal cell carcinomas; (2) hereditary (familial) clear cell carcinoma, and (3) hereditary papillary carcinoma an autosomal dominant form manifested by multiple bilateral tumors with pappilary histology, cytogenic abnormalities and mutations in the MET proto-oncogene. Clear cell carcinoma is the most common type accounting for 70 to 80% of renal cell cancer. Papillary carcinoma accounts for 10 to 15% of renal cancers. The three classic diagnostic features of renal cell carcinoma are costovertebral pain, palpable mass and hematuria, but these are seen in only 10% of cases. Hematuria is the most reliable, but may be microscopic and tumors may reach 10 cm before being discovered. Renal cell carcinoma is classified as one of the great mimics in medicine because it tends to produce a diversity of systemic symptoms not related to the kidney. In addition to fever and constitutional symptoms, renal cell carcinomas produce a number of paraneoplastic syndromes ascribed to abnormal hormone production, including polycythemia, hypercalcemia, hypertension, hepatic dysfunction, feminization or masculinization, Cushing syndrome, eosinophilia, leukemoid reactions and amyloidis. One of the common characteristics of this tumor is its tendency to metastasize widely before giving rise to any local symptoms or signs. In 25% of new patients with renal cell carcinoma, there is radiologic evidence of metastases at the time of presentation. The most common locations of metastasis are the lungs (more than 50%) and bones (33%) followed by the regional lymph nodes, live adrenal and brain. The average 5-year survival rate of persons with renal cell carcinoma is about 45% and as high as 70% in the absence of distant metastases. With renal vein invasion or extension into the perinephric fat, the figure is reduced to approximately 15 to 20%. Nephrectomy has been the treatment of choice but partial nephrectomy to preserve renal function is being done with increasing frequency and similar outcome. Approximately 5 to 10% of primary renal tumors originate from the urothelium of the renal pelvis and are known as **urothelial carcinomas of the renal pelvis**. These tumors span the range from apparently benign papillomas to invasive urothelial (transitional cell) carcinomas. Urothelial tumors may occasionally be multiple, involving the pelvis, ureters and bladder. In 50% of renal pelvic tumors there is a preexisting or concomitant bladder urothelial tumor. There is an increased risk of urothelial carcinomas of the renal pelvis and bladder in individuals with analgesic nephropathy and Balkan nephropathy. Infiltration of the wall of the pelvis and calyces is common. The prognosis for these tumors is not good. 5 year survival rates vary from 50 to 100% for low-grade non-invasive lesions to 10% with high-grade infiltrating tumors (Alper '10: 963-967).

Immunotherapy is considered one of the standard treatment options for kidney cancer patients with advanced metastatic disease. Well-documented, but very rare, cases of spontaneous regressions in kidney cancer patients with metastatic disease suggest that the immune system can play an important role in the control and potential treatment of this disease. The building blocks of immunotherapy are biologic response modifiers (BRMs). They are substances that enhance the body's immune system and improve its ability to fight cancer. BRMs do their work by regulating the intensity and duration of immune responses. A BRM can be either a manmade drug or a natural substance produced by the body. Several BRMs can boost the body's natural immune defenses. The cytokines are an important family of BRMs that include Interleukin-2 (IL-2) and Interferons. Used either alone or in combination, they have represented the standard in the treatment of kidney cancer. Interleukin-2 is a biologic response modifier (BRM) available for the treatment of advanced kidney cancer. It stimulates the growth of two types of white blood

cells: T cells and “natural killer” (NK) cells. T cells are very important in your body’s fight against cancer because they recognize cancer cells and set off an alarm to the body. The NK cells respond to this alarm and are transformed into lymphokine-activated killer (LAK) cells, which are capable of destroying cancer cells. Proleukin (interleukin-2) was approved by the FDA in 1992 for the treatment of metastatic renal cell carcinoma. A genetically engineered product, recombinant IL-2, is available for use in various therapeutic regimens. Several different routes of administration may be used: IV bolus, subcutaneous (SC), and continuous IV infusion (CIV).

Interferons are widely used to treat kidney cancer, alone or in combination with other drugs. Interferon therapy is typically self-administered by injection under the skin several times per week. Interferons work by “interfering” with the life processes within the cancer cell, preventing its growth and making the cell more susceptible to attack by other elements of the immune system. There are three major types of interferons — alfa, beta, and gamma — but interferon alfa has been most widely studied in the treatment of kidney cancer. Several interferon alfa products are available in the United States and have been used in the treatment of kidney cancer. INTRON* A, a product of Schering Corporation (Kenilworth, NJ), has been designated as interferon alfa-2b. Roferon*-A is manufactured by Roche Laboratories (Nutley, NJ) and has been designated as interferon alfa-2a. These drugs are very similar, and kidney cancer may be treated with either. Most insurance companies recognize the value of interferon alfa in treating kidney cancer and reimburse for this therapy. In several dozen clinical trials, an overall response rate of about 13% has been achieved with interferon alfa.29 However, in patients with high performance status (i.e., lack of symptoms related to their disease), previous nephrectomy, and metastases predominantly in the lung, the major response rate (complete plus partial responses) with interferon alfa treatment is usually from 6 to 10%. It is also recognized that patients who receive interferon alpha, when compared with those who are treated with hormones or chemotherapy, have improved survival rates. Response to interferon alfa is characterized by slow regression of tumors; the average time from start of treatment to objective response is three to four months. The most common side effects of interferon therapy are flu-like in nature.

Though it is not considered a primary form of therapy, radiation can be used in the treatment of kidney cancer that has metastasized to the bone, brain or spine. Although chemotherapy is the standard treatment for most solid tumors, kidney cancer is generally resistant to chemotherapy.35 The reason for the resistance of kidney cancer cells to chemotherapy is not completely understood. However, it is now known that kidney cancer cells produce an overabundance of multidrug-resistance-associated protein, which acts to repel various chemotherapeutic agents away from the cancer cell. 5-Fluorouracil (5FU) appears to be the most effective conventional chemotherapeutic agent currently available for kidney cancer, but response rates are only in the range of 5% to 8%. In 2005 and 2006, the U.S. Food and Drug Administration (FDA) approved the first new medications to treat kidney cancer in more than a decade: sorafenib tosylate and sunitinib malate. Both of these new drugs disrupt the angiogenesis process. Known as tyrosine kinase inhibitors, they interfere with the proteins inside cancer cells, thus interfering with certain cell functions. These drugs are also known as “multi-kinase inhibitors” because they target both the tumor cell and the tumor blood vessel structures. They work by interfering with reproduction of cancer cells as they attempt to grow and divide uncontrollably. They also have the advantage of being administered orally. The goal of treatment with these newer medications is to slow the rate of growth of the cancer and, if possible, shrink the size of existing tumors. Some patients may experience a significant decrease in the amount of cancer in their body. Some patients may not experience shrinkage in the size of their tumors, but have long periods of “stable” disease. A physician will discuss how the cancer is responding to treatment, and will have additional

options to consider for treatment when necessary. It should be noted that some patients will not receive any benefit from a medication. In some cases, a medication that was effective in treating a patient's cancer stops working and other treatment options must be considered. **Sutent** (sunitinib malate) claims to reduce tumor size and is not only seems to be the most highly recommended chemotherapy for kidney cancer, but is available in capsule form for oral consumption, but hepatoxicity and cardiotoxicity has been deadly, it is prescribed once a day for four weeks and two weeks off.

Nexavar (sorafenib tosylate) is a medication that targets the blood supply of a tumor, depriving it of the oxygen and nutrients it needs for growth. By blocking the vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), Nexavar can interfere with the tumor cell's ability to increase its blood supply. By blocking the Raf-kinase pathway, Nexavar can also interfere with tumor cell growth and proliferation. Clinical studies show that it can significantly slow the progression of tumors. In the Phase III trial which led to the FDA approval of Nexavar, the median time for tumor progression was doubled for patients taking Nexavar, compared with patients taking a placebo. **Sutent** (sunitinib malate) also deprives tumor cells of the blood and nutrients needed to grow by interfering with VEGF and PDGF signaling pathways. Sutent was approved by the FDA in 2006 for kidney cancer patients because of its ability to reduce the size of tumors. Clinical studies showed a favorable response rate in patients with metastatic kidney cancer whose tumors had progressed following immunotherapy. **Torisel** (temsirolimus) is another recently approved kidney cancer drug. It was designed to inhibit the mTOR (mammalian target of rapamycin) kinase, which is important in cell growth and cell survival. By blocking the mTOR pathway, Torisel can interfere with the tumor's ability to multiply as well as reducing its ability to stimulate angiogenesis. **Afinitor** (everolimus), approved by the FDA in March 2009, is an orally administered mTOR inhibitor. Afinitor works by blocking a specific protein known as the mammalian target of rapamycin (mTOR) and acts as a multifunctional inhibitor of cell growth and proliferation, angiogenesis, and cell metabolism. The drug is intended for those patients with advanced renal cell cancer who have already tried a kinase inhibitor, such as Sutent or Nexavar. **Votrient** (pazopanib), the sixth drug to be approved for kidney cancer since 2005, is an oral medication that interferes with angiogenesis, the growth of new blood vessels needed for solid tumors to grow. It is a kinase inhibitor indicated for the treatment of patients with advanced renal cell carcinoma. **Inlyta** (axitinib), approved by the FDA in January 2012, is a prescription medicine used to treat advanced kidney cancer (advanced renal cell carcinoma or RCC) when one prior drug treatment for this disease has not worked. As with antibiotics chemotherapeutic drugs require **probiotic supplementation** to avoid vitamin B12 deficiency, chronic diarrhea, pernicious anemia and dental cavities. Curing cancer always requires a vegan diet, **no lipids**, with little or **no protein**, because protein is the primary dietary cancer growth factor, as well as pesticides. A very high level of athletic performance is exhibited by many cancer survivors and **cardiovascular exercise and/or strength exercises** are absolutely necessary to metabolize neoplasms and atherosclerotic plaques.

III.B.9 Leukopenia, Lymphoma, Leukemia and Myeloma

Disorders of white cells may be classified into two broad categories, proliferative and leukopenias characterized by a deficiency of leukocytes. Proliferations of white cells and lymph nodes can be reactive or neoplastic. Reactive proliferation in response to an underlying microbial disease is fairly common. Neoplastic disorders, although less frequent, are much more severe. **Leukopenia** is an abnormally low white cell count usually resulting from reduced numbers of neutrophils (neutropenia, granulocytopenia). **Lymphopenias** are much less

common, and in addition to the congenital immunodeficiency diseases, they are associated with specific clinical syndromes (e.g Hodgkin's disease, nonlymphocytic leukemias, following corticosteroid therapy and occasionally in chronic diseases. Neutropenia, a reduction in the number of granulocytes in the peripheral blood may be seen in a wide variety of circumstance. A marked reduction in neutrophil count predisposes to infection. Inadequate or ineffective granulopoiesis may be encountered with (1) suppression of myeloid stem cells as occurs in aplastic anemia, a variety of leukemias and lymphomas, where granulocytopenia is accompanied by anemia and thrombocytopenia; (2) suppression of the committed granulocytic precursors, which occurs after exposure to certain drugs such as alkylating agents and antimetabolites used in cancer treatment which produce neutropenias in a dose-related fashion and other drugs in an idiosyncratic reaction with aminopyrine, chloramphenicol, sulfonamides, chlorpromazine, thiouracila and phenylbutazone; (3) megloblastic anemias due to vitamin B_{12} or folate deficiency and (4) monoclonal proliferations of CD8+ large granular lymphocytes. Ulcerating necrotizing lesions of the gingiva, floor of the mouth, buccal mucosa, pharynx, or anywhere within the oral cavity (agranulocytic angina) are characteristic of agranulocytosis. The ulcers are typically deep, undermined and covered by gray to green black necrotic membranes for which numerous bacteria or fungi can be isolated. Similar ulcerations may occur less frequently in the skin, vagina, anus, or gastrointestinal tract. In many instances the bacteria and fungi grow in colony formations. The regional lymph nodes draining these infections are enlarged and inflamed but the spleen and liver are rarely enlarged. The symptoms and signs of **neutropenias** are those of bacterial infections – malaise, chills, and fever, followed by weakness and fatigability. In severe agranulocytosis with virtual absence of neutrophils, these infections may become so overwhelming as to cause death within a few days. Characteristically the total white cells count is reduce to 1000 cells per mm^3 of blood, and when counts fall below 500 per mm^3 serious infections tend to occur. In addition to control of bacterial infections with antibiotics, treatment efforts are aimed toward increasing the production of neutrophils by administration of recombinant human granulopoietic factors such as granulocyte-macrophage colony stimulating factor (GM-CSF) and G-CSF (Saunders '94: 630, 631).

Leukocytosis is a common reaction to a variety of inflammatory states. Pyogenic infections are common causes of neutrophilic leukocytosis, but it may as a result from nonmicrobial stimuli, such as tissue necrosis caused by burns or myocardial infarctions. In patients with severe, life-threatening sepsis, in addition to leukocytosis there may be morphologic changes in the neutrophils, such as toxic granulations and cytoplasmic vacuoles. Eosinophilic leukocytosis is characteristic of allergic disorders, such as bronchial asthma, hay fever, parasitic infections and some diseases of the skin. The skin diseases include pemphigus, eczema and dermatitis herpetiformis. In hospitalized adult patients the most likely cause of eosinophilia is an allergic drug reaction. Elevations in monocyte may be seen in several chronic infections including tuberculosis, bacterial endocarditis, brucellosis, rickettsiosis, and malaria. Certain collagaen vascular diseases, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis are associated with monocytosis, as are inflammatory bowel diseases such as ulcerative colitis and Crohn's disease. Lymphocytosis may accompany monocytosis in chronic inflammatory states such as brucellosis and tuberculosis. The lymphocyte count may also be increased in acute viral infections such as viral hepatitis, in cytomegalovirus infections and particularly infectious mononucleosis. In most instances, reactive leukocytosis is easy to distinguish from neoplastic proliferation of the white cells (i.e. leukemias) by the rarity of immature cells in the blood. However, in some inflammatory states, many immature white cells may appear in the blood and a picture of leukemia may be simulated (leukemoid reaction). Infections and other inflammatory

stimuli may not only cause leukocytosis but also involve the lymph nodes, which act as defensive barriers (Saunders ’94: 63, 632).

Malignant proliferative disorders constitute the most important part of white cell disorders. **Malignant lymphomas** take the form of cohesive tumorous lesions, composed mainly of lymphocytes and rarely of histiocytes, that arise in lymphoid tissue anywhere in the body, most commonly within lymph nodes. **Leukemias** and myeloproliferative disorders are neoplasms of the hematopoietic stem cells arising in the bone marrow that secondarily flood the circulating blood or other organs with transformed cells. **Plasma cells dyscrasias** and related disorders usually arising in the bones, take the form of localized or disseminated proliferations of antibody forming cells. Thus, this category is marked by the appearance in the peripheral blood of abnormal levels of complete immunoglobulins or the light or heavy chains of the immunoglobulins. The histiocytoses represent proliferative lesions of histiocytes that include rare histiocytic neoplasms that present as malignant lymphomas,. A special category of histiocytes referred to as Langerhans’ cell histiocytes gives rise to a spectrum of disorders, some of which behave disseminatd malignant tumors and others as localized benign proliferations (Saunders ’94: 633, 634).

The concept that **myeloproliferative disorders** result from clonal neoplastic proliferations of the multipotent myeloid stem cells is well established. Several environmental factors have been implicated in the causation of leukemias and lymphomas. Well-established influences include ionizing radiation, chemicals and alkylating agents used in chemotherapy. Two viruses, HTLV-2 and EBV, have been associated with acute T-cell leukemia/lymphoma and Burkitt’s lymphoma respectively. Recent studies have implicated HTLV-1 and HTLV-2 in the causation of mycosis fungoides as well (Saunders ’94: 658, 656). **Multiple myeloma** is plasma cell cancer that originates in the bone marrow and is characterized by involvement of the skeleton at multiple sites with peak incidence between 50 and 60 years. Infiltration of bone is manifested by pain and stress fractures. Multiple myeloma presents most often as multifocal destructive bone lesions throughout the skeletal system vertebral column 66%, ribs 44%, skull 41%, pelvis 28%, femur 24% clavicle 10% and scapula 10%. Focal lesions begin in the medullary cavity, and progressively destroy the cortical bone. Fractures are often produced by plasma cell lesions. On section, the bony defects are typically filled with soft, red, gelatinous tissue. Most commonly the lesions appear radiographically as punched out defects, usually 1 to 4 cm in diameter. Increased numbers of plasma cells in the marrow constituting 10 to 90% of total. Renal involvement, generally called myeloma nephrosis, causes abnormal plasma cells to be encountered or at least proteinaceous casts surrounded by giant cells, and hypercalcemia and pyelonephritis may occur. Hypercalcemia resulting from bone resorption may give rise to neurologic manifestations such as confusion, weakness, lethargy, constipation and polyuria. Recurrent infections with bacteria such as *Streptococcus pneumonia*, *Staphylococcus aureus* and *E. coli* resulting from severe suppression of normal immunoglobulins, also pose a major clinical problem. In 99% of patients with multiple myeloma, electrophoretic analysis reveals increases levels of immunoglobulins in the blood and/or light chains (Bence Jones proteins) in the urine. It may also spread to extraosseous sites. Renal insufficiency is the second leading cause of death after infection. The neoplastic plasma cells synthesize complete or incomplete immunoglobulins. Diagnosis rests on radiographic and laboratory findings. The lesions appear as sharply punched out defects having a rounded soap-buble appearance on x-ray film, but generalized osteoporosis may be seen. Marrow examination revels aggregates of plasma cells that suppress and replace normal hematopoietic elements. The resultant marrow failure gives rise to a normocytic normochromic anemia, sometimes accompanied by moderate leukopenia and thrombocytopenia. Rarely plasma

cells flood the peripheral blood, giving rise to plasma cell leukemia. Prognosis depends on the stage at the time of diagnosis. Patients with multiple bony lesions, if untreated, rarely survive for more than 6 to 12 months. Chemotherapy in the form of alkylating agents induces remission in 50 to 70% of patients, bu the median survival is still a dismal 3 years. Autologous and allogeneic bone marrow transplantation after intensive chemotherapy offers the promise of cure. High serum levels of cytokine IL-6 is associated with a poor prognosis. Loss of bone is in large part due to osteoclastic reabsorption induced by the tumor. **Solitary myeloma (plasmacytoma)** lesion occurs in 3 to 5% of monoclonal gammopathies. Estaosseous lesions are often located in the lungs, oronaspharynx, or nasal sinuses. Progression to classic multiple myeloma becomes manifest in most patients with osseous plasmacytoma, whereas extaosseous primaries rarely disseminate. Solitary plamacytoma involving the bones is an early stage of multiple myeloma, but in some individual sit may be present for 10 to 20 years without progression. Extraosseous plasmacytomas, particularly involving the upper respiratory tract, are limited disease that can usually be cured by local resection (Saunders ’94: 663-665).

Plasma cell dyscrasias account for 15% of all deaths from malignant white cell disease. Plasma cell myeloma is the most important and most common syndrome characterized by multiple neoplastic tumorous masses of plasma cells scattered throughout the skeletal system. Waldenström’s macroglobulinemia associated with lymphadenopathy and hepatosplenomegaly, but the lytic bone lesions are not present. Heavy-chain disease is rare gammopathy infiltrating plasma cells and precursors that synthesize only heavy chains. Primary or immunocyte associated amyloidosis is a monoclonal proliferation of plasma cells, with excessive production of free light chains that are deposite as amyloid. Monoclonal gammopathy of undetermined significant. Expansion of incomplete monoclonal immunoglobulin secreting cells in the plasma and/or urine called dyscracias, gammopathies, monoclonal gammopathies, dysproteinemias, and paraproteinemias (Saunders ’94: 662, 663). Normocytic, normochromic anemia is present in 60% of patients at diagnosis. It is due primarily to the decreased production of red blood cells by marrow, infiltration with plasma cells, and the suppressive effect of various cytokines. Patients with renal failure may also have decreased levels of erythropoietin (Drug information on erythropoietin), which can worsen the degree of anemia. Among newly diagnosed patients, up to 20% have hypercalcemia (corrected serum calcium level > 11.5 mg/dL) secondary to progressive bone destruction, which may be exacerbated by prolonged immobility, especially in the context of fracture. Hypercalcemia should be suspected in patients with myeloma who have nausea, fatigue, confusion, polyuria, or constipation. It may also suggest high tumor burden. It should be considered an oncologic emergency and requires prompt treatment with aggressive hydration, use of bisphosphonates, calcitonin, and antimyeloma therapy, including steroids. Approximately 20% of patients present with renal insufficiency and at least another 20% to 40% develop this complication in later phases of the disease. Light-chain cast nephropathy is the most common cause of renal failure. Additional causes include hypercalcemia, dehydration, and hyperuricemia. Less commonly, amyloidosis, light-chain deposition disease, nonsteroidal anti-inflammatory agents taken for pain control, intravenous radiographic contrast administration, and calcium stones may contribute to renal failure. Bisphosphonate therapy has been associated with the kidney problem azotemia, which is usually reversible with treatment cessation.

Common Laboratory Features of Plasma Cell Dyscracias and Myeloma

Disease	Laboratory Features
Multiple Myeloma	Marrow plasmacytosis >10%

	Clonal immunoglobulin peak > 3.0 g/dL Presence of Bence-Jones protein Lytic bone lesions and/or diffuse osteopenia Related organ or tissue impairment
Smoldering myeloma	Monoclonal immunoglobin level > 3.0 g/dL No symptoms due to plasma cell dyscracia No lytic bone disease Normal calcium and renal function No anemia
Solitary plasmocytoma of bone	Solitary lesion due to plasma cell tumor Normal skeletal survey and MRI of skull, spine and pelvis Normal bone marrow plasmacytosis No anemia, hypercalcemia or renal disease Preserved levels of uninvolved immunoglobulins
Monoclonal gammopathy of unkown significance (MGUS)	Monoclonal immunoglobin level < 3.0 g/dL Bone marrow plasma cells < 10% No bone lesions No symptoms due to plasma cell dyscracia Usually preserved levels of uninvolved immunoglobulins No related organ or tissue impairment

Source: Jagannath. Cancernetwork '11

Oral Thalidomide, used in conjunction with dexamethsaome, a corticosteroid, are the first FDA approved drugs usually taken by people diagnosed with multiple myeloma and plasma cell dyscracias. Others include: Bortezomib, Carfilzomib, Clafen (Cyclophosphamide), Cyclophosphamide, Cytoxan (Cyclophosphamide), Doxil (Doxorubicin Hydrochloride Liposome), Doxorubicin Hydrochloride Liposome, Dox-SL (Doxorubicin Hydrochloride Liposome), Evacet (Doxorubicin Hydrochloride Liposome), Kyprolis (Carfilzomib), Lenalidomide, LipoDox (Doxorubicin Hydrochloride Liposome), Mozobil (Plerixafor), Neosar (Cyclophosphamide), Plerixafor Pomalidomide (Pomalyst), Pomalyst, Revlimid (Lenalidomide), Synovir (Thalidomide), Thalidomide, Thalomid (Thalidomide), Velcade (Bortezomib), Zoledronic Acid Zometa (Zoledronic Acid). Radiation therapy may be done to relieve bone pain or treat a bone tumor. Two types of bone marrow transplantation may be tried: Autologous bone marrow or stem cell transplantation makes use of one's own stem cells. Allogeneic transplant makes use of someone else's stem cells. This treatment carries serious risks but offers the chance of improved survival. Many patients with myeloma develop bacterial infections that may be serious, and infectious complications remain the most common cause of death in myeloma patients. In the past, gram-positive organisms (eg, *Streptococcus pneumoniae, Staphylococcus aureus*) and *Haemophilus influenzae* were the most common pathogens. More recently, however, infections with gram-negative organisms, anaerobes, and fungi have become frequent. The increased susceptibility of patients with multiple myeloma to bacterial infections, specifically with encapsulated organisms, has been attributed to impairments of host-defense mechanisms, such as hypogammaglobulinemia, qualitative deficiency in immunoglobulin function, granulocytopenia, decreased cell-mediated immunity, and the prolonged use of steroids.

Waldenström macroblobulinemia, constituting about 5% of monoclonal gammopathies, is a disease of old age, usually the sixth and seventh decades. Half of patients have lymphadenopathy, hepatomegaly and splenomegaly. Visual impairment from distention and hemorrhage of retinal veins, neurologic problems such as headaches, dizziness, dafness and stupor, from sluggish blood flow; bleeding , cryoglobulinemia from precipitation of macroglobulins at low temperatures produces symptoms such as Raynaud's phenomenon and cold urticarial. It is marked by a diffuse, leukemia-like infiltration of the bone marrow by lymphocytes, plasma cells and hybrid forms that synthesize a monoclonal IgM immunoglobulin, leading to macroglobulinemia. The tumor cells diffusely infiltrate the lymphoid tissues, including bone marrow, spleen and lymph nodes. **Heavy chain disease** is an extremely rare monoclonal gammopathy characterized by elevated levels in the blood or urine of specific heavy chain immunoglobulins. Gamma-chain disease is found most often in the elderly, and resembles malignant lymphoma, manifesting in lymphadenopathy, anemia, and fever, often accompanied by malaise, weakness and hepatomegaly or splenomegaly. The course can be rapidly downhill to death within a few months or protracted for years. Alpha-chain disease is most common occurring mostly in young adults in the Mediterranean area. Mu-chain disease is the rarest, most often encountered in patients with chronic lymphocytic leukemia, hepatomegaly and splenomegaly are usually present but peripheral lymphadenopathy is inconspicuous. M proteins can be identified in the serum of 1% of asymptomatic healthy persons older than 50 years of age and in 3% older than 70 years. To this dysproteinemia without associated disease, the term **monoclonal gammopathy of undetermined significance** (MGUS) is applied. MGUS is the most common monoclonal gammopathy. Approximately 20% of patients develop well-defined plasma cell dyscrasia (myeloma, Waldenström's macroglubinemia or amyloidosis) over a period of 10 to 15 years. In general patients with MGUS have less than 3 gm/dl of monoclonal protein in the serum and no Bence Jones proteinuria. Whether a given patient will follow a benign course, as most do, or develop well-defined plasma cell neoplasm cannot be predicted wherefore periodic assessment of serum M component levels and Bence Jones proteinuria is warranted (Saunders '94: 665, 666). In recent years, the drugs Fludara (fludarabine) and Leustatin (cladribine) have become the first chemotherapy drugs given to people with Waldenstrom's macroglobulinemia. Sometimes Cytoxan (cyclophosphamide) is added. Other commonly used chemotherapy drugs are Luekeran (chlorambucil) and prednisone, usually given together, or Adriamycin (doxorubicin). Sometimes an individual may start with one combination of drugs, then switch to another combination that is more effective. Another drug used to treat Waldenstrom's macroglobulinemia is Rituxan (rituximab). Some doctors may use this drug for hard-to-treat disease; others may combine it with chemotherapy drugs at the start of treatment. Campath (alemtuzumab) has also been an effective treatment, as has Velcade (bortezomib).

The term histiocytosis is an umbrella designation for a varity of proliferative disorders of histiocytes of macrophages. Some histiocytic lymphomas are clearly malignant but reative histiocytic proliferations in the lymph nodes are benign. The **Langerhans' cell histiocytoses** are associated with tumor like proliferations, but they are not truly neoplastic. The proliferating cell is the Langerhans' cell of marrow origin which is normally found in the epidermis. Langerhans' cell histiocytosis presents as three clincopathoogic entities. Acute disseminated Langerhans' cell histiocytosis (Letterer-Siwe disease) occurs most frequently before two years of age but occasionally may affect adults. Cutaneous lesions resemble a seborrheic eruption secondary to to infiltration of Langerhans' histiocytes over the front and back of the trunk and on the scalp. Most patients have hepatosplenomegaly, lymphadenopathy, pulmonary lesions and eventually destructive osteolytic bone lesions. Extensive infiltration of the marrow often leads to anemia, thrombocytopenia, and predisposition to recurrent infections such as otitis

media and mastoiditis. The course of untreated disease is rapidly fatal with intensive chemotherapy 50% of patients survive 5 years. Unifocal lesions usually affect the skeletal system, they may be asymptomatic or cause pain and tenderness predisposing to stress fracture. It may heal spontaneously or be cured by local excision or irradiation. Multifocal Langerhans' cell histiocytosis usually affects children who present with fever, diffuse eruptions, particularly on the scalp and in the ear canals, and frequent bouts of otitis media, mastoiditis and upper respiratory tract infections. An infiltrate of Langerhans' cells may lead to mild lymphadenopathy, hepatomegaly, and splenomegaly. In about 50% of patients, involvement of the posterior pituitary stalk of the hypothalamus leads to diabetes insipidus,which does not seem to be treated with chemotherapy. The combination of calvarial bone defects, diabetes insipidus and exophthalmos is referred to as the Hand-Schüller-Christain triad. Many patients experience spontaneous regression, others can be treated with chemotherapy (Saunders '94: 666, 667). Langerhans' cell histiocytoses is treated with oral methotrexate (20 mg/m^2) weekly for 6 months or oral thalidomide 50 mg to 200 mg nightly, with prednisone are taken for low risk disease or vinblastine IV and prednisone for patients with more complicated cases requiring radiation and surgery.

The infections that lead to **lymphadenitis** are numerous. Lymph nodes undergo reactive changes whenever challenged by microbiologic agents or their toxic products, or by cell debris and foreign matter introduced into wounds or into the circulation, as in drug addiction. Acutely inflamed nodes are most commonly caused by direct microbiologic drainage and are seen most frequently in the cervical area in association with infections of the teeth or tonsils, or in the axillary or inguinal regions secondary to infections in the extremities. Generalized **acute nonspecific lymphadenopathy** is characteristic of viral infections and bacteremia. The nodal reactions in the abdomen may induce acute abdominal symptoms resembling acute appendicitis. The nodes become swollen, gray-red and engorged to the unaided eye. Clinically, nodes with acute nonspecific lymphadenitis are enlarged because of the cellular infiltration and edema. As a consequence of the distention of the capsule, they are tender to touch. When abscess formation is extensive, they become fluctuant. The overlying skin is frequently red, and sometimes penetration of the infection to the skin surface produces draining sinuses, particularly when the nodes have undergone suppurative necrosis. Healing of such lesions is associated with scarring (Saunders '94: 631, 632).

Chronic nonspecific lymphadenitis assumes one of three patterns depending on their causation (1) follicular hyperplasia, (2) paracortical lymphoid hyperplasia and (3) sinus histiocytosis. Characteristically, lymph nodes in chronic reactions are not tender, because they are not under increased pressure. Chronic lymphadenitis is particularly common in inguinal and axillary nodes. Both groups drain relatively large areas of the body. **Follicular hyperplasia** is caused by chronic infections with microbes that activate B cells such as rheumatoid arthritis, toxoplasmosis, and early stages of human immunodeficiency virus (HIV) infection. It is distinguished by prominence of the large germinal centers, which appear to bulge against the surrounding collar of small B lymphocytes. There is generally striking hyperplasia of the mononuclear phagocytic cells lining the lymphatic sinuses. The lymph node architecture is preserved with normal lymphoid tissue between germinal centers, there is variation in the size and shape of lymphoid nodules and a mixed population of lymphocytes in different stages of differentiation. **Paracortical lymphoid** hyperplasia is characterized by reactive changes within the T-cell regions of the lymph node that encroach on, and sometimes efface the germinal follicles. There is hypertrophy of the sinusoidal and vascular endothelial cells and a mixed cellular infiltrate, principally of macrophages. Such changes are encountered with drugs such as

Dilantin or following smallpox vaccination or other vaccine. **Sinus histiocytosis** refers to distention and prominence of the lymphatic sinusoids, encountered in lymph nodes draining cancers, particularly carcinoma of the breast. The lining endothelial cells are markedly hypertrophied, and the sinuses may be engorged with histiocytes. This pattern of reaction has been thought to represent an immune response on the part of the host against the tumor or its products (Saunders '632, 633).

Lymphomas are malignant neoplasms characterized by the proliferation of cells native to the lymphoid tissues – lymphocytes, histiocytes and their precursors and derivatives. There are no benign lymphomas. Among the broad group of malignant lymphomas, Hodgkin's lymphoma is segregated from all other forms, which constitute the non-Hodgkin's lymphomas. Although both have their origin in the lymphoid tissues, Hodgkin's disease is set apart by the presence of a distinctive morphologic feature, the Reed-Sternberg giant cell. In addition the nodes contain non-neoplastic inflammatory cells, which in most cases outnumber the neoplastic element represented by the Reed-Sternberg cell. Non-Hodgkin's lymphomas (NHL) presents as a localized or generalized lymphadenopathy. Lymph node enlargement due to lymphomatous disease must be differentiated from that caused by the more frequent infectious and inflammatory disorders. Although variable, all forms of lymphoma have the potential to spread from their origin in a single node or chain of nodes to other nodes, and eventually disseminate to the spleen, liver and bone marrow when it creates a leukemia-like picture in the peripheral blood. The vast majority of NHLs (80-85%) are of B cell origin, the remainder are in large part T cell tumors. Growth patterns are either clustered into identifiable nodules or spread diffusely throughout the node. Nodular or follicular architecture has a superior prognosis to that of diffuse pattern. Divided into three prognostic groups, NHLs are designated as low, intermediate and high grade lymphomas with 10 years survival rates of 45, 36 and 23% respectively (Saunders '94: 634-636). Drug for the treatment of Non-Hodgkin's lymphoma are Abitrexate (Methotrexate), Adcetris (Brentuximab Vedotin), Adriamycin PFS (Doxorubicin Hydrochloride), Adriamycin RDF (Doxorubicin Hydrochloride), Ambochlorin (Chlorambucil), Amboclorin (Chlorambucil), Arranon (Nelarabine), Bendamustine Hydrochloride, Bexxar (Tositumomab and Iodine I 131 Tositumomab), Blenoxane (Bleomycin), Bleomycin, Bortezomib, Brentuximab Vedotin, Chlorambucil, Clafen (Cyclophosphamide), Cyclophosphamide, Cytoxan (Cyclophosphamide), Denileukin Diftitox, DepoCyt (Liposomal Cytarabine), Doxorubicin Hydrochloride, DTIC-Dome (Dacarbazine), Folex (Methotrexate), Folex PFS (Methotrexate), Folotyn (Pralatrexate), Ibritumomab Tiuxetan, Intron A (Recombinant Interferon Alfa-2b), Istodax (Romidepsin), Leukeran (Chlorambucil), Linfolizin (Chlorambucil), Liposomal Cytarabine, Matulane (Procarbazine Hydrochloride), Methotrexate, Methotrexate LPF (Methotrexate), Mexate (Methotrexate), Mexate-AQ (Methotrexate), Mozobil (Plerixafor), Nelarabine, Neosar (Cyclophosphamide), Ontak (Denileukin Diftitox), Plerixafor Pralatrexate, Recombinant Interferon Alfa-2b, Rituxan (Rituximab), Rituximab, Romidepsin, Tositumomab and Iodine I 131 Tositumomab, Treanda (Bendamustine Hydrochloride), Velban (Vinblastine Sulfate), Velcade (Bortezomib), Velsar (Vinblastine Sulfate), Vinblastine Sulfate, Vincasar PFS (Vincristine Sulfate), Vincristine Sulfate, Vorinostat, Zevalin (Ibritumomab Tiuxetan), Zolinza (Vorinostat) and combinations CHOP, COPP, CVP, EPOCH, ICE, R-CHOP.

Non-Hodgkin's Lymphomas

Lymphoma type	% of Cases	Morphology	Immuno-	Comments

			phenotype	
Small lymphocytic Lymphoma	3-4	Small unstimulated lymphocytes in a diffuse pattern	>95% B cells	Occurs in old age; generalized lymphadenopathy with marrow involvement and blood picture resembling CLL
Follicular lymphomas	40	Germinal center cells arranged in follicular pattern	B cells	Follicular small cleaved cell type most common; occur in older patients; generalized lymphadenopathy ; difficult to cure
Diffuse lymphomas	40-50	Various cell types; predominantly large germinal center cells, some mixed with smaller cells; others with immunoblastic morphology	~80% B cells ~20% post-thymic T cells	Occur in older patients as well as pediatric age group; greater frequency of extranodal, visceral disease; marrow involvement and leukemia very uncommon at diagnosis and poor prognostic sign; aggressive tumors but up to 60% are curable.
Lymphoblastic lymphoma	4	Cells somewhat larger than lymphocytes; in many cases nuclei markedly lobulated; high mitotic rate	>95% immature intrathymic T cells	Occurs predominantly in children (40% of all childhood lymphomas); prominent mediastinal mass; early involvement of bone marrow and progression to T-cell ALL, very aggressive
Small noncleaved (Burkitt's) Lymphoma	<1	Cells intermediate in size between small lymphocytes and	B cells	Endemic in Africa, sporadic elsewhere; predominantly affects children;

		immunobasts; prominent nucleoli; high mitotic rate		extranodal visceral involvements presenting features; rapidly progressive but responsive to therapy; translocation characteristic
Mycosis fungoides and Sézary Syndrome	Uncommon	Medium to large cells with markedly convoluted (cerebriform) nucleus	CD4+ T cells	Occur in older males; proclivity for involvement of skin in both forms; tumorous masses in mycosis fungoides; Sézary syndrome is a leukemic variant
Adult T-cell leukemia lymphoma	Rare	Very variable; cells may have cerebriform nuclei	CD4+ T cells	Associated with HTLV-1 infection; endemic in Japan and the Caribbean;cutaneous lesions, leukemia, spleen and lymph node involvement; rapidly fatal

Source: Saunders ’94: Table 14-4, 644

Hodgkin’s lymphoma is characterized by the presence of distinctive neoplastic giant cells called Reed-Sternberg (RS) cells, admixed with a variable inflammatory infiltrate and fever. It accounts for 0.7% of all new cancers in the United States (7,400 new cases). It is one of the most common forms of malignancy in young adults, with an average age of at diagnosis of 32 years. It is now considered to be curable in most cases. There are four subtypes of Hodgkin’s disease (1) lymphocyte predominance, (2) mixed cellularity, (3) lymphocyte depletion and (4) nodular sclerosis. The staging of Hodgkin’s disease is of great clinical importance, since the course, choice of therapy and prognosis all are intimately related to the distribution of the disease that must be investigated with lymphangiography or computed tomography of abdomen and pelvis, chest radiograph, biopsy of bone marrow and ultrasonography of liver and spleen. Hodgkin’s disease presents with a painless enlargement of lymph nodes. Younger patients tend to present in clinical stage I or II and are usually free from systemic manifestations. Patients with disseminated disease (stages III and IV) are more likely to present with systemic complaints, such as fever, unexplained weight loss pruritus and anemia. Cutaneous anergy resulting from depressed cell-mediated immunity is seen in most cases. The 5- year survival rate of patients with stages I and IIA is close to 90% and many can be cured. Even with advanced

disease (stages IVA and IVB), 60 to 70% 5 year disease free survival can be achieved. Long-term survivors of chemotherapy and radiotherapy have an increased risk of developing second cancers. Acute nonlymphocytic leukemia and lung cancer lead the list of second malignancies, but also include NHL, breast cancer, gastric cancer and malignant melanoma. The many therapeutic steps forward in the light of this unhappy byproduct, may involve a few steps backward (Saunders '94: 643, 644, 647, 648). Drug treatments for Hodgkin's Lymphoma include Adcetris (Brentuximab Vedotin), Adriamycin PFS (Doxorubicin Hydrochloride), Adriamycin RDF (Doxorubicin Hydrochloride), Ambochlorin (Chlorambucil), Amboclorin (Chlorambucil), Blenoxane (Bleomycin), Bleomycin, Brentuximab Vedotin, Chlorambucil, Clafen (Cyclophosphamide), Cyclophosphamide, Cytoxan (Cyclophosphamide), Dacarbazine, Doxorubicin Hydrochloride, DTIC-Dome (Dacarbazine), Leukeran (Chlorambucil), Linfolizin (Chlorambucil), Lomustine, Matulane (Procarbazine Hydrochloride), Neosar (Cyclophosphamide), Procarbazine Hydrochloride, Velban (Vinblastine Sulfate), Velsar (Vinblastine Sulfate), Vinblastine Sulfate, Vincasar PFS (Vincristine Sulfate), Vincristine Sulfate, combinations; ABVD, ABVE, ABVE-PC, BEACOPP, COPP, ICE, MOPP, STANFORD and VAMP.

The cure of Hodgkin lymphoma in the 20th century is another one of cancer's biggest success stories. Breakthroughs in radiation therapy and chemotherapy paired with surgical removal of metastatic tumors and careful clinical research transformed an invariably fatal disorder into one that is routinely cured. The recognition of late adverse effects from radiation therapy and chemotherapy in the form of second cancers, heart and blood vessel disease, and sterility shaped subsequent research efforts to maintain or improve cure rates with fewer complications, an important goal in a disease that primarily affects individuals in their 20s and 30s. Today, as more than 80 percent of patients are cured after primary treatment. Sir Thomas Hodgkin is credited with the initial description of the clinical disorder that bears his name. In 1832, he reported on a group of patients with enlargement of lymph nodes and spleen that differed from the major known maladies of the day. The introduction of the linear accelerator (a radiation machine used to treat cancer) in the treatment of Hodgkin lymphoma at Stanford University resulted in cures of early-stage lymphoma. Meanwhile, a team at the National Cancer Institute safely combined four chemotherapy drugs (mustard, vincristine, procarbazine, and prednisone) known as the "MOPP" regimen and reported the first cures of advanced Hodgkin lymphoma in 1964. Steadily improving techniques for defining the extent and location of disease (staging) has allowed appropriate modalities of treatment to be selected for individual patients. The late 1970s and 80s presented new challenges in the recognition of adverse effects associated with MOPP and radiation therapy, some of which were not apparent for decades after treatment. This time period also featured another major advance in an alternative four-drug chemotherapy regimen (doxorubicin, bleomycin, vinblastine, and dacarbazine), known as "ABVD," that proved to be more effective than MOPP in treating advanced disease and had fewer side effects. In the 1990s, even more effective and less toxic treatments for early-stage lymphoma were devised by reducing the dose and area of the body treated with radiation therapy in combination with brief chemotherapy such as ABVD. The German Hodgkin Study Group introduced an intensive seven-drug chemotherapy program, "BEACOPP," to address the fact that approximately 30 percent of advanced Hodgkin's lymphoma was not cured with ABVD. Although associated with more severe early toxicity and sterility, a higher cure rate and improved survival were achieved with BEACOPP in a randomized clinical trial (Horning '08). Although orally available methotrexate is prescribed for non-Hodgkin's lymphoma, there does not seem to be any FDA approved alternative to IV chemotherapy.

The development of the drug rituximab as a therapy for B-cell lymphoma (a type of cancer affecting cells of the immune system) provides an excellent illustration of how great improvements in patient care were made through the discovery of a therapy that destroys cancer cells without harming other cells in the body. The discovery of rituximab, an antibody that recognizes CD20, a target shared by malignant lymphoma cells from almost all patients, but also found on normal, immune B cells. Rituximab proved to be effective in treating B-cell lymphoma, and the elimination of normal B cells was surprisingly not harmful. Because rituximab does not affect other normal cells in the body, it can be combined with other therapies. Today, rituximab is part of the regular treatment for almost all patients with B-cell lymphoma, and it has prolonged the lives of many of them. Rituximab can also treat many non-cancerous diseases caused by overactive B cells of the immune system. Rituximab has been used to treat rheumatoid arthritis, multiple sclerosis, and a growing list of non-cancerous conditions (Levy, Malony & Miller '08).

There were 48,610 new cases and 23,720 deaths from leukemia estimated in the United States in 2013. The leukemias are malignant neoplasms of the hematopoietic stem cells characterized by diffuse replacement of the bone marrow by neoplastic cells. These cells may also infiltrate the liver, spleen, lymph nodes and other tissues throughout the body. Although the presence of excessive numbers of abnormal cells in the peripheral blood is the most dramatic manifestation of leukemia, it should be remembered that the leukemias are primary disorders of the bone marrow although some patients with a diffusely infiltrated bone marrow may present with leukopenia. Traditionally, leukemias are classified on the basis of the cell type involved and the state of maturity of the leukemic cells. Thus acute leukemias are characterized by the presence of very immature cells (called blasts) and by a rapidly fatal course in untreated patients. On the other hand, chronic leukemias are associated, at least initially, with well-differentiated (mature) leukocytes and with a relatively indolent course. Two major variants of acute and chronic leukemias are recognized: lymphocytic and myelocytic (myelogenous). Thus, a simple classification would have four patterns of leukemia: acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), acute myelocytic (myeloblastic) leukemia (AML), and chronic myelocytic leukemia (CML). **Acute leukemias** are associated with replacement of normal marrow elements by a sea of proliferating "blast cells" that do not seem to undergo normal maturation. Consequently, there is a loss of mature myeloid elements such as red cells, granulocytes, and platelets, and hence clinical features of acute leukemias are dominated by anemia, infections and hemorrhages. In **chronic leukemia** the grouping together of chronic lymphocytic and myelogenous leukemias is problematic. Neither of these disorders is rapidly fatal, but the clinical and morphological features that seem to unite the acute leukemias are lacking. In chronic myelogenous leukemia (CML), polycythemia vera, essential thrombocytopenia, and myeloid metaplasia are related disorders that represent clonal, neoplastic proliferations of the multipotent myeloid stem cells. The term **chronic myeloproliferative disorders**, best describes these neoplasms of the myeloid stem cell (Saunders '94: 648, 649).

Differential Diagnosis of Leukemias and Lymphomas

Type of Leukemia	Diagnosis	Comments
Acute Leukemias	Anemia almost always present. White cell count elevated as high as 100,000 cells per µL but in 50% is less than 10,000 cells per µL. Immature white cells, including blast forms, make up	Presents within 3 months of onset of fatigue due to anemia, fever reflecting an infection due to absence of mature leukocytes, bleeding (petechiae, ecchymoses, epistaxis gum bleeding secondary to thrombocytopenia; bone

	60 to 100% of all blood and marrow cells. Platelet count usually depressed to depressed to less than 100,000 per μL	pain and tenderness, lymphadenopathy, splenomegaly and hepatomegaly; Central nervous system manifestations, such as headache, vomiting and nerve palsies resulting from meningeal spread.
Acute lymphoblastic leukemia (ALL)	90% of patients have numerical or structural changes to chromosomes of the leukemia cells hyperdiploidy >50 chromosomes is a good indicator, pseudoploidy of 46 structurally rearranged chromosomes, or translocations come with a poor prognosis for which allogenic bone marrow transplantation offers hope.	2500 new cases per year. Primarily disease of children and young adults. 80% of childhood leukemias. Twice as common in whites as in nonwhites and more frequent in boys than in girls. Testicular involvement is common. More than 90% remission and two-thirds cure rate with modern chemotherapy. 90% of patients have chromosomal changes
Acute myeloblastic leukemia (AML)	Diagnosed if bone marrow contains more than 30% myeloblasts. Chromosomal abnormalities in 90% of patients. 50 to 70% of cases karyotypic changes can be detected by standard cytogenetic techniques. AML divided into eight categories depending on the degree of maturation (1) minimally differentiated AML, (2) AML without differentiation, (3) AML with maturation, (4) Acute promyelocytic leukemia, (5) acute myelomonocytic leukemia, (6) acute monocytic leukemia, (7) acute erytroleukemia, (8) acute megakaryocytic leukemia	Affects adults from ages 15 to 39 years. 20% of childhood leukemias. Diverse origin transformation of multipotent (trilineage) myeloid stem cells as evidenced by common cytogenetic abnormalities in granulocytic and erythroid precursors, though myeloblasts dominate the blood and bone marrow. Or common granulatocyte monocyte precursor involvement gives rise to myelomonocytic disease. Difficult to treat, 60% achieve remission but only 15 to 30% remain free for five years. 50 to 60% of those who undergo allogeneic bone marrow transplantation at first remission appeared cured.
Myelodysplastic syndromes	Group of clonal stem cell disorders with maturation defects resulting in ineffective hematopoiesis and an increased risk of transformation to acute myeloblastic leukemias. Bone marrow is partly or wholly replaced by the clonal progeny of a mutant pluripotent stem cell that retains the capacity to differentiate into red cells, granulocytes and platelets, but in a manner that is both ineffective	Pre-leukemic condition affecting older people between 60 and 70 years of age. Patients present with weakness, infections and hemorrhages, all due to pancytopenia. Approximately half of the patients are asymptomatic, and the disease is discovered incidentally to blood tests. Ten to forty percent progress to frank AML. Median survival varies from 9 to 29 months.

	and disordered resulting in bone marrow that is usually hypercellular or normocellular, but the peripheral blood shows pancytopenia. The abnormal stem cell clone is unstable and prone to acute leukemia.	
Chronic myeloid leukemia (CML)	Neoplastic cloned pluripotent stem cell affecting virtually all hematopoietic lineages. Distinctive cytogenetic and molecular abnormality. >90% Ph chromosome reciprocal translocation t(9;22)(q34;q11). 10-20 fold increase in the mass of granulocytic precursor cells with smaller number of normal progenitor cells in the marrow. Usually elevated leukocyte count commonly exceeding 100,000 cell per mm^3 circulating cells predominantly neutrophis and metamyelocytes, but basophils and eosinophils are also prominent. A small number of myeloblasts (<10%) can be found in peripheral blood. Up to 50% have thrombocytosis early in the course of disease. Almost total lack of alkaline phosphatase in granulocytes. The diagnostic feature is the presence of Ph chromosome and *bcr-c-abl* rearrangements.	15 to 20% of all cases of leukemia. Primarily affects adults between the ages of 25 and 60 years, with the peak incidence in the fourth and fifth decades of life. Initial symptoms are anemia or hypermetabolism due to increased cell turnover and include easy fatigability, weakness, weight loss and anorexia. Slow progression, without treatment a median survival of 3 years can be expected. After a variable period averaging 3 years, about 50% of patients have a leukemic "blast crisis". In 70% the blasts have the features of myeloblasts, whereas the remaining 30% contain the enzyme TdT and express B-lineage antigens. Treatment is unsatisfactory. Although it is possible to induce remissions with chemotherapy, the median survival of 3 to 4 years is unaltered. Bone marrow transplantation is the only curative treatment. After the development of blast crisis all forms of treatment become virtually ineffective.
Chronic lymphocytic leukemia (CLL)	Lymphoid malignancy of B cells, T cells rare <5%. 50% of patients will CLL have abnormal karyotypes, Trisomy 2 is most common, in one-third of patients, with a poor prognosis. Total leukocyte count may be increased slightly or can reach 200,000 per mm^3. Smudge cells with crushed nuclei of lymphocytes are common in peripheral blood smears.	25% of all leukemias in the US and Europe. Typically occurs in persons over 50, median 60 years, males twice as often as females. Uncommon in Japan and other Asian countries. Often asymptomatic, easy fatigability, loss of weight and anorexia. Generalized lymphadenopathy and hepatosphenomegaly are present in 50 to 60% of cases. Median survival is 4 to 6 years and blast crisis are uncommon.
Hairy cell leukemia	Fine hairlike projections on leukemic cells. Tartrate resistant acid phosphatase (TRAP) in	Hairy cell leukemia occurs mainly in older males and its manifestations result largely form infiltration of bone

	neoplastic B cells. Pancytopenia, resulting from marrow failure and splenic sequestration, is seen in more than half the cases. Leukocytosis present in only 25% of patients. Hairy cells can be identified in the peripheral blood smear in most cases.	marrowy, liver and spleen. Splenomegaly is more common than hepatomegaly. Lymphadenopathy is rare. Splenectomy is of benefit in two-thirds of patients. With old treatment median survival was less than 5 years, however, treatment with interferon-α and newer chemotherapeutic agents has led to lasting remissions and possibly cures.
Polycythemia vera	Proliferation of erythroid, granulocytic and megakaryocytic elements, all derived from clonal expansion of a pluripotent stem cell. Absolute increase in red cell mass due to domination of erythroid precursors. Associated with virtually undetectable levels of serum erythropoietin. Hemoglobin concentration ranges from 14 to 28 gm/dl with hematocrit values of 60% or more. The white cell count is elevated, ranging between 12,000 and 50,000 cells per mm^3. The major anatomic changes stem from the increase in blood volume and viscosity brought about by the erythrocytosis. Plethoric congestion of all tissues and organs. The bone marrow is hypercellular. Hematopoiesisn expands markedly to replace fatty marrow. As the disease progresses the marrow becomes fibrotic (myelofibrosis) or may be replaced by blasts (leukemic transformation). The liver is enlarged and frequently contains foci of myeloid metaplasia. The spleen is also slightly enlarged, up to 250 to 300 gm.	Appears insidiously in late middle age ~60 years. Blood is deoxygenated, patient has headache, dizziness, gastrointestinal symptoms, hematemesis, and melena common, 30% develop thrombotic complications affecting the brain and heart. Hemorrhages occur in a third of patients. Life threatening hemorrhages occur in 5 to 10% of cases. In patients who receive no treatment, death from vascular episodes occurs within months, however if that red cell mass can be maintained at nearly normal levels by phlebotomies, median survival of 10 years can be achieved.
Myeloid metaplasia with myelofibrosis	Proliferation of neoplastic myeloid stem cells occurs principally in the spleen (myeloid metaplasia) and in the fully developed syndrome the bone marrow is hypercellular and fibrotic (myelofibrosis). Spleen	Uncommon in individuals younger than 60 years. Usually begins with progressive anemia or marked splenic enlargement, producing a dragging sensation in the left upper quadrant. Fatigue, weight loss and night sweats from increased metabolism from

	is sometimes as large as 4000gm. Moderate to severe normochromic norocytic anemia. Red cells show all manner of variation in size and shape, but characteristic are teardrop-shaped erythrocytes (poikilocytes). The white cell count may be normal , reduced or elevated to 80,000 to 100,000 cells per mm^3 basophils are usually prominent. Platelet count is normal or elevated at time of diagnosis but thrombocytopenia supervenes. Biopsy of the marrow to detect the early deposition of reticulin or the more advanced fibrosis is essential for diagnosis.	expanded mass of myeloid cells. Hyperuricemia and secondary gout may complicate the picture. Median survival time varies from 1 to 5 years. Threats to life are recurrent infections, thrombotic episodes or bleeding related to platelet abnormalities and in 5 to 20% of cases, transformation to acute myeloid leukemia.

Source: Saunders ’94: 648-662

Historically, patients with CML lived no more than three to five years, during which time the disease would quickly transform from a chronic leukemia to an aggressive and fatal acute leukemia. In 1960, Peter Nowell and David Hungerford, working in Philadelphia, described a shortened chromosome in the blood and bone marrow of patients with CML. This was the first consistent chromosomal abnormality associated with a human cancer. Then, in 1973, Janet Rowley showed that this abnormal chromosome, now called the Philadelphia chromosome, came about because of an exchange of genetic material between two chromosomes. In the 1980s, it was demonstrated that the consequence of this chromosome exchange was the production of an abnormal gene called *BCR-ABL* fueling the excess growth of white blood cells in CML. With the target identified, a drug discovery program was started, aimed at developing a drug to shut down the activity of *BCR-ABL*. The compound that became known as imatinib (Gleevec) was developed in 1992, and studies showed that this compound killed CML cells without harming normal cells. In 1998, the drug was tested in patients with CML who had exhausted standard treatment options and whose life expectancy was limited. Within six months of starting the clinical trials of imatinib, all of the patients had their blood counts return to normal. Remarkably, this once-a-day pill had minimal side effects. These unprecedented results were confirmed in much larger clinical trials, and imatinib was approved by the U.S. Food and Drug Administration (FDA) in 2001, less than three years from the start of the clinical trials. With longer follow-up, this once routinely fatal leukemia now has a five-year survival rate of 95 percent. Newer drugs (dasatinib and nilotinib) have been developed that can shut down most of the mutated forms of *BCR-ABL*, and have significant activity in patients with resistance to imatinib; these drugs are also FDA-approved (Druker '08).

The spleen is secondarily involved in a wide variety of system disorders. As the largest unit of monomuclear phagocyte system, the spleen is involved in all systemic inflammations and generalized hematopoietic disorders and many metabolic disturbances. When the spleen is involved in systemic disease, splenic enlargement usually develops, and therefore splenomegaly is a major manifestation of disorders of this organ. When sufficiently enlarged, the spleen may cause a dragging sensation in the left upper quadrant and through pressure on the stomach, cause

discomfort after eating. It storage function may lead to the sequestration of significant numbers of blood elements, giving rise to a syndrome known as hypersplenism, which is characterized by the triad of (1) splenomegaly, (2) a reduction of one or more of the cellular elements of the blood leading to anemia, leukopenia, thrombocytopenia, or any combination of these, in association with hyperplasia of the marrow precursors of the deficient cell types and (3) correction of the blood cytopenia(s) by splenectomy (Saunders '94: 669, 670).

Enlargement of the spleen, sometimes also called **acute splenic tumor**, occurs in any blood-borne infection. The spleen is enlarged up to 200 to 400 gm. The splenic substance may be so soft as to flow out form the cut surface. Microscopically the major change is acute congestion of the red pulp, which may encroach on and sometimes efface the lymphoid follicles. At times there is acute necrosis of the centers of the splenic follicles. **Congestive splenomegaly** occurs when chronic congestion of the splenic vein or extrahepatic portal vein causes enlargement of the spleen, referred to as congestive splenomegaly, most commonly caused by the various forms of cirrhosis of the liver but particularly alcoholic cirrhoses. The venous congestion ultimately leads to portal or splenic vein hypertension. Thrombosis of the splenic vein may be initiated by the pressure of tumors in the neighboring organs. Systemic or central venous, congestion is encountered in cardiac decompensation involving the right side of the heart, as may occur in tricuspid or pulmonic valvular disease or chronic cor-pulmonale or following left-sided heart failure causing only moderate enlargement of the spleen, that rarely exceeds 500 gm in weight. Long-standing congestive splenomegaly produces enlargement of the spleen from 1000 – 5000 gm. The impairment of blood fow results in excessive destruction (hypersplenism). Focal hemorrhage give rise to Gandy-Gamna nodules fibrosis containing deposits of iron and calcium salts encrusted with connective tissue and elastic fibers. **Splenic infarcts** are comparatively common lesions caused by occlusion of the major splenic artery or any of its branches, alsmoalways due to emboli in the heart. The infarcts may be small or large pale wedge-shaped emboli, usually of the bland, anemic type. Septic infarcts are found in infective endocarditis of the valves of the left side of the heart. **Neoplastic involvement** of the spleen is rare except in tumors of the lymphohematopoietic system and the following types of benign tumors may aris in the spleen: fibromas, osteomas, chondromas, lymphangiomas, and hemangiomas. Congenital anomalies may involve rarely a complete absence of the spleen usually with other abnormalities such as situs inversus and cardiac malformations. Hypoplasia is more common and accessory spleens (**spleniculi**) are common and have been encountered singly or multiply. In some heatologic disorders such as hereditary spherocytosis, thrombocytopenic purpura and hypersplenism, splenectomy is a standard method of treatment but if a large accessory spleen is overlooked, the benefit of removal of the definitive spleen may be lost. **Rupture** of the spleen is usually caused by crushing injury or severe blow but rarely spontaneously ruptures in the absence of physical trauma most often in infectious monoceosis, malaria, typhoid fever, leukemia and the other types of acute splenitis. Rupture is usually followed by extensive, sometimes massive, intraperiotoneal hemorrhage. The condition usually must be treated by prompt surgical removal of the spleen to prevent death from loss of blood and shock (Saunders '94: 670, 671).

III.B.10 Vascular Neoplasms

Primary tumors of the heart are rare but metastatic tumors to the heart occur in about 5% of patients dying from cancer. The most common primary tumors, in descending order of frequency are myxomas, fibromas, lipomas, papillary fibroelastomas, rhabdomyomas, angiosarcomas and other sarcomas. The five most common all are benign and account

collectively for 80 to 90% of primary tumors of the heart. **Myxomas** are the most common primary tumor of the heart in adults. About 90% are located in the atria. Surgical removal is usually curative, although rarely the neoplasm recurs months to years later. **Lipomas** are most often located in the left ventricle, right atrium or atrial septum and are not necessarily neoplastic. In the atrial septum, the depositions are called "lipomatous hypertrophy". **Papillary fibroelastomas** cluster as hair-like projections up to 1 cm in diameter, covering up to several centimeters of the endocardial surface. **Rhabdomyomas** are the most frequent primary tumor of the heart in infants and children. **Cardiac angiosarcomas** and other sarcomas are not distinctive from their counterparts in other locations. Occasionally cardiac complications represent the dominant feature of the presentation of a noncardiac malignant tumor. Chemotherapy and radiation also manifest their own district cardiovascular side effects and toxicities (Schoen '94; 569-571). In patients with carcinoid tumors, cardiac involvement, is one of the **sequelae of the carcinoid syndrome**. The syndrome is characterized by distinctive episodic flushing of the skin and cramps, nausea, vomiting and diarrhea in almost all patients; bronchoconstrictive episodes resembling asthma in about one-third of patients, and cardiac lesions in about one-half. The carcinoid syndrome is encountered in about 1% of patients who have carcinoid tumors (argentaffinomas) whatever the primary site and in 10% of those with gastrointestinal carcinoid tumors with hepatic metastes (Schoen '94: 555).

Peripheral artery disease refers to changes in the aorta and its branches, the arteries. Aortic aneurysms can form along any part of this main blood vessel, or one of its branches. Sometimes the force of blood under high pressure will rip the lining of the aorta, this is called aortic dissection, or a dissecting aneurysm if it occurs in one of the enlarged areas. A number of changes can occur in the arteries, the veins and the optic nerve that connect to the eye, and the retina, where vision is detected on the back surface of the eyeball. Treatment for severe diabetic eye complications is more successful when blood pressure is normal (Wilson & Childre '06: 9, 40). Varicose veins and phlebothrombosis/thrombophlebitis together account for at least 90% of **clinical venous disease**. **Varicose veins** are abnormally dilated, tortuous veins produced by prolonged, increased intraluminal pressure. The superficial veins of the leg are the preponderant site of involvement, however, portal hypertension, usually due to cirrhosis of the liver, leads to varices in the esophageal and hemorrhoidal veins. It is estimated that 10 to 20% of the general population eventually develop varicose veins in the lower legs. The condition is much more common over age 50, in obese persons, and in women, a reflection of the elevated venous pressure in the lower legs caused by pregnancy. Occupations that require long periods of standing and long automobile or airplane rides frequently lead to marked venous stasis and pedal edema, even in normal individuals. Varicose dilation of veins renders the valves incompetent and leads to venous stasis, congestion edema, and thrombosis. Despite thrombosis of superficial varicose veins, embolism is very rare. Distention of the veins is often painful, but most patients have no symptoms until marked venous stasis and edema develop. Some of the most disabling sequelae are the development of persistent edema in the extremity and trophic changes in the skin that lead to stasis dermatitis and ulcerations. Because of the impaired circulation the tissues of the affected part are extremely vulnerable to injury. Wounds and infections heal slowly or tend to become chronic varicose ulcers. Because **venous thrombosis** inevitably leads to inflammatory changes within the vein wall, thrombophlebitis and phlebothrombosis are two designations for a single entity. Cardiac failure, neoplasia, pregnancy, obesity, the postoperative state, and prolonged bed rest or immobilization predispose to venous thrombosis. The deep leg veins account for more than 90% of cases of thrombophlebitis (Schoen '94: 504, 505, 506).

Vascular neoplasms are divided into benign, intermediate and malignant based on two major anatomic characteristics (1) the degree of which the neoplasm is composed of well-formed vascular channels and (2) the extent and regularity of the endothelial cell proliferation. In general benign neoplasms are made up largely of well-formed vessels with well-differentiated endothelial cell proliferation, in contrast, malignant tumors are solidly cellular and anaplastic, with scant number of only poorly developed vascular channels. Benign tumors are several types of hemangioma, including capillary, cavernous, epithelioid, granuloma pyogenicum and deep soft tissue hematoma; Glomus tumor, and vascular ectasias. Intermediate tumors are hemangioendothelioma and epithelioid hemangioendothelioma. Malignant tumors are angiosarcoma, hemangiopericytoma and Kaposi's sarcoma (Schoen '94: 506).

Angiogenesis is the formation of new blood vessels. This process involves the migration, growth, and differentiation of endothelial cells, which line the inside wall of blood vessels. The process of angiogenesis is controlled by chemical signals in the body. These signals can stimulate both the repair of damaged blood vessels and the formation of new blood vessels. Other chemical signals, called angiogenesis inhibitors, interfere with blood vessel formation. Normally, the stimulating and inhibiting effects of these chemical signals are balanced so that blood vessels form only when and where they are needed. Bevacizumab was the first **angiogenesis inhibitor** that was shown to slow tumor growth and, more important, to extend the lives of patients with some cancers. The FDA has approved other drugs that have antiangiogenic activity, including sorafenib (Nexavar), sunitinib (Sutent), pazopanib (Votrient), and everolimus (Afinitor). Sorafenib is approved for hepatocellular carcinoma and kidney cancer, sunitinib and everolimus for both kidney cancer and neuroendocrine tumors, and pazopanib for kidney cancer. Angiogenesis inhibitors are unique cancer-fighting agents because they tend to inhibit the growth of blood vessels rather than tumor cells. In some cancers, angiogenesis inhibitors are most effective when combined with additional therapies, especially chemotherapy.

Hemangiomas are extremely common tumors, particularly in infancy and childhood, constituting 7% of all benign tumors. **Capillary hemangiomas** are composed of blood vessels that resemble cappilaries, narrow, thin-walled, and lined by relatively thin endothelium, usually occurring in the skin, subcutaneous tissues and mucous membranes of the oral cavities and lips, they may also occur in the internal viscera, such as the liver, spleen, and kidneys. Varying in size from a few millimeters up to several centimeters in diameter, they are bright red to blue, level with the surface of the skin or slightly elevated, with intact covering epithelium. The "strawberry type" of capillary hemangioma (juvenile hemangiomas) of the skin of newborns grows rapidly in the first few months, begins to fade when the child is one to three years old, and regresses by age five in 80% of cases. **Cavernous hemangiomas** are distinguished by the formation of large cavernous vascular channels. Often occurring in childhood, they have a predilection for the skin of the head and neck and mucosal surfaces of the body but are also found in many viscera, particularly the liver, spleen, pancreas and occasionally the brain. The usual cavernous hemangioma is a red-blue, soft, spongy mass 1 to 2 cm in diameter. In most situations the tumors are of little significance but can be a cosmetic disturbance, and when present in the brain, and potential source of increased intracranial pressure or hemorrhage (Schoen '94: 507).

Granuloma Pyogenicum are of uncertain neoplastic nature. These masses appear as exophytic red nodules on the skin and gingival or oral mucosa and are often ulcerated. One-third of lesions develop after trauma, growing rapidly to reach a maximum size of 1 to 2 cm within a few weeks. Pregnancy tumor (granuloma gravidarum) is a granuloma pyogenicum occurring in the gingiva

of 1 to 5% of pregnant women that regresses after delivery. **Glomus tumor** (Glomangioma) is a benign but exquisitely painful tumor that arises from the modified smooth muscle cells of the glomus body, a neuromyoarterial receptor that is sensitive to variations in temperature and regulates arteriolar flow. Glomus bodies may be located anywhere in the skin but are most commonly found in the distal portion of the digits, especially under the fingernails. Lesions are usually under 1 cm in diameter, and many are less than 3 mm. When present in the skin, they are slightly elevated, round, red-blue, firm, exquisitely painful modules (Schoeb '984: 507, 509).

Vascular extasias (Telangiectases) designates a group of abnormally prominent capillaries, venules, and arterioles that creates a small focal red lesion, usually in the skin or mucous membranes, and are more representative of congenital anomalies than true neoplasms. **Nevus flammeus**, is a "ten-dollar" term for the ordinary birthmark. Most commonly on the head and neck, they range in color from light pink to deep purple and are ordinarily flat. The vast majority ultimately fade and regress. A special form of nevus flammeus, the so-called port-wine stain, may grow proportionately with a child, thicken the skin surface and become unsightly. Port wine stains in the distribution of the trigeminal nerve may be associated with the Sturge-Weber syndrome (encephalotrigeminal angiomatosis). **Spider telangiectasis** consists of a focal minute network of subcutaneous small arteries or arterioles arranged in a radial fashion about a central core. It is usually found on the upper pasts of the body, particularly the face, neck and upper chest, and is most common in pregnant women or in patients with liver disease, particularly cirrhosis of the liver, or with high levels of estrogen. **Hereditary Hemorrhagic Telangiectasia** (Osler-Weber-Rendu Disease) is characterized by multiple small aneurysmal telangiectases distributed over the skin and mucous membranes, present from birth as a dominant trait, affecting both sexes equally, about 20% of cases lack a family history. The small (less than 5 mm) lesions are found directly beneath the skin or mucosal surfaces of the oral cavity, lips, alimentary tract, respiratory and urinary tract as well as in the liver, brain and spleen. Nosebleeds and bleeding into the intestinal, urinary or respiratory tract are common clinical manifestations. The hemorrhagic tendency becomes more pronounced with age and sever hemorrhage may necessitate transfusions, patients with this condition have a normal life expectancy. **Bacilllary angiomatosis** is a potentially fatal infectious disease that causes a distinct non-neoplastic proliferation of small blood vessels, that appear as one to numerous red papules and nodules or rounded subcutaneous masses, in the skin, lymph nodes, and visceral organs of patients with human immunodeficiency virus (HIV) infection and other states of immunocompromise, it is treated with doxycycline (Schoen '94: 509).

Hemangioendothelioma is used to denote a true neoplasm of vascular origin composed predominantly of masses of endothelial cells growing in and about vascular lumina. The hemangioendotheliioa represents an intermediate grade between the well-differentiated hemangiomas and the frankly anaplastic, totally cellular angiosarcomas. Most frequently seen in the skin but may affect the spleen and liver. Epithelioid hemangioendothelioma is a unique vascular tumor occurring around medium-sized and large veins in the soft tissue of adults. Occurring in the lung as a so-called intravascular bronchoalveolar tumor, such a tumor can be misdiagnosed as metastatic carcinoma. Clinical behavior is variable, most are cured by excision, but up to 40% recur, and 20% eventually metastasize (Schoen '94: 509, 510). **Angiosarcoma** (Hemangiosarcoma) is a malignant neoplasm of vascular origin. It may occur in both sexes and at all ages, anywhere in the body, but most often in the skin, soft tissue, breast and liver. Beginning small, most angiosarcomas become large, fleshy masses of pale gray-white, soft tissue. Clinically, angiosarcomas, have all the usual features of malignancy, with local invasion and distal metastatic spread. Some patients survive only weeks to months, whereas others may

live for many years. Angiosarcomas are usually treated with paclitaxel (Taxol), docetaxel (Docefrez, Taxotere), sorafenib (Nexavar), or bevacizumab (Avastin). **Hemangiopericytoma**, a rare neoplasm, may occur anywhere in the body, but most commonly on the lower extremitites and in the retroperitoneum. Electron microscropic studies have clearly traced the origin of these tumors to pericytes. Most of these neoplasms are small, but rarely they achieve a diameter of 8 cm. They consist of numerous capillary channels surrounded by and enclosed within nests and masses of spindle-shaped cells, which occasionally can be ovoid or even round. The tumors may recur, and as many as 50% metastasize to lungs, bone and liver. Regional lymph nodes are sometimes affected (Schoen '94: 510, 511). Resection is the standard treatment in most, although regrowth and metastases are common even after resection.

Lymphangiomas are the lymphatic analog of the hemangiomas of blood vessels. Simple (Capillary) Lymphangioma are masses composed of small lymphatic channels, tend to occur subcutaneously in the head and neck region and in the axilla. Rarely, they are found in the trunk, within internal organs, or in the connective tissue in and about the abdominal or thoracic cavities. On endothelium lined lymph spaces they are slightly elevated or sometimes pedunculated lesions, 1 to 2 cm in diameter, differentiated from the capillary channels only by the absence of blood cells. **Cavernous lymphangioma** (Cystic hygroma) are benign lymphatic tumors composed of cavernous lymphatic spaces and therefore are analogous to the cavernous hemangioma. Almost invariably occurring in children on the neck or axilla and only rarely retroperiotoneally, they occasionally achieve considerable size, up to 15 cm in diameter. The margins of the tumor are not discrete and these lesions are not encapsulated making their removal difficult. When bits of tumor are left in surgical resections, recurrence may be expected. **Lymphangiosarcoma** is a rare tumor that develops after prolonged lymphatic obstruction with lymphedema. Most cases occur in the edematous arms of patients treated by radical mastectomy for carcinoma of the breast. The nodules are frequently multiple, on average, they appear about 10 years after the mastectomy and have a poor prognosis. They may also develop after prolonged lymphedema in the lower legs (Schoen '94: 512). Amputation of the affected limb is prescribed. Chemotherapeutic drugs such as paclitaxel, doxorubicin, ifosfamide, and gemcitabine exhibit antitumor activity. Recently, there has been interest in evaluating the effectiveness of anti-angiogenic drugs in the treatment of lymphangiosarcoma. Early evidence suggests that treatment with one such drug, Bevacizumab, may be effective in treating lymphangiosarcoma. Investigation of bevacizumab in combination with other chemotherapy agents is underway.

Long considered an obscure tumor **Kaposi's sarcoma** frequently occurs in patients with acquired immunodeficiency syndrome (AIDS). Four forms of the disease are recognized. (1) the classic, or European form, first described by Kaposi in 1862, was endemic to older men of Eastern European (especially Ashkenazic Jews). This form consists of red to purple skin plaques or nodules primarily in the lower extremities, slowly increasing in size and number and spreading to more proximal sites. Rarely do they involve visceral organs or cause the death of the patients. **African Kaposi's** is clinically similar to the European form, but occurs in children and younger men in equatorial Africa. It has a very high prevalence in these regions, representing up to 10% of all tumors. In young children, the disease is often associated with generalized involvement of lymph nodes, resembling lymphoma. (3) transplant associated Kaposi's sarcoma occurs in organ transplant recipients who receive high doses of immunosuppressive therapy. Lesions are either localized to the skin or widely metastatic but

often regress when immunosuppressive therapy is discontinued. (4) AIDS-associated Kaposi's sarcoma is found in approximately one-third of AIDS patients, and it is more common in male homosexuals than in other risk groups. The tumors respond to cytotoxic chemotherapy and to therapy with alpha-interferon. Most patients eventually succumb to the infectious complications of AIDS rather than directly from the consequences of Kaposi's sarcoma. About one-third of these patients with Kaposi's sarcoma, however, subsequently develop a second malignancy, usually lymphoma, leukemia or myeloma (Schoen '94: 511).

Interferon-alfa was the first drug specifically approved for the treatment of Kaposi's. It is of particular interest because of its antiproliferative, antiviral (anti-HIV), antiangiogenic, and immune-modulating properties. Etoposide (VP-16) has been evaluated as both an oral and an intravenous treatment for KS. As an oral agent, VP-16 has been evaluated primarily in patients who have undergone prior treatment with multiple cytotoxic agents. When VP-16 is given intravenously (150 mg/m^2 on days 1 to 3 every 4 weeks), high response rates (78%) have been reported in patients without prior treatment and with good prognosis (no history of opportunistic infection and no constitutional symptoms). The primary toxicity of this agent is myelosuppression, which may necessitate the use of colony-stimulating factors, particularly in patients with advanced disease receiving other myelosuppressive agents. Additionally, alopecia frequently occurs in association with etoposide therapy, and is a consideration for patients who are receiving treatment of their KS for primarily cosmetic purposes. In patients with KS of poor prognosis, bleomycin given intramuscularly (5 mg/day for 3 days) or as a 4-day continuous infusion (6 mg/m^2/day) produced a 48% partial response rate. Results of a small, single-institution study in which bleomycin was given as a 72-hour infusion (20 mg/m^2/day) to 17 patients indicated a partial response rate of 65%. Bleomycin toxicity appears to be acceptable, with neutropenia an infrequent complication. Doxorubicin (also known by its trade name Adriamycin) is a component of the most widely used combination regimen for HIV-associated KS. In one trial, however, weekly treatment with doxorubicin (25 mg/m^2) in patients with AIDS-related KS achieved a partial response rate of only 10%. The primary toxicity of weekly doxorubicin is myelosuppression, even with the relatively low doses prescribed for KS treatment. Alternating vincristine and vinblastine weekly achieves a response rate of 33%. Toxicity includes vincristine-induced neurotoxicity (which limits its usefulness as a single agent) and vinblastine-induced myelosuppression. Paclitaxel A partial response was reported in 13 of 20 patients (65%), with 5 of 6 patients with known pulmonary KS responding, as well as 6 previously treated patients with nonpulmonary KS achieving a partial response. In a second trial, of the 30 evaluable patients, 16 (53%) achieved a partial response. The time to response was short (median of three cycles of treatment). Dramatic improvement in symptomatic lymphedema was noted in 25 of 26 patients. Therapy was well tolerated. Vinorelbine, a semisynthetic vinca alkaloid with a favorable therapeutic index compared to other vinca alkaloids, was evaluated in previously treated patients with progressive AIDS-related KS. Thirty-five evaluable patients were treated with vinorelbine 30 mg/m2 every 2 weeks. Clinical complete and partial remissions were achieved in 43% of patients, with a median progression-free survival of 151 days. The agent was well tolerated, with neutropenia the most frequent dose-limiting toxicity. Two liposomal agents are currently approved for the treatment of KS: liposome-encapsulated daunorubicin (DaunoXome) and liposome-encapsulated doxorubicin (Doxil). Both agents are highly active against KS and have less toxicity than the nonliposomal anthracyclines. Myelosuppression, however, remains the dose-limiting toxicity.

III.B.11 Anemia

The **hemoglobin and hematocrit** (H&H) levels are used to determine the presence and severity of anemia. Normal hemoglobin and hematocrit values (H&H) vary. For adolescents normal is a hemoglobin value of 130 g/L and hematocrit of 40. For adult males it is 160 (+/- 20) and 47 (+/- 6). For adult women it is 130 (+/- 20) and 40 (+/- 6). For postmenopausal women it is 140 (+/- 20) and 42 (+/- 6). For pregnant women in the 3rd trimester it is 120 (+/- 20) and 37 (+/-6). Higher normal values may be established for adults who live at a high altitude or smoke more than 1 pack of cigarettes a day. Heavy smokers can show an increase in the hemoglobin level of 5 to 10 g/L secondary to carbon monoxide binding to hemoglobin. When the hemoglobin value falls below 100 to 120 g/L (10 to 12 g/dL) new cells are recruited and erythropoietin levels increase logarithmically according to the severity of the anemia. This stimulates erythroid production severalfold but requires normal renal function, healthy marrow and an adequate supply of key nutrients, especially iron (Hillman '98: 334-336).

Anemia may be defined as a reduction in the oxygen transport capacity of the blood, usually resulting from a deficiency of red cells, diagnosed when a blood test shows a hemoglobin value of less than 13.5 gm/dl in a man or less than 12.0 gm/dl in a woman. Normal values for children vary with age. Plasma volume and fluid loss may create abnormalities in clinical measurements. The skin is pale and usually becomes thin and inelastic as the epidermis and dermis atrophy. Frequently, the nails become brittle and lose their normal convexity to assume a concave spoon-shape (koilonychia), particularly in iron deficiency anemia. Weakness, malaise, dyspnea (shortness of breath) and fatigue are common complaints. Cells that are vulnerable to hypoxia may undergo fatty change or ischemic necrosis, usually in the myocardium, convoluted tubules of the kidney, the centrilobular hepatic cells, and the sensitive ganglion cells of the cortex and basal ganglia. Angina pectoris, and cardiac failure may develop and compound the respiratory difficulty caused by reduced oxygen transport. The increased demand for erythropoiesis in anemia causes the fatty marrow to become active and red if the marrow is capable of response. When the need is great extramedullary hematopoiesis ensues. With acute blood loss and shock, oliguria and anuria may develop in the shock kidney. Central nervous system hypoxia may be evidenced by headache, dimness of vision and faintness (Saunders '94: 586, 587).

With **acute blood loss**, the alterations reflect principally the loss of blood volume rather than the loss of hemoglobin. Shock and death may follow. If the patient survives, the blood volume is rapidly restored by sift of water from the interstitial fluid compartment. The resulting hemodilution lowers the hematocrit. Reduction in the oxygenation of tissues triggers the production of erythropoietin, and the marrow responds by increasing erythropoietin, and the marrow responds by increasing erythropoiesis. When the blood is lost internally, as into the peritoneal cavity, the iron can be recaptured, but if the blood is lost externally, the adequacy of the red cell recovery may be hampered by iron deficiency when insufficient reserves are present. Mobilization of platelets and granulocytes from the marginal pools leads to thrombocytosis and leukocytosis in the period immediately following acute blood loss. Soon after acute blood loss the red blood cells appear normal in size and color, however, as the marrow begins to regenerate, changes occur in the peripheral blood. Most striking is an increase in reticulocyte count, reaching 10 to 15% after 7 days. **Chronic blood loss** induces anemia only when the rate of loss exceeds the regenerative capacity of the erythroid precursors or when iron reserves are depleted. In addition to chronic blood loss, any cause of iron deficiency such as malnutrition, malabsorption states, or an increased demand above the daily intake as occurs in pregnancy will lead to an identical anemia. (Saunders '94: 587).

Blood transfusions are the transfer of blood, its components, or products from one person (donor) into another person's bloodstream (recipient). Every year in the U.S., more than 20 million units of red blood cells, platelets, and plasma are transfused to treat hematologic conditions such as severe anemia, leukemia, and sickle cell disease. Transfusions have long been associated with some risk to patients. The HIV epidemic during the 1980s was a major cause of fear; regular transfusions, especially of clotting factor concentrates, spread the virus quickly and nearly undetected. That outbreak prompted the development of biovigilance or hemovigilance: tracing and tracking transfusion-related adverse events and incidents, both infectious and non-infectious, that affect blood donors and recipients. Another of the most significant issues complicating transfusion safety has been bacterial contamination of blood products, particularly of platelets. However, steps have been taken in the last decade to avoid, detect, and eliminate this complication through improved donor selection, specialized preparation of the arm before needle insertion, and special screening techniques. Blood is regularly tested for infectious disease transmission, particularly for viruses such as Hepatitis B and C, HIV, and West Nile Virus. Serum tests have been replaced by molecular testing called nucleic acid amplification testing (NAT), which finds active viruses in the donor's blood to determine infection risk. If an active virus is found, the donor unit is discarded. Experts anticipate that new methods, including new molecular and microarray testing, which can identify many infectious agents rapidly and accurately, will replace or augment serum studies and NAT in the near future. Blood transfusion has never been safer from known infectious risk than it is today (Luban '08).

Potential **post-transfusion reactions** include transfusion-related lung injury (TRALI), during which the donor's immune antibodies cause breathing problems in the recipient; transfusion associated cardiac overload (TACO), which is swelling caused by the increased blood volume; and post-transfusion iron overload, which is a buildup of iron in the body, usually caused by multiple or regular transfusions. Immune reactions, which happen when the body's immune system is affected by the donor blood, also pose several risks to transfused patients. Alloimmunization occurs when the recipient develops an allergic reaction to the donor's red blood cells: transfusion-related immune modulation (TRIM) can lead to increased risk of infections and cancer recurrence, post-transfusion graft-versus-host disease (GVHD, when the donor's immune system attacks the recipient's blood cells), and microchimerism (when a small amount of donor blood persists in the recipient's body, causing ongoing low-grade GVHD). Removing white blood cells or radiating blood to prevent white blood cell growth can reduce the likelihood that the recipient will reject the donor blood. New techniques can isolate specialized cell populations from blood – most importantly, hematopoietic progenitor cells (HPCs) that are used for stem cell transplantation. Because HPCs are easier to extract and the process is safer for donors, HPC transplantation has replaced bone marrow transplantation for many cancers and other diseases. Researchers are also using umbilical cord stem cells (UCSCs) as a source of HPCs. UCSCs are collected and processed in a method similar to whole blood and are a rich resource for transplantation therapy in pediatric and some adult patients. In the future, these cells may be grown and expanded for clinical use. Furthermore, researchers have isolated specialized cell types other than HPCs that play an important role in cellular therapy because they can modify proliferation and immune responses during the engraftment of transplanted cells (Luban '08).

The **hemolytic anemias** are all characterized by (1) shortening of the normal red cell life span, premature destruction of red cells; (2) accumulation of the products of hemoglobin catabolism; and (3) a marked increase in erythropoiesis within the bone marrow, in an attempt to compensate for the loss of red cells. In general, hereditary disorders are due to intracorpuscular defects and

the acquired disorders to extrinsic factors such as autoantibodies. The leading cause of kidney failure in US and Canadian children is hemolytic uremic syndrome of which 85 percent of cases are caused by E. coli 0157:H7. Incidence of hemolytic uremic syndrome in the US is 7,500 and in the Netherlands 25 (Robbins '01: 133). **Hereditary spherocytosis** (HS) is an inherited disorder (autosomal recessive) characterized by an intrinsic defect in the red cell membrane that renders erythrocytes spheroidal, less deformable and vulnerable to splenic sequestration and destruction. The prevalence of HS is highest in people of northern European extraction, in whom rates of 1 in 5000 have been reported. Although a deficiency of any one of the membrane skeletal proteins could adversely affect the red cells, a deficiency of spectrin seems to be the most common abnormality in patients with all forms of HS. Moderate splenic enlargement is characteristic of HS (500 to 1000 mg), in few other hemolytic anemias is the spleen enlarged as much or as often. The clinical features are anemia, splenomegaly and jaundice. The severity of the disease varies. A hemolytic crisis may develop, a sudden onset of a wave of massive hemolysis accompanied by fever, abdominal pain, increasing jaundice, low blood pressure and even shock. Alternatively, an aplastic crisis (triggered usually by parvovirus infection of the marrow red cell precursors) may appear. Transfusions may be necessary to support the patient, but eventually both these crises remit in most instances. Gallstones may also produce symptoms so diagnosis is usually based on family history and evidence of spherocytosis. The cardinal role of the spleen in the premature demise of the spherocytes is proved by the invariably beneficial effect of splenectomy. The spherocytes persist, but the anemia is corrected (Saunders '94: 589-591).

Hemolytic disease can be due to erythrocyte enzyme defects: **glucose-6-phosphate dehydrogenase deficiency** (G6PD). The erythrocyte and its membrane are vulnerable to injury by exogenous and endogenous oxidants. Normally, intracellular reduced glutathione (GSH) inactivates such oxidants. Abnormalities in the hexose monophosphate shunt or in glutathione metabolism resulting from deficient or impaired enzyme function reduce the ability of red cells to protect themselves against oxidative injuries and lead to hemolytic disease. Several hundred G6PD genetic variants have been identified, but only two variants, designated $G6PDA^-$ and G6PD Mediterranean (more severe anemia), lead to significant hemolysis. Infection or exposure to oxidant drugs causes oxidation by means of the production hydrogen peroxide which accumulates and causes oxidation leading to denaturation of hemoglobin and formation of precipitates (Heinz bodies) within the cell. Macrophages pluck out the Heinz bodies giving rise to red cells that appear to have a bite of cytoplasm removed which leads to further membrane damage and induces the formation of spherocytes. After lag period of 2 to 3 days, acute intravascular hemolysis, characterized by hemoglobinemia, hemogobinuria and decreased hematocrit levels, is triggered. Since only senescent red cells lysed, the episode is self-limited and hemolysis stops when only the younger red cells remain in the circulation despite continued administration of the oxidant drug). The recovery phase is heralded by reticulocytosis, as in the case of other hemolytic anemias (Saunders '94: 591, 592).

Sickle cell disease is the prototype of hereditary hemoglobinopathies, characterized by the production of structurally abnormal hemoglobin, HbS. If an individual is homozygous for the sickle mutation, almost all hemoglobin in the erythrocyte is HbS. In the heterozygote, only about 40% is HbS, the remainder being normal hemoglobins. Where malaria is endemic, as many as 30% of black Africans are heterozygous. This protection may be related to the slight protection against falciparum malaria imparted by HbS. On deoxygenation the changes that occur in the HbS molecules convert hemoglobin from a freely flowing liquid to a vicious gel, leading ultimately to distortion of the red cells, which acquire a sickle or holly-leaf shape.

Sickled cells lose potassium and water and at the same time gain calcium, which normally is rigorously excluded. The formation of HbS has two major consequences (1) a chronic hemolytic anemia, and (2) occlusion of small blood vessels, resulting in ischemic tissue damage. Irreversibly sickled cells (ISC) have a very rigid non-deformable cell membrane and have difficulty negotiating the splenic sinusoids. They become sequestered in the spleen, where they are destroyed by the mononuclear phagocyte system. Some intravascular hemolysis may also occur due to the increased mechanical fragility of the sickle cells. The average red cell survival correlates with the percentage of ISC in circulation and is shortened to approximately 20 days. In children, the continued scarring caused by this disease often causes a progressive shrinkage of the spleen so that by adolescence or early adulthood only a small nubbin of fibrous tissue may be left, this is called autosplenectomy, which predisposes to septicemia and meningitis by *Streptococcus pneumoniae* and *Haemophilus influenzae*, the most common causes of death in children with sickle cell anemia. Chronic hemolysis in a fairly severe anemia exhibits hematocrit values ranging between 18 and 30%. Vaso-occlusive crises, also called painful crises, represent episodes of hypoxic injury and infarction with extreme pain in abdomen, chest or joints, and may produce a seizure or stroke. Aplastic crisis represents a temporary cessation of bone marrow activity, usually triggered by parvovirus infection of erythroid progenitor cells causing reticulocytes to disappear from the peripheral blood and there is sudden and rapid worsening of anemia. A sequestration crisis may appear in children with splenomegaly caused by massive sequestration of deformed red cells and sometimes shock. Despite improvement in therapy sickle cell anemia shortens longevity and many patients die within the first 3 years owing to overwhelming infections, and those who cross these hurdles may live up to the fourth or fifth decade (Saunders '94: 592-596).

The **thalassemia syndromes** are a heterogeneous group of mendelian disorders characterized by a lack of or decreased synthesis of either the alpha or the beta-globin chain of hemoglobin A ($\alpha_2\beta_2$). β – thalassemia is characterized by deficient synthesis, or total lack, of the beta chain, whereas α – thalassemia is characterized by deficient synthesis of the alpha chain. The hematologic consequences of diminished synthesis of one globin chain derive not only from the low intracellular hemoglobin (hypochromia) but also from the relative excess of the other chain. **β–thalassemia** syndromes can be classified into two categories (1) β^0- thalassemia associated with total absence of beta-globin chains in the homozygous state and (2) β^+-thalassemia with a reduced (but detectable) beta-globin synthesis in the homozygous state. Sequencing reveals approximately 100 different mutations responsible for these two disorders. Cell membrane damage, caused by unbound α chain aggregation, leads to a loss of K^+, excessive absorption of dietary iron, and impaired DNA synthesis. The net effect is destruction of the red cell precursors within the bone marrow, 70 to 85% of marrow normoblasts are destroyed in severely affected patients. In general, individuals who are homozygous for the β – thalassemia genes (β^0 or β^+) have a very severe transfusion dependent anemia and are said to have β – thalassemia major. Thalassemia major is most common in Mediterranean countries and parts of Africa and Southeast Asia. The anemia is very severe and first manifests 6 to 9 months after birth. In untransfused patients Hb levels range between 3 and 6 gm/dl. The spleen may increase up to 1500 gm. Unless supported by transfusion, children suffer from growth retardation and die at an early age from anemia. In those who survive the face is overlarge and somewhat distorted with malocclusion. Cardiac disease resulting from progressive iron overload and secondary hemochromatosis is an important cause of death even in patients who can otherwise be supported by transfusion. To reduce iron overload most patients receive iron chelators. Many patients survive into the third decade. Bone marrow transplantation from an HLA-identical sibling is the only therapy that offers a cure.

The presence of one normal gene in the heterozygotes usually leads to enough normal beta-globin chain synthesis so that the affected individuals are usually asymptomatic with only a mild anemia, referred to as β – thalassemia minor or β – thalassemia trait, or for intermediate cases β – thalassemia intermedia, predominantly in the same ethnic groups. Because the non-alpha chains in general form more soluble and less toxic aggregates than those derived from alpha chains, the hemolytic anemia and ineffective erythropoiesis tend to be less severe in α – thalassemia. The most common cause of reduced alpha-chain synthesis seems to be the deletion of alpha-globin genes. α – thalassemia is classified on the basis of the number and position of the alpha-globin genes deleted, which determine the clinical syndrome. The silent carrier state is characterized by the deletion of a single alpha-globin gene and barely detectable reduction in alpha-globin chain synthesis. These individuals are completely asymptomatic and do not have anemia. α-thalassemia trait is characterized by deletion of two alpha-globin genes and although they have minimal or no anemia and no abnormal physical signs, the position of the deleted genes makes a big difference to the likelihood of severe forms of the disease such as HbH disease or hydrops fetalis. Hemoglobin H disesase is associate with deletion of three of the four alpha-globin genes. HbH is seen mostly in Asians and rarely in Africans. Patients have a moderately severe anemia. Hydrops fetalis is the most severe form of α – thalassemia, resulting from the deletion of all four alpha-globin genes. Severe tissue anoxia associated with the total failure to deliver oxygen to the tissues, invariably leads to intrauterine fetal death (Saunders ’94: 596-601).

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare but fascinating acquired clonal disorder of disorder, involving a somatic mutation affecting a pluripotent stem cell; that sometimes evolves into other stem cell disorders, such as aplastic anemia and acute leukemia. The clonal progeny of the mutant stem cell (red cells, white cells, platelets) are deficient in a family of proteins that are attached to the cell membrane by a glycosyl phosphatidyl inositol (GPI) anchor and their absence renders blood cells unusually sensitive to lysis by endogenous complement. Patients classically have intravascular hemolysis, which is paroxysmal and nocturnal in only 25% of cases. Most of the remaining patients have chronic hemolysis without dramatic hemoglobinuria. Over the long course, hemosiderinuria with loss of iron eventually leads to iron deficiency. Multiple episodes of venous thrombosis in the hepatic, portal or cerebral veins, are fatal in 50% of cases. The course of this disease is chronic with a median survival of 10 years (Saunders ’94: 601).

Immunohemolytic anemia is caused by extracorpuscular mechanisms, sometimes the immune reaction is initiated by ingestion of drugs such as penicillin, cephalosporins, quinidine, phenacetin or α-methyldopa. Differentiation of immunohemolytic anemias form other forms of hemolytic anemias depends on demonstration of anti-red cell antibodies in the Coombs’ antiglobulin test. **Warm antibody hemolytic anemia** is the most common form of immune hemolytic anemia. In about 60% of patients the condition is idiopathic and primary and in the remaining 40% there is an underlying predisposing condition or some drug exposure. Ig-G coated red cells are bound to Fc receptors on monocytes and splenic macrophages and undergo spheroidal transformation. The spherocytes are then sequestered and removed in the spleen, the major site of red cell destruction, and moderate to severe splenomegaly manifests. **Cold agglutinin immune hemolytic anemia** is caused by IgM antibodies that bind avidly to red cells at low temperatures (0 to 4°C). These antibodies occur acutely during the recovery phase of certain infectious disorders such as mycoplasmal pneumonia and infectious mononucleosis, and is self-limited and rarely induces hemolysis. Chronic cold agglutinins occur with lymphoproliferative disorders and as an idiopathic condition. The clinical symptoms result from

agglutination of red cells and fixation of complement in distal body parts, and the IgM bound to red cells is released when it reaches 37°C, leaving the cell vulnerable to phagocytosis by mononuclear phagocytes in the liver and spleen. The hemolytic anemia is of variable severity. Vascular obstruction cause by red cell agglutinates results in pallor, cyanosis of the body parts exposed to cold temperatures and Raynaud's phenomenon. **Cold hemolysin hemolytic anemia** autoantibodies are characteristic of the disease paroxysmal cold hemoglobinuria which is noted for acute intermittent massive hemolysis, often with hemoglobinuria, following exposure of the affected patient to cold. When the temperature is elevated, the hemolysis due to IgG antibodies occur. The antibody is also known as the Donath-Landsteiner (DL) antibody, previously associated with syphilis. Most cases of PCH follow various infections such as mycoplasma pneumonia, measles, mumps and some ill-defined viral and flu symptoms (Saunders '94: 601-603).

Red cell trauma can cause fragmentation of red blood cells, such as by the insertion of valve prostheses and diffuse deposition of fibrin in the microvasculature, may be severe enough to cause significant intravascular hemolysis. Hemolysis due to narrowing or obstructions in the microvasculature is called microangiopathic hemolytic anemia. This form of anemia is encountered in disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura (TTP), the hemolytic uremic syndrome, malignant hypertension, renal cortical necrosis, systemic lupus erythematosus (SES) and metastatic adenocarcinoma. The common denominator is the presence of some vascular lesion. In patients with prosthetic heart valves, particularly aortic valves, the red cells are damaged by the sheer stress resulting from the turbulent blood flow and abnormal pressure gradients. **Diminished erythropoiesis** may result from a deficiency of some vital substrate necessary for red cell formation, such as iron deficiency anemias, in which heme synthesis is impaired and anemia of vitamin B_{12} and folate deficiency, characterized by defective DNA synthesis (megaloblastic anemias). Other causes of decreased erythropoiesis include anemia of chronic disease and marrow stem cell failure that occurs in such conditions as aplastic anemia, pure red cell aplasia and anemia of renal failure (Saunders '94: 603).

Megaloblastic anemias constitute a diverse group of entities, having in common impaired DNA synthesis and distinctive morphologic changes in the blood and bone marrow. The erythroid precursors and erythrocytes are abnormally large, thought to be related to impairment of cell maturation and division. Vitamin B_{12} and folic acid are coenzymes in the DNA synthetic pathway. A deficiency of these vitamins or impairment in their utilization results in deranged or inadequate synthesis of DNA that may lead to megaloblastic anemia and usually presents in the form of chronic diarrhea. **Vitamin B_{12}** is a complex organometallic compound known as cobalamin, for the cobalt atom attached to a corrin ring, therapeutically synthesized as stable cyanocobalamin. Vitamin B_{12} is required for methylcobalamin to convert homocysteine to methionine and to metabolize polyglutamate forms of folate. Under normal circumstances, human are totally dependent on dietary animal products for the vitamin B_{12}. Strictly vegan or macrobiotic diets do not provide enough of this essential nutrient. The daily requirement is 2 to 3 μg daily and the normal balanced diet contains significantly larger amounts which takes years of vegan diet to deplete (Saunders '94: 603-607). A **vitamin B_{12} deficiency** normally manifests as chronic post-infectious **diarrhea**, about once a day, and is highly susceptible to food borne pathogens, neurological symptoms may manifest. The symptoms tend to go away temporarily with **vitamin B_{12} supplementation**.

The hypothesis that lack of **folate** is the proximate cause of anemia in vitamin B12 deficiency is supported by the observation that the anemia improves with the administration of folic acid.

Folate is most necessary for (1) the synthesis of purines.; (2) the synthesis of methionine from monocysteine, a reaction that also requires vitamin B_{12}; and (3) the synthesis of deoxythymidylate monophosphate (dTMP). **Folic acid deficiency** results in megaloblastic anemia without the neurological changes, but is not common, except with a very marginal diet, without adequate green vegetables. Despite their abundance in raw foods folate is sensitive to heat and cooking foods for 5 to 10 minutes destroy up to 95% of the folate. Folic acid antagonist drugs such as methotrexate, 6-mercaptopurine and cyclophosphamide inhibit folate function leading to ulcerative lesions in the gastrointestinal tract as well as megloblastic anemia. Human require 50 to 200 µg of folate daily especially due to the increased demand for folate during pregnancy and dietary inadequacies found in chronic alcoholics, the indigent and very elderly. Megaloblastic anemia resulting from folic acid and vitamin B12 deficiency are identical (Saunders '94: 605-610).

The feature that sets **pernicious anemia** apart from dietary vitamin B_{12} deficiency is that the cause of the malabsorption is atrophic gastritis with failure of the production of intrinsic factor (IF). Chronic atrophic gastritis is marked by a loss of parietal cells, a prominent infiltrate of lymphocytes and plasma cells, and megaloid and atypical changes to the mucosal cells. It is an auto-immune disorder resulting from the presence of blocking, binding and gastric antibodies. Absorption of vitamin B_{12} requires IF, which is secreted by the parietal cells with HCl. Diagnostic features include (1) a marked to severe megaloblastic anemia; (2) leukopenia with hypersegmented granulocytes; (3) mild to moderate thrombocytopenia; (4) neurologic changes related to involvement of the posterolateral spinal tracts; (5) achlorhydria even after histamine stimulation; (6) inability to absorb an oral dose of cobalamin (assessed by urinary excretion of radiolabeled cyanocobalamin given orally, called the Schilling test; (7) low serum levels of vitamin B_{12} ; (8) excretion of methymalonic acid in the urine; and (9) a striking reticulocytic response and improvement in hematocrit levels following parenteral administration of vitamin B_{12} (Saunders '94: 605, 608).

Iron deficiency is probably the most common nutritional disorder in the world. Although more common in developing countries this form of anemia is also common in the United States. Normally, the total body iron content is in the range of 2gm in women and up to 6 gm in men. Approximately 80% of the functional iron is found in hemoglobin, myoglobin and iron-containing enzymes such as catalase and the cytochromes contain the rest in pools of hemosiderin and ferritin containing approximately 15 to 20% of total body iron. Because women have substantially smaller stores of iron than males they have a much more precarious iron balance and are vulnerable to excessive loss or increased demands associated with menstruation and pregnancy. In iron deficiency, **serum ferritin** is always below 12 µg/liter, whereas in iron overload very high values approaching 5000 µg/liter may be obtained. With liver damage and inflammatory states, serum ferritin levels may be high despite normal body stores. **Storage iron pool** is readily mobilized in the event of an increase in body iron requirements, as may occur following loss of blood. Iron is transported by **transferrin** which delivers iron to the cells, including erythroid precursors, where iron is required for hemoglobin synthesis. Immature red cells possess high-affinity receptors for transferrin. The most active site of iron absorption is the duodenum, but the stomach, ileum, and colon may also participate to a small degree.

Approximately 25% of the **heme iron** derived from hemoglobin, myoglobin, and other animal proteins is absorbed, but only 1 to 2% of nonheme iron is absorbed. Daily losses of iron range between 1 and 1.5 mg. Thus to maintain a **normal iron balance**, approximately 1 mg of iron

must be absorbed from the diet every day. Because only 10 to 15% of the ingested iron is absorbed, the daily iron requirement for adult males is 5 to 10 mg and for adult females 7 to 20 mg. The **average daily dietary intake** of iron in the Western World is about 15 to 20 mg. An iron deficiency may result from (1) dietary lack; (2) impaired absorption; (3) increased requirement; or (4) chronic blood loss. **Dietary inadequacy** is found in the elderly, very poor, infants because milk contains very small amounts of iron and children who need dietary iron to accommodate growth and expansion of blood volume. **Impaired absorption** is encountered in sprue, intestinal steetorrhea and chronic diarrhea. **Chronic blood loss** is the most important cause of iron deficiency in the Western world. Bleeding within the tissues or cavities of the body may be followed by total recovery and recycling of iron, however, external hemorrhage depletes the reserves of iron. Iron deficiency induces a **hypochromic microcytic anemia** and may cause other changes, including koilonychias, alopecia, atrophic changes in the tongue and gastric mucosa and intestinal malabsorption. The **diagnosis of iron deficiency anemia** rests on laboratory studies. Both hemoglobin and hematocrit are depressed, usually to moderate levels, and are associated with hypchromia, microcytosis and some poikilocytosis. The serum iron and serum ferritin are low, and the total plasma iron-binding capacity is high. Low serum iron with increased iron-binding capacity results in a reduction of transferrin saturation levels to below 15%. Reduced heme synthesis leads to elevation of free erythrocyte protoporphyrin. Unexplained iron deficiency anemia can be caused by an occult lesion or cancer (Saunders ’94: 610-613).

Marrow failure can be occupied by myelophthisic anemia caused by (1) space-occupying lesions, usually metastatic cancer, that destroy a significant amount of bone marrow or disturb the marrow architecture depressing its productive capacity, (2) diffuse liver disease with the contributing factors of folate deficiency and iron deficiency due to gastrointestinal blood loss or (3) chronic renal failure is almost always associated with anemia in proportion to the severity of the uremia, often with iron deficiency secondary to a tendency to bleeding, resulting in reduced red cell production although there is increased demand, with inadequate formation of erythropoietin. Recombinant erythropoietin results in significant improvement of anemia in patients with renal failure. **Impaired red cell production associated with chronic disease** is perhaps the most common cause of anemia among hospitalized patients in the United States. It is associated with defective iron utilization and may mimic iron deficiency but this anemia is instead caused by chronic illness from chronic microbial infections, such as osteomyelitis, bacterial endocarditis and lung abscess; chronic immune disorders, such as rheumatoid arthritis and enteritis; or neoplasms, such as Hodgkin’s disease and carcinomas of the lung and breast. The common features of anemia in these clinical settings is a low serum iron and reduced total iron-binding capacity in association with abundant stored iron in the mononuclear phagocytic cells, and there seems to be a defect in the reutilization of iron. The anemia is usually mild and treatment of the underlying condition corrects the anemia (Saunders ’94: 615, 613).

Polycythemia, or erythrocytosis, denotes an increased concentration of red cells, usually with a corresponding increase in hemoglobin levels. Such an increase may be relative, when there is hemoconcentration due to decreased plasma volume, or absolute, when there is an increase in total red cell mass. **Relative polycythemia** results from any cause of dehydration or **stress polycythemia**, called Gaisbock’s syndrome. **Absolute polycythemia** is said to be primary when the increase in red cell mass results from an intrinsic abnormality of the myeloid stem cell and secondary when the red cell progenitors are normal but proliferate in response to increased levels of erythropoietin. Primary polycythemia is one of several expressions of clonal, neoplastic proliferation of myeloid stem cells.

Aplastic anemia refers to pancytopenia characterized by (1) anemia; (2) neutropenia and (3) thrombocytopenia as the result of a suppression of multipotent myeloid stem cells, with inadequate release of differentiated cell lines. Most cases of aplastic anemia follow exposure to chemicals and drugs. With some agents the marrow damage is predictable and reversible when the use of the offending agent is stopped, usually benzene, chloramphenicol, alkylating agents, and antimetabolites (e.g. 6-mercaptopurine, vincristine and busulfan) or idiosyncratically with chloramphenicol, phenylbutazone, methylphenylethylhydantoin, streptomycin and chlorpromazine. Whole body irradiation causes dose related destruction of hematopoietic stem cells. Some forms of marrow insult cause genetic damage that results in the generation of stem cells with poor proliferative and differentiative capacity. If one such altered stem cell dominates, the resultant picture is one of aplastic anemia. The occasional transformation of aplastic anemia into acute leukemia lends further credence to this hypothesis. Although aplastic anemia may appear following a variety of infections (including HIV), it most commonly follows viral hepatitis of the non-A, non-B type. Anemia may cause the progressive onset of weakness, pallor and dyspnea. Splenomegaly is characteristically absent. Diagnosis rests on examination of bone marrow biopsy and peripheral blood. It is important to distinguish aplastic anemia from other causes of pancytopenia, such as "aleukemic" leukemia and myelodysplastic syndromes. **Fanconi's anemia** is a rare autosomal recessive disorder characterized by defects in DNA repair causing marrow hypofunction in early life accompanied by multiple congenial anomalies. The idiopathic form has a poor prognosis and there is increasing use of bone marrow transplantation to replace defective stem cells and in selected cases this is effective. Benefit may also be derived from immunosuppressive therapy with antithymocyte globulin, which presumably neutralize the marrow-suppressive effect of immune cells (Saunders '94: 616, 614-615).

Hemorrhagic diatheses, excessive bleeding, may result from (1) increased fragility of vessels, (2) platelet deficiency or dysfunction, (3) derangements in the coagulation mechanisms and (4) combinations of these. Bleeding disorders caused by vessel wall abnormalities, called **nonthrombocytopenic purpuras**, do not usually cause serious bleeding problems most often they induce small hemorrhages (petechieae and purpura) in the skin or mucous membranes, particularly the gingivae, however occasionally more significant hemorrhages can occur into joints, muscles and subperiosteal locations or take the form of menorrhagia, nosebleeds, gastrointestinal bleeding or hematuria. The platelet count, bleeding time and coagulation time are usually normal. Many infections induce petechial and purpuric hemorrhages, but especially implicated are meningococcemia, other forms of septicemia, severe measles and several rickettsioses. Drug reactions may induce abnormal bleeding. **Scurvy and Ehlers-Danlos syndrome** impair the formation of the collagenous support of vessel walls predisposing to hemorrhage. **Henoch-Schönlein purpura** is a systemic hypersensitivity disease of unknown cause characterized by a purpuric rash, colicky abdominal pain (presumably due to gastrointestinal hemorrhage), polyarthralgia and acute glomerulonephritis. **Hereditary hemorrhagic telangiectasia** is an autosomal dominant disorder characterized by dilated, tortuous blood vessels that have thin walls and hence bleed readily anywhere in the body but most commonly under the mucous membranes of the nose (epistaxis) tongue, mouth and eyes (Saunders '94: 616, 617).

Thrombocytopenia, reduced platelet number, constitutes an important cause of generalized bleeding. Platelet counts normally range between 150,000 to 300,000/mm^3 and a count below 100,000/mm^3 is generally considered to constitute thrombocytopenia. However spontaneous bleeding does not become evident until the count falls below 20,000/mm^3. Platelet counts in the

range of 20,000 to 50,000/mm^3 are associated with post-traumatic bleeding. Rarely thrombocytopenia can be caused by diseases of the bone marrow, ineffective megakaryopoiesis in megaloblastic anemias resulting from a deficiency of folate or vitamin B_{12}; increased destruction of platelets following drug ingestion or infection most commonly quinine, quinidine, methyldopa, thiazide diuretics and heparin; most common hematological manifestation of AIDS; acute postviral thrombocytopenia, may appear in children following recovery from viral exanthema or upper respiratory tract infection, but resolves spontaneously in 4 to 6 weeks; mechanical injury, such as by prosthetic heart valves or hypertense arteries; hypersplenism, normally sequestering 30 to 40% of the mass of circulating platelets, sequestrates as much as 90% of all platelets; and massive transfusions with blood stored for longer than 24 hours that contains virtually no viable platelets.

Neonatal and post-transfusion (Isoimmune) thrombocytopenia results from the development of antibodies. In addition to HLA an ABO antigens, platelets possess several antigenic determinants not present in other blood cells – including Duzo, PL and Bak antigen systems. PL^{A1} antigen is believed to be the cause of both the purpura associated with post-transfusion and neonatal thrombocytopenia. **Idiopathic thrombocytopenic purpura** (ITP) is a chronic autoimmune disorder in which lesions are found in the spleen and bone marrow and platelets are destroyed by the formation of antiplatelet IgC antibodies targeting two platelet glycoprotein complexes – IIb/IIIa and Ib/IX, that can be demonstrated in 80% of patients. ITP occurs most commonly in adults, particularly in women of childbearing age. About 75 to 80% of patients are remarkably improved or cured following splenectomy but a diagnosis of ITP should be made only after all the possible known causes for platelet deficiencies have been ruled out. **Thrombotic microangiopathies** encompass a spectrum of clinical syndromes that include thrombotic thrombocytopenic purpura (TTP) and hemolytic-uremia syndrome (HUS). TTP traditionally occurs in adult females with fever, thrombocytopenia, microangiopathic hemolytic anemia, transient neurologic deficits and renal failure. HUS is also associated with microangiopathic hemolytic anemia and thrombocytopenia but is distinguished from it by the absence of neurologic symptoms, the dominance of acute renal failure and onset in childhood. At one time these conditions were uniformly fatal, but with recent improvements in treatment, including plasma exchange, approximately 80% survival can be expected (Saunders ’94: 617, 620).

Qualitative defects of platelet function may be congenital or acquired. **Congenital disorders** are rare and can be classified into three groups on the basis of the predominant functional abnormality (1) defects of adhesion, (2) defects of aggregation and (3) disorders of platelet secretion (release reaction). **Defective adhesion** is best illustrated by the autosomal recessive Bernard Soulier syndrome in which there is an inherited deficiency of platelet membrane glycoprotein complex (GpIb/IX) that is a receptor for von Willebrand’s factor which is essential in normal platelet adhesion to collagen. **Defective platelet aggregation** is exemplified by the autosomal recessive trait thrombasthenia in which platelet fail to aggregate with ADP, collagen, epinephrine, or thrombin, owing to a deficiency of GpIIb/IIIa, the fibrinogen receptor. **Disorders of platelet secretion** are characterized by normal initial aggregation with collagen or ADP, but the subsequent responses, such as secretion of prostaglandins and release of granulebound ADP, are impaired causing storage pool disease. There are two clinically significant acquired defects of platelet function (1) related to aspirin and other NSAIDs, which may significantly prolong bleeding time and lead to bruising, with ingestion of as little as 1g in 10% of normal healthy subjects and (2) uremia (Saunders ’94: 619, 620).

A deficiency of every one of the known clotting factors has been reported at one time or another as the cause of a bleeding disorder. The bleeding differs somewhat from that encountered in platelet deficiencies. The bleeding manifests as large ecchymoses or hematomas following an injury, or as prolonged bleeding after a laceration or any form of surgical procedure. Acquired disorders are usually characterized by multiple clotting abnormalities. **Vitamin K deficiency** results in depressed synthesis of factors II, VII, IX and X and protein C. Since the liver makes virtually all the clotting factors, severe parenchymal liver disease may be as associated with hemorrhagic diathesis. Hereditary deficiencies have been identified for each of the clotting factors. Deficiencies of factor VIII (hemophilia A) and of factor IX (Christmas disease, or hemophilia B) are transmitted as sex-linked recessive disorders that are usually autosomal. In most cases four screening procedures will localize the hemostatic abnormality, (1) bleeding time, (2) platelet count, (3) the prothrombin time, and (4) the partial thromboplastin time (Saunders '94: 620, 621).

Hemophilia A and von Willebrand's disease, are two of the most common inherited disorders of bleeding, both caused by qualitative or quantitative defects involving the factor VIII-vWF complex. Plasma factor VIII-vWF is a complex made up of two separate proteins. Synthesized separately through noncovalent bonds, factor VIII is linked to a much larger protein called von Willebrand's factor (vWF) which forms approximately 99% of the complex, which circulates in the plasma to promote clotting and the platelet vessel wall interactions necessary to ensure hemostatis. Von Willebrand's factor binds to several other proteins involved in hemostasis, most importantly subendothelial collagens, but also heparin and platelet membrane glycoproteins (GpIb and IIb/IIIa). The half-life of factor VIII in the circulation is 12 hours if vWF is present but only 2.4 hours if the latter is lacking. vWF can be assayed with a ristocetin aggregation test. With an estimated frequency of 1% **von Willbrand's disease** (vW) is one of the most common inherited disorders of bleeding in humans. It manifests as sponataneous bleeding from mucous membranes, excessive bleeding from wounds, menorrhagia and a prolonged bleeding time in the presence of a normal platelet count. More than 20 variants have been described, most are autosomal dominant. Types I and III vWD are associated with a reduced quantity of circulating vWF. Type I, an autosomal dominant disorder, accounts for approximately 70% of these cases and is relatively mild. Type III, an autosomal recessive disorder is associated with extremely low levels of vWF and correspondingly clinical manifestations are severe, but is much less common. Type II vWD involves a qualitative defect in vWF, that is inherited as an autosomal dominant disorder, where the vWF that is formed is abnormal, and intermediate multimers, the most active forms of vWF are missing from plasma. Type II vWD accounts for 10 to 15% of all cases and is associated with mild to moderate disease. Patients with von Willebrand's disease have a compound defect involving platelet function and the coagulation pathway. However, except in the most severely affected (e.g. homozygous) patients, effects of factor VIII deficiency such as bleeding into the joints, which characterizes hemophilia, are uncommon (Saunders '94: 621, 622).

Hemophilia A is the most common hereditary disease with serious bleeding caused by a reduction in the amount or activity of factor VIII. Hemophilia A is inherited as an X-linked recessive trait, and thus occurs in males and in homozygous females. However, excessive bleeding has been described in heterozygous females. Approximately 30% of patients have no family history presumably because the disease is caused by new mutations. Those with less than 1% of normal activity develop severe disease, levels between 2 to 5% of normal are associated with moderate disease and patients with 6 to 50% of activity develop mild disease. Typically patients wit hemophilia A have normal bleeding time and platelet counts, with

prolonged partial thromboplastin time. Factor VIII assays are required for diagnosis. Treatment of hemophilia A involves infusion of factor VIII, currently derived from human plasma. Replacement therapy however carries the risk of transmission of viral diseases. Until the mid-1980s, before routine screening of blood for HIV antibodies, thousands of hemophiliacs received factor VIII concentrates containing HIV and many developed AIDS. Although blood bank standards have improved the only safe factor VIII will be a recombinant factor VIII derived from cloned factor VIII gene. **Hemophilia B**, also known as Christmas disease, involves a severe factor IX deficiency that is clinically indistinguishable from hemophilia A, the partial thromboplastin time is prolonged and bleeding time is normal. It is also inherited as an X-linked recessive trait and may occur asymptomatically or with associated hemorrhage. In about 14% of these patients, factor IX is present but nonfunctional. Identification of Christmas disease, named after the first patient) is possible only by assay of the factor levels (Saunders '94: 622, 623).

Disseminated intravascular coagulation (DIC), sometimes referred to as consumption coagulopathy, is an acute, subacute or chronic thrombohemorrhagic disorder occurring as a secondary complication in a variety of diseases, it is not a primary disease. It is characterized by activation of the coagulation sequence that leads to the formation of microthrombi throughout the microcirculation of the body, but often in a quixotically uneven distribution. DIC may present with signs and symptoms relating to tissue hypoxia, and infarction caused by the myriad mirothrombi, or as a hemorrhagic disorder related to depletion of the elements required for hemostasis. DIC occurs in the course of a variety of clinical conditions. Clotting can be initiated by either of two ways (1) the extrinsic pathway, with is triggered by the release of tissue factor (tissue thromboplastin) and (2) the intrinsic pathway, which involves the activation of factor XII by surface contact with collagen or other negatively charged substances. Both pathways result in the generation of thrombin, which in turn converts fibrinogen to fibrin. This process is regulated by clot-inhibiting influences which include the activation of fibrinolysis involving generation of plasmin, the clearance of activated clotting factor by the mononuclear phagocyte system or by the liver and activation of endogenous anticoagulants such as protein C. There are two major mechanisms which trigger DIC (1) release of tissue factor thromboplastic substance such as the placenta into the circulation and (2) widespread injury to the endothelial cells which causes the release of tissue factor activating the intrinsic coagulation pathway. DIC is most likely to follow obstetric complications, malignancy, sepsis and major trauma. Infections, particularly those caused by gram-negative bacteria, endotoxins released by the bacteria may activate both the intrinsic and extrinsic pathways producing endothelial cell injury, furthermore endotoxins inhibit the anticoagulant activity of protein C. Endothelial cell damage may also be caused by meningococci, rickettsiae and viruses. Among cancers acute promyelocytic leukemia and carcinomas of the lung, pancreas, colon and stomach are most frequently associated with DIC.

The consequences of DIC are twofold. First there is widespread deposition of fibrin with the microcirculation which may lead to ischemia and to hemolytic anemia from the fragmentation of red cells as they squeeze through the narrowed microvasculature (microangiopathic hemolytic anemia). A hemorrhagic diathesis may dominate the clinical picture resulting from consumption of platelets and clotting factors as well as activation of plasminogen by plasmin which can not only cleave fibrin but also digest factors V and VIII. Thrombi are found in decreasing order of frequency in the brain, heart, lungs, kidneys, adrenals, spleen and liver. In giant hemangiomas thrombi are localized to the neoplasm. The onset may be fulminant, as in endotoxic shock or amniotic fluid embolism, or may be insidious and chronic, as in the cases of carcinomatosis or retention of a dead fetus. About 50% of individuals with DIC are obstetric patients having complications with pregnancy this disorder tends to be reversible with delivery of the fetus.

About 33% of patients have carcinomatosis. Acute DIC associated for example with obstetric complications or major trauma, is dominated by bleeding diathesis, whereas chronic DIC, such as may occur in patients with cancer, tends to present initially with thrombotic complications. It is usually necessary to monitor the fibrinogen, platelets, prothrombin time, partial thromboplastin time and fibrin degradation products for a laboratory confirmed diagnosis. The prognosis is highly variable and depends on the underlying disorder. The management of these cases requires meticulous maneuvering between the Scylla of the thrombotic tendency and the Charybdis of the bleeding diathesis. Thus is posed the dilemma of whether or not to attempt to block coagulation or to control bleeding by the administration of anticoagulants such as heparin and antithrombin III or coagulants in the form of fresh-frozen plasma may be administered. Platelet transfusion may sometimes be necessary (Saunders ’94: 623-626).

A blood clot is called a **thrombus**, and formation of a clot is called thrombosis; because platelet clumps are white, they are sometimes called white thrombus. A red thrombus forms when strands of fibrin, a blood-clotting protein, grow longer and longer, forming a mesh like fiberglass wool. The mesh entraps red blood cells and platelets and tends to keep growing. The red blood cells give the clot a red appearance. The drugs used to prevent red thrombus act by reducing the levels of blood-clotting proteins, thus preventing the coagulation of blood, so they are called anticoagulants. Acetylsalicylic acid (ASA, or Aspirin) and new drugs that prevent platelet clumping are called antiplatelet agents (blood thinners). The two main types are heparin, which is given by injection and warfarin (Coumadin, which is taken in pill form (Spence ’06: 6, 7). Dissolution of a clot in an unwanted location, **thrombolysis**, was originally used for the treatment of deep vein thrombosis and pulmonary embolism but is now also used for treating acute peripheral arterial thrombosis and embolism and for thrombosed prosthetic heart valves, catheters and shunts. Thrombolytic agents used currently act directly or indirectly as plasminogen activators. Thrombolytic therapy with various fibrinolytic agents such as streptokinase or tissue-type plasminogen activator (tPA) is used in about 15% of myocardial infarcts, in an attempt to dissolve the thrombus that initiated the infarct, to re-establish blood flow to the area at risk for infarction, and possibly to rescue the ischemic heart muscle.

Thrombolysis re-establishes the patency of the occluded coronary artery in about 70% of cases, and significantly improves survival rates. Reperfusion of the myocardium with blood, sufficiently early, within 15 to 20 minutes, after onset of ischemia may prevent all necrosis. Reperfusion after a longer interval can salvage at least some myocytes that would have died with more prolonged or permanent ischemia. However, reperfusion injury can cause cell death of myocytes that were still viable before reperfusion. Persistance of total occlusion with failure of clot lysis occurs in approximately 30% of patients undergoing thromblytic therapy. The major complications of thrombolytic therapy that lessen enthusiasm for its use in patients with occlusive vascular disorders include hemorrhage due to the systemic fibrinolytic state (15% of patients) and thrombotic reocclusion (15 to 35% of patients). Reocclusion is related to the continued presence of the factors, responsible for the original thrombus initiation (Schoen ’94: 535, 537, 512).

Because platelet aggregation has been strongly implicated in the pathogenesis of unstable angina pectoris and myocardia infarction, Aspirin, a platelet inhibitor, shows a 51% lower incidence of myocardial infarction and death in the aspirin group (324 mg/day) than the placebo group, although it is generally conceded that lower doses (1mg/kg) work as well and are less inhibitory to the arterial endothelium's production of prostacyclin than higher doses. Aspirin causes irreversible acetylation of platelet cyclooxygenase, thereby preventing the formation of

thromboxane A_2 an extremely potent vasoconstrictor and platelet activator. The thienopyridine drugs ticlopidine and clopidogrel (Plavix) are also effective antiplatelet drugs used to prevent stent closure, generally, clopidogrel is preferred, because it is safer, more potent, and faster acting and can be taken once a day. Plavix is used with acetylsalicylic acid (aspirin) after placement of a stent to prevent the stent and coronary artery from occluding. Glycoprotein (GB) IIb/IIIa Receptor Antagonists prevent fibrinogen binding and platelet aggregation and is used by paitents at high risk and those undergoing percutaneous coronary intervention. Three GP IIb/IIIa receptor antagonists are currently available – abciximab (long lasting 12 hours affect on platelets) an, eptifibatide, and tirofiban that have short half live of 2 to 3 hours. Severe thrombocytopenia (less than 20,000/mL) is seen in 0.5% of patients. Unfractionated heparin (UFH) reduces the risk of sudden cardiac death, myocardial infarction and recurrent ischemic events when combined with ASA in the setting of unstable angina pectoris. Unless there is a contraindication, full-dose heparin anticoagulation appears to be a logical therapy in the earl coronary care unit setting followed by chronic low-dose aspirin in patients with intermediate or high risk unstable angina pectoris. Most of the benefit is short term and most trials have limited heparin use to 2 to 5 days. Severe thrombocytopenia (less than 100,000/mL) occurs in 1 to 2% UFH auto-immune induced thrombocytopenia with thrombosis occurs in less than 0.2% of cases. Low-molecular-weight heparin (LMWH) is safer and alleviates the need for partial thromboplastin time testing (Heger et al '04: 124-126).

III.B.12 Congenital Defects

Congenital heart disease is a general term used to describe abnormalities of the heart or great vessels that are present from birth. Most such disorders arise from faulty embryogenesis, during gestational weeks 3 through 8, when major cardiovascular structures undergo development. Most are associated with live births. Some may produce manifestations soon thereafter but others do not become evident until adulthood (e.g. aorti coarctation or atrial septal defect (ASD). **Congenital anomalies** of blood vessels may predispose the myocardium to infarction or may cause sudden death. Among these diverse vascular anomalies, two have particular importance: developmental or berry aneurysms (involving the cerebral vessels) and arteriovenous fistulas or aneurysms. Congenital heart disease is the most common type of heart disease among children. The incidence is higher in premature infants and in stillborns. Interestingly, monozygotic twins, despite having identical genes, have only a 10% concordance for ventricular septal defects. Nevertheless, chromosomal abnormalities compose about 5% of cases. Fewer than 1% are attributed to environmental influences. The increased risk in subsequent children is small (probably below 5%). The varied structural anomalies in hearts with congenital defects fall primarily into two major categories: shunts or obstructions. A **shunt** is an abnormal communication between changers or blood vessels (or both). The adult congenital heart disease patient population includes those who have never had cardiac surgery, those who have had reparative cardiac surgery and require no further operation, those who have had incomplete or palliative surgery and those who are inoperable, apart from organ transplantation. More than 85% of the estimated 25,000 infants born annually with congenital malformations of the heart are likely to reach adulthood. Many patients with congenital heart disease have an increased risk of endocarditis, those with cuanotic congenital heart disease may have specific difficulties owing to hyperviscosity, abnormal hemostasis and abnormal renal function and urate metabolism. With certain congenital cardiac malformations, childbearing imposes a formidable threat to maternal and fetal survival (Schoen ’94: 579).

Hereditary Hemorrhagic Telangiectasia (Osler-Weber-Rendu Disease) is characterized by multiple small aneurysmal telangiectases distributed over the skin and mucous membranes, present from birth as a dominant trait, affecting both sexes equally, about 20% of cases lack a family history. The small (less than 5 mm) lesions are found directly beneath the skin or mucosal surfaces of the oral cavity, lips, alimentary tract, respiratory and urinary tract as well as in the liver, brain and spleen. Nosebleeds and bleeding into the intestinal, urinary or respiratory tract are common clinical manifestations. The hemorrhagic tendency becomes more pronounced with age and severe hemorrhage may necessitate transfusions, patients with this condition have a normal life expectancy (Schoen '94: 509).

In approximately 1 to 2% of the population, the aortic valve is **congenitally bicuspid**. Bicuspid aortic valves are generally neither stenotic nor symptomatic at birth or throughout early life, but they are predisposed to progressive calcification. The raphe that composes the incomplete commissure is frequently a major site of calcific deposits. With or without calcification, bicuspid aortic valves may also become incompetent or be complicated by infective endocarditis. As the stenosis worsens, angina or syncope, and risk of sudden death, may appear. The onset of symptoms such as angina, syncope of congestive heart failure, in aortic stenosis carries a poor prognosis if not treated by surgery (death in more than 50% within 3 years). Patients with aortic stenosis are often drastically improved by surgical aortic valve repair or replacement. Doppler echocardiography, which measures the flow velocities a well as structure, can be used repetitively to examine the progression of disease with time (Schoen '94: 545).

Coarction of aorta is a frequent obstructive structural anomaly. Males are affected three to four times more often than females, although females with Turner's syndrome frequently have coarction. Murmurs are often present throughout systole and sometimes a thrill is present. With uncomplicated coarctation, surgical resection and end-to-end anastomosis or replacement of the affected aortic segment by a prosthetic graft yields excellent results. Postoperative persistent hypertension is a complication in some patients. Untreated, the mean duration of life if about 40 years, and death are usually caused by CHF, intracranial hemorrhage, infective aortitis at the point of narrowing and rupture or dissection of the precoarctation aorta. **Pulmonary stenosis** or atresia with intact ventricular septum is a relatively frequent malformation of the pulmonary valve. With atresia, ther is no communicatoion between right ventricle and lungs, and so flow bypasses the right ventricle through an AD, entering the lungs through a PDA. Pulmonary stenosis may be mild to severe. Mild stenosis may be asymptomatic and compatible with long life. Valvular stenosis is easily corrected with surgery or in some bases by ballon valvuloplasty. When these lesions are associated with right ventricular hypertrophy, the surgical options are more complex and risky. **Aortic stenosis** and atresia may result from acquired calcific disease or congenital anomaly or a combination of both. The most common congenital anomaly is a biscuspid aortic valve, that is of little significance early in life, but predisposed to calcification in adulthood. Aortic stenosis is an isolated lesion in 80% of cases. A prominent systolic murmur is usually detectable. In general congenital stenosis are well tolerated unless very severe. Mild stenosis can be managed conservatively with antibiotic prophylaxis and avoidance of strenuous activity, but the threat of sudden death with exercise always looms. Surgical correction is usually eventually indicated, for both mild and severe stenosis (Schoen '94: 578, 579).

Ventricular septal defect is a congenital abnormality that allows the free communication between right and left ventricles, usually in association with other structural defects particularly tetralogy, transposition and trucus, but also PDA ASD and aortic coarctation. About 30% occur as isolated anomalies. Depending on the size of the defect it may produce difficulties from birth,

or, with smaller lesions, may not be recognized until later or may even spontaneously close. Small defects (less than 0.5 cm in diameter) are known as Roger's disease, most are muscular and 50% close spontaneously, and the remainder are generally well tolerated for years. They induce a loud murmur however, heart throughout systole. Surgical closure is generally not attempted during infancy, in hope of spontaneous closure. Correction, however, is indicated in older children with large defect, before pulmonary hypertension and obstructive pulmonary vascular disease develops and renders the lesion inoperable. Wolff-Parkinson-White (WPW) syndrome is a condition in which there is an extra connection between the atrium and ventricle (accessory pathway) (Cohen '10: 62).

The four features of **Fallot's tetralogy**, the most common form of cyanotic congenital heart disease are (1) VSD, (2) obstruction of the right ventricular outflow tract (subpulmonary stenosis), (3) an aorta that overrides the VSD and (4) right ventricular hypertrophy. Even untreated, patients with tetralogy often survive into adult life, about 10% were alive at 20 years and 3% at 40 years. The prognosis depends on the severity of subpulmonary stenosis and most infants are cyanotic from brith. Complete surgical repair is possible for classic tetralogy but is more complicated for patients with pulmonary atresia and dilated bronchial arteries. **Transposition of Great Arteries** implies ventriculoarterial discordance, such that the aorta arises from the right ventricle, and the pulmonary artery emanates from the left ventricle. The result is separation of the systemic and pulmonary circulations, a condition incompatible with postnatal life, unless a shunt exists for adequate mixing of blood. This malformation, particularly common in offspring of diabetic mothers, causes cyanosis from birth. Without surgery most patients die within the first months of life with only a few making it to young adulthood. **Truncus arteriosus** arises from a developmental failure of separation of the embryologic truncus arteriosus into the aorta and pulmonary artery. This results in a single great artery that receives blood from both ventricles. Truncus arteriosus is associated with a large number of concomitant defects, including right aortic arch (30%). There is early systemic cyanosis as well as increased pulmonary blood flow. Surgical correction is attempted at an early age, often with gratifying results. **Tricuspiud atresia** describes complete occlusion of the tricuspid valve orifice which causes the mitral valve to be larger than normal and underdevelopment (hypoplasia) of the right ventricle. Cyanosis is present virtually from birth, there is a high mortality in the first weeks or months of life. Palliative or reparative surgery is usually possible. **Total anomalous pulmonary venous connection** (TAPVC) describes a condition in which no pulmonary veins directly joint the left atrium, resulting embryologically when the common pulmonary vein fails to develop or becomes atretic, causing primitive systemic venous channels from the lungs to remain patent. The left atrium is hypoplastic but the left ventricle is usually normal in size. Cyanosis may be present owing to a large right-to-left shunt (Schoen '94: 571-577).

Congenital heart defects that produce right-to-left shunts which causes a dusky blueness of the skin and mucous membranes (cyanosis) from poorly oxygenated blood entering systemic circulation, and clubbing of the fingersare known as **cyanotic congenital heart disease** (e.g. tetralogy of Fallot, transportation of the great arteries (TGA), persistent truncous arteriosus, tricuspid atresia and total anomalous pulmonary venous connection (TAPVC). **Left-to-right shunts** are not usually associated with cyanosis but can result in progressive pulmonary hypertension and right ventricular overload with hypertrophy. The shunt can reverse creating what is called late cyanotic congenital heart disease or **Eisenmenger's syndrome**. **Atrial septal defect** (ASD) represents an abnormal opening in the atrial septum that allows free communication of blood between the right and left atria. A nonfunctional oblique slit known as

a *patent foramen ovale* persists in about one-third of individuals, but permits little or no flow because of the flap valve. Pulmonary blood flow may be two to three times normal. An isolated large ASD usually does not become symptomatic in a patient before 30 years of age, whereas a small ASD is virtually always asymptomatic. A murmur is often present. Irreversible pulmonary hypertension develops in fewer than 10%. The objective of surgical closure of an ASD are the reversal of the hemodynamic abnormalities and the prevention of complications, including heart failure, paradoxic embolization and irreversible pulmonary vascular disease. Mortality is low and postoperative survival is comparable to that of a normal population.

Patent ductus arteriosus (PDS) results when the ductus arteriosus, a normal aortopulmonary vascular channel during intrauterine life, remains open after birth. There is generally agreement that a PDA should be closed up as early in life as is feasible by surgery, or more commonly pharmacologic closure using indomethacin to suppress vasodilatory prostaglandin E synthesis. Preservation of ductal patency (by administering prostaglandin E) assumes great importance in the survival of infants with various forms of congenital heart disease with obstructed pulmonary or systemic blood flow. **Atrioventricular (AV) septal defects** result from abnormal development of the embryologic AV canal, in which the superior and inferior endocardial cushions fail to fuse adequately resulting in incomplete closure of the AV septum and inadequate formation of the septal tricuspid and anterior mitral leaflets. The two most common combinations are partial AV septal defect and complete AV septal defect, essentially a hole in the center of the heart that allows all four cardiac chambers to freely communicate, inducing volume hypertrophy of each. More than one-third of all patients with the complete AV septal defect have Down syndrome. Surgical repair may be possible.

Common associated gene subtypes for inherited rhythm disorders

Disorder	Gene subtypes
Arrhythmogenic right ventricular dysplasia (fat deposits in right ventricular wall)	PKP2, DSP, GSG2
Hypertrophic cardiomyopathy (thickened heart muscle	MYH7, MYBPC3
Long QT syndrome (has specific ECG patterns)	KCNQ1 (long QT1); KCNH2 (long QT2); SCN5A (long QT3)
Brugada syndrome (has specific ECG pattern)	SCN5A

Source: Table 35.1 Cohen ’10: pg. 143

Hereditary spherocytosis (HS) is an inherited disorder (autosomal recessive) characterized by an intrinsic defect in the red cell membrane that renders erythrocytes spheroidal, less deformable and vulnerable to splenic sequestration and destruction. The prevalence of HS is highest in people of northern European extraction, in whom rates of 1 in 5000 have been reported. Although a deficiency of any one of the membrane skeletal proteins could adversely affect the red cells, a deficiency of spectrin seems to be the most common abnormality in patients with all forms of HS. Moderate splenic enlargement is characteristic of HS (500 to 1000 mg), in few other hemolytic anemias is the spleen enlarged as much or as often. The clinical features are anemia, splenomegaly and jaundice. The severity of the disease varies. A hemolytic crisis may develop, a sudden onset of a wave of massive hemolysis accompanied by fever, abdominal pain, increasing jaundice, low blood pressure and even shock. Alternatively, an aplastic crisis (triggered usually by parvovirus infection of the marrow red cell precursors) may appear. Transfusions may be necessary to support the patient, but eventually both these crises remit in

most instances. Gallstones may also produce symptoms so diagnosis is usually based on family history and evidence of spherocytosis. The cardinal role of the spleen in the premature demise of the spherocytes is proved by the invariably beneficial effect of splenectomy. The spherocytes persist, but the anemia is corrected (Saunders '94: 589-591).

Sickle cell disease is the prototype of hereditary hemoglobinopathies, characterized by the production of structurally abnormal hemoglobin, HbS. If an individual is homozygous for the sickle mutation, almost all hemoglobin in the erythrocyte is HbS. In the heterozygote, only about 40% is HbS, the remainder being normal hemoglobins. Where malaria is endemic, as many as 30% of black Africans are heterozygous. This protection may be related to the slight protection against falciparum malaria imparted by HbS. On deoxygenation the changes that occur in the HbS molecules convert hemoglobin from a freely flowing liquid to a vicious gel, leading ultimately to distortion of the red cells, which acquire a sickle or holly-leaf shape. Sickled cells lose potassium and water and at the same time gain calcium, which normally is rigorously excluded. The formation of HbS has two major consequences (1) a chronic hemolytic anemia, and (2) occlusion of small blood vessels, resulting in ischemic tissue damage. Irreversibly sickled cells (ISC) have a very rigid non-deformable cell membrane and have difficulty negotiating the splenic sinusoids. They become sequestered in the spleen, where they are destroyed by the mononuclear phagocyte system. Some intravascular hemolysis may also occur due to the increased mechanical fragility of the sickle cells. The average red cell survival correlates with the percentage of ISC in circulation and is shortened to approximately 20 days. In children, the continued scarring caused by this disease often causes a progressive shrinkage of the spleen so that by adolescence or early adulthood only a small nubbin of fibrous tissue may be left, this is called autosplenectomy, which predisposes to septicemia and meningitis by *Streptococcus pneumoniae* and *Haemophilus influenzae*, the most common causes of death in children with sickle cell anemia. Chronic hemolysis in a fairly severe anemia exhibits hematocrit values ranging between 18 and 30%. Vaso-occlusive crises, also called painful crises, represent episodes of hypoxic injury and infarction with extreme pain in abdomen, chest or joints, and may produce a seizure or stroke. Aplastic crisis represents a temporary cessation of bone marrow activity, usually triggered by parvovirus infection of erythroid progenitor cells causing reticulocytes to disappear from the peripheral blood and there is sudden and rapid worsening of anemia. A sequestration crisis may appear in children with splenomegaly caused by massive sequestration of deformed red cells and sometimes shock. Despite improvement in therapy sickle cell anemia shortens longevity and many patients die within the first 3 years owing to overwhelming infections, and those who cross these hurdles may live up to the fourth or fifth decade (Saunders '94: 592-596).

The **thalassemia syndromes** are a heterogeneous group of mendelian disorders characterized by a lack of or decreased synthesis of either the alpha or the beta-globin chain of hemoglobin A ($\alpha_2\beta_2$). β – thalassemia is characterized by deficient synthesis, or total lack, of the beta chain, whereas α – thalassemia is characterized by deficient synthesis of the alpha chain. The hematologic consequences of diminished synthesis of one globin chain derive not only from the low intracellular hemoglobin (hypochromia) but also from the relative excess of the other chain. **β–thalassemia** syndromes can be classified into two categories (1) β^0- thalassemia associated with total absence of beta-globin chains in the homozygous state and (2) β^+-thalassemia with a reduced (but detectable) beta-globin synthesis in the homozygous state. Sequencing reveals approximately 100 different mutations responsible for these two disorders. Cell membrane damage, caused by unbound α chain aggregation, leads to a loss of K^+, excessive absorption of dietary iron, and impaired DNA synthesis. The net effect is destruction of the red cell precursors

within the bone marrow, 70 to 85% of marrow normoblasts are destroyed in severely affected patients. In general, individuals who are homozygous for the β – thalassemia genes (β^0 or β^+) have a very severe transfusion dependent anemia and are said to have β – thalassemia major. Thalassemia major is most common in Mediterranean countries and parts of Africa and Southeast Asia. The anemia is very severe and first manifests 6 to 9 months after birth. In untransfused patients Hb levels range between 3 and 6 gm/dl. The spleen may increase up to 1500 gm. Unless supported by transfusion, children suffer from growth retardation and die at an early age from anemia. In those who survive the face is overlarge and somewhat distorted with malocclusion. Cardiac disease resulting from progressive iron overload and secondary hemochromatosis is an important cause of death even in patients who can otherwise be supported by transfusion. To reduce iron overload most patients receive iron chelators. Many patients survive into the third decade. Bone marryow transplantation from an HLA-identical sibling is the only therapy that offers a cure. The presence of one normal gene in the heterozygotes usually leads to enough normal beta-globin chain synthesis so that the affected individuals are usually asymptomatic with only a mild anemia, referred to as β – thalassemia minor or β – thalassemia trait, or for intermediate cases β – thalassemia intermedia, predominantly in the same ethnic groups. Because the non-alpha chains in general form more soluble and less toxic aggregates than those derived from alpha chains, the hemolytic anemia and ineffective erythropoiesis tend to be less severe in α – thalassemia. The most common cause of reduced alpha-chain synthesis seems to be the deletion of alpha-globin genes. α – thalassemia is classified on the basis of the number and position of the alpha-globin genes deleted, which determine the clinical syndrome. The silent carrier state is characterized by the deletion of a single alpha-globin gene and barely detectable reduction in alpha-globin chain synthesis. These individuals are completely asymptomatic and do not have anemia. α-thalassemia trait is characterized by deletion of two alpha-globin genes and although they have minimal or no anemia and no abnormal physical signs, the position of the deleted genes makes a big difference to the likelihood of severe forms of the disease such as HbH disease or hydrops fetalis. Hemoglobin H disesase is associate with deletion of three of the four alpha-globin genes. HbH is seen mostly in Asians and rarely in Africans. Patients have a moderately severe anemia. Hydrops fetalis is the most severe form of α – thalassemia, resulting from the deletion of all four alpha-globin genes. Severe tissue anoxia associated with the total failure to deliver oxygen to the tissues, invariably leads to intrauterine fetal death (Saunders ’94: 596-601).

Qualitative defects of platelet function may be congenital or acquired. **Congenital disorders** are rare and can be classified into three groups on the basis of the predominant functional abnormality (1) defects of adhesion, (2) defects of aggregation and (3) disorders of platelet secretion (release reaction). **Defective adhesion** is best illustrated by the autosomal recessive Bernard Soulier syndrome in which there is an inherited deficiency of platelet membrane glycoprotein complex (GpIb/IX) that is a receptor for von Willebrand’s factor which is essential in normal platelet adhesion to collagen. **Defective platelet aggregation** is exemplified by the autosomal recessive trait thrombasthenia in which platelet fail to aggregate with ADP, collagen, epinephrine, or thrombin, owing to a deficiency of GpIIb/IIIa, the fibrinogen receptor. **Disorders of platelet secretion** are characterized by normal initial aggregation with collagen or ADP, but the subsequent responses, such as secretion of prostaglandins and release of granulebound ADP, are impaired causing storage pool disease. There are two clinically significant acquired defects of platelet function (1) related to aspirin and other NSAIDs, which may significantly prolong bleeding time and lead to bruising, with ingestion of as little as 1g in 10% of normal healthy subjects and (2) uremia (Saunders ’94: 619, 620).

Hemophilia A and von Willebrand's disease, are two of the most common inherited disorders of bleeding, both caused by qualitative or quantitative defects involving the factor VIII-vWF complex. Plasma factor VIII-vWF is a complex made up of two separate proteins. Synthesized separately through noncovalent bonds, factor VIII is linked to a much larger protein called von Willebrand's factor (vWF) which forms approximately 99% of the complex, which circulates in the plasma to promote clotting and the platelet vessel wall interactions necessary to ensure hemostatis. Von Willebrand's factor binds to several other proteins involved in hemostasis, most importantly subendothelial collagens, but also heparin and platelet membrane glycoproteins (GpIb and IIb/IIIa). The half-life of factor VIII in the circulation is 12 hours if vWF is present but only 2.4 hours if the latter is lacking. vWF can be assayed with a ristocetin aggregation test. With an estimated frequency of 1% von Willbrand's disease (vW) is one of the most common inherited disorders of bleeding in humans. It manifests as sponataneous bleeding from mucous membranes, excessive bleeding from wounds, menorrhagia and a prolonged bleeding time in the presence of a normal platelet count. More than 20 variants have been described, most are autosomal dominant. Types I and III vWD are associated with a reduced quantity of circulating vWF. Type I, an autosomal dominant disorder, accounts for approximately 70% of these cases and is relatively mild. Type III, an autosomal recessive disorder is associated with extremely low levels of vWF and correspondingly clinical manifestations are severe, but is much less common. Type II vWD involves a qualitative defect in vWF, that is inherited as an autosomal dominant disorder, where the vWF that is formed is abnormal, and intermediate multimers, the most active forms of vWF are missing from plasma. Type II vWD accounts for 10 to 15% of all cases and is associated with mild to moderate disease. Patients with von Willebrand's disease have a compound defect involving platelet function and the coagulation pathway. However, except in the most severely affected (e.g. homozygous) patients, effects of factor VIII deficiency such as bleeding into the joints, which characterizes hemophilia, are uncommon (Saunders '94: 621, 622).

Hemophilia A is the most common hereditary disease with serious bleeding caused by a reduction in the amount or activity of factor VIII. Hemophilia A is inherited as an X-linked recessive trait, and thus occurs in males and in homozygous females. However, excessive bleeding has been described in heterozygous females. Approximately 30% of patients have no family history presumably because the disease is caused by new mutations. Those with less than 1% of normal activity develop severe disease, levels between 2 to 5% of normal are associated with moderate disease and patients with 6 to 50% of activity develop mild disease. Typically patients wit hemophilia A have normal bleeding time and platelet counts, with prolonged partial thromboplastin time. Factor VIII assays are required for diagnosis. Treatment of hemophilia A involves infusion of factor VIII, currently derived from human plasma. Replacement therapy however carries the risk of transmission of viral diseases. Until the mid-1980s, before routine screening of blood for HIV antibodies, thousands of hemophiliacs received factor VIII concentrates containing HIV and many developed AIDS. Although blood bank standards have improved the only safe factor VIII will be a recombinant factor VIII derived from cloned factor VIII gene. **Hemophilia B**, also known as Christmas disease, involves a severe factor IX deficiency that is clinically indistinguishable from hemophilia A, the partial thromboplastin time is prolonged and bleeding time is normal. It is also inherited as an X-linked recessive trait and may occur asymptomatically or with associated hemorrhage. In about 14% of these patients, factor IX is present but nonfunctional. Identification of Christmas disease, named after the first patient) is possible only by assay of the factor levels (Saunders '94: 622, 623).

About 10% of all people are born with potentially significant malformations of the urinary system. Renal dysplasias and hypoplasias account for 20% of chronic renal failure in children. Congenital renal disease can be hereditary but is most often the result of an acquired developmental defect that arises during gestation. Genetic abnormalities may also cause enzymatic or metabolic defects in tubular transport, such as syctinuria and renal tubular acidosis. All except horseshoe kidney are uncommon. **Horseshoe kidney** is caused by fusion of the upper or lower poles of the kidneys produces a horseshoe-shaped structure that is found in 1 in 500 to 1,000 autopsies. Ninety percent of such kidneys are fused at the lower pole and 10% are fused at the upper pole. Agenesis of the kidney can be bilateral, which is incompatible with life, usually encountered in stillborn infants, and is often associated with other congenital disorders and leads to early death. Unilateral agenesis is compatible with normal life if no other abnormalities exist. The opposite kidney is usually enlarged as a result of compensatory hypertrophy. Some patients eventually develop progressive glomerular sclerosis in the remaining kidney. **Hypoplasia** refers to a failure o fhte kidneys to develop to a normal size. This anomaly may occur bilaterally, resulting in renal failure in early childhood, but it is more commonly encountered as a unilateral defect. Most cases probably represent acquired scarring but a truly hypoplastic kidney shows no scars and has a reduced numer of renal lobes and pyramids, usually six or fewer. In one form of hypoplastic kidney, oligomeganephronia, the kidney is small with fewer nephrons that are markedly hypertrophied. **Ectopic kidneys** lie either just above the pelvic brim or within the pelvis. They are usually normal or slightly small in size but otherwise not remarkable, because of their abnormal position, kinking or tortuosity of the ureters may cause some obstruction to urinary flow, which predisposes to bacterial infection. **Multicystic renal dysplasia** is characterized by the persistence in the kidney of abnormal structures-cartilage, undifferentiated mesenchyme and immature collecting ductures, and by abnormal lobar organization. Most cases are associated with ureteropelvic obstruction, ureteral agenesis or atresis and other anomalies of the lower urinary tract. Dysplasia, enlargement of the kidney, can be unilateral or bilateral and is almost always cystic. When unilateral surgical nephrectomy is performed, when bilateral renal failure may ultimately result (Alper '10: 954-956).

Cystic diseases of the kidney may be hereditary, developmental or acquired disorders. Besides Multicystic renal dysplasia, explained above, polycystic kidney disease is a hereditary disorder. **Polycystic kidney disease** can be autosomal-dominant (adult) polycystic disease (ADPKD) or autosomal-recessive (childhood) polycystic disease (ARPKD). **ADPKD** is characacterized by multiple expanding cysts of both kidneys that ultimately destroy the renal parenchyma and cause renal failure. It is a common condition affecting roughly 1 of every 400 to 1000 live births and accounting for 5-10% of cases of chronic renal failure requiring transplantation or dialysis. The likelihood of developing renal failure with a PKD1 mutation is less than 5% by 40 years of age, rising to more than 35% by 50, more than 70% at 60 and m ore than 95% by 70. With a PKD2 mutation the odds of renal failure are less than 5% by 50, 15% at 60, and about 45% at 70. Progression is accelereated in blacks (largely correlated with the sickle cell trait), in males, and in the presence of hypertension. Individuals with PKD tend to have extrarnal congenital anomalies and about 40% have one to several cysts in the liver (polycystic liver disease) that are usually asymptomatic. Cysts are derived from biliary epithelium. Cysts occur much less frequently in the spleen, pancreas, and lungs. Intracranial berry aneurysms arise in the circle of Willis, and subarachnoid hemorrhages from these account for death in about 4-10% of inviduals. Mitral valve prolapse and other cardiac valvular anomalies occur in 20-25% of patients, but most are asymptomatic. Patients may survive for many years with azotemia slowly progressing to uremia. Ultimately, about 40% of adult patients die of coronary or hypertensive heart disease, 25% of infection, 15% of a ruptured berry aneurysm or hypertensive intracerebral hemorrhage,

and the rest of other causes. ARPKD is genetically distinct. Patients who survive infancy may develop a peculiar type of congenital hepatic fibrosis. In older children the hepatic disease is the predominant clinical concern. Such patients may develop portal hypertension with splenomegaly (Alper '10: 956- 959).

Alport Syndrome is a hereditary nephritis that is manifest by hematuria with progression to chronic renal failure, accompanies by nerve deafness and various eye disorders, including lens dislocation, posterior cataracts and corneal dystrophy. The disease is inherited as an X-linked trait in 85% of cases with males expressing the full syndrome and females as carriers limited to hematuria although autosomal recessive and autosomal dominant pedigrees exist. Symptoms appear at ages 5 to 20 years, and the onset of overt renal failure is between the ages of 20 and 50 years in men. **Thin basement membrane lesion** (Benign Familial Hematuria) is a fairly common hereditary entity manifested clinically by familial asymptomatic hematuria and diffuse thinning of the GBM to between 150 and 250 nm (compared with 300-400 nm in normal adults) renal function is normal and prognosis is excellent but most patients are heterozygous for the defective gene and may be carriers, homozygotes or compound heterozygotes may progress to renal failure (Alpers '10: 929-933).

Lysosomal storage diseases are a family of over 30 disorders classified according to the nature of the primary stored material and include mucopolysaccharidoses, lipid storage diseases, mucolipidoses, glycoprotein storage diseases and others. Lysosomes are are cytoplasmic organelles containing acid hydrolases that degrade macromolecules to their basic building blocks: peptides, amino acids, monosaccharides, nucleic acids and fatty acids. Defects of myelin degradation cause white matter disease; defective glycolipid degradation causes organomegaly; and defects in the degradation of mucoplysaccharides, which are ubiquitous, cause abnormalities in numerous tissues. The disorders are progressive, and most affected individuals appear normal at birth and develop manifestations after months or years. Many of the disorders are fatal in childhood or adolescence, although there is extensive phenotypic variability (McGovern '98: 2169). Of the three common autosomal trisomies found in live-born babies, only trisomy 21 is compatible with survival past infancy. The phenotype produced by an extra chromosome 21, formerly known as mongolism but now called the Down syndrome or Trisomy 21 syndrome, is characteristic and easily diagnosed. Cardiac malformations lead to death in infancy in one-third of individuals, However, subjects who survive infancy often reach adulthood, and many reach old age (German '98: 401).

Down's syndrome, mongolism, is the result of an extra number, trisomy of 21 chromosome, that causes mental retardation and hypotonia as well as systemic problems with congenital heart defects and gastrointestinal anomalies that shorten life-expectancy. About one of every 691 babies born in the United States each year is born with Down syndrome, about 6,000 annually. At maternal age 20 to 24, the probability is one in 1562; at age 35 to 39 the probability is one in 214, and above age 45 the probability is one in 19. Down syndrome is the most common chromosome abnormality in humans. It is typically associated with a delay in cognitive ability (mental retardation, or MR) and physical growth, and a particular set of facial characteristics. The average IQ of young adults with Down syndrome is around 50, whereas young adults without the condition typically have an IQ of 100. (MR has historically been defined as an IQ below 70.). Following improvements to medical care, particularly with heart problems, evident at birth in 50 percent, the life expectancy among persons with Down syndrome has increased from 12 years in 1912, to 60 years and the oldest on record is 87 (Wiederhort '88:

302). To prevent heart disease it is important to eat a healthy diet, without salt, fat and sugar and exercise regularly (Cohen ’10: 153).

IV. Treatment

IV.1 Exercise

For minimal cardiorespiratory health, sedentary persons must run more than three miles a day, for an hour or more, to be reduced to three miles in half an hour, 60% of normal or less, down to 1 ½ miles, due to crippling injury, illness or non-sedentary employment. **Regular physical activity** improves chances of living longer and living healthier, helps protect from heart disease, high blood pressure and high cholesterol, helps protect against certain cancers, including colon and breast cancer, helps prevent adult-onset diabetes, helps prevent arthritis, osteoporosis, reduces risk of falling, relieves symptoms of depression and anxiety, improves mood and controls weight. A sedentary life causes muscles to gradually waste away. The less muscle, the less energy the body uses at rest and the easier it is to gain weight. Lost muscle is usually replaced by fat. For a fifty-year-old person who isn't physically active, a ten-pound weight gain over the years may really mean a loss of five pounds of muscle and gain of fifteen pounds of fat. Unlike muscles, fat has very low metabolic activity, meaning it uses very little glucose and burns few calories. Conversely, fat can be turned into muscle in a few minutes of bodybuilding and half-hours of cardiovascular exercise everyday. A person needs to intentionally burn at least two thousand calories a week to begin reaping the benefits of physical activity. Thirty minutes of physical activity is a daily minimum for maintaining health and weight, however most people will benefit from more (Willet '01: 49, 50, 52). Respiration or breathing rate increases with exercise. Breathing rate is the number of breaths per minute. Depth of breathing is the amount of air moved in and out with each breath. Rate of breathing is the amount of air moved in and out with each breath. Rate of breathing is usually not more than 60 breaths per minute even in the most vigorous adult exercise. For normal people, inability to increase doesn’t limit exercise capacity. Normally, exercise ability is limited by the heart’s ability to keep up. However, with lung disease such as COPD, exercise capacity may be limited by breathing (Tucker et al '01: 129).

The American College of Sports Medicine defines **physical fitness** as a set of attributes that people have, or achieve, that relates to the ability to perform physical activity. The fitness components of cardio-respiratory endurance, muscular strength and endurance, flexibility, and body composition are all inherent within a generalized exercise prescription. The Surgeon General’s Report, Physical Activity and Health, states: “…significant health benefits can be obtained by including a moderate amount of physical activity (e.g. brisk walking, running, resistance training, recreational sports) on most, if not all, days of the week. Additional health benefits can be gained through greater amounts of physical activity. People who can maintain a regular regimen of activity that is of longer duration, or of more vigorous intensity, are likely to derive greater benefit.” The vast majority of physically active adults are not involved in structure, formal exercise programs, nor do they need to be. There is however excellent evidence that good physical fitness reduces all-cause mortality, and coronary artery disease; good evidence that it reduces disease rates of hypertension, obesity, colon cancer, non-insulin dependent diabetes and osteoporosis; some evidence that it reduces disease rates of stroke, breast, prostate and lung cancer; although there is no apparent difference in disease rates across activity categories in peripheral vascular disease, rectal, stomach or pancreatic cancer, or osteoarthritis (Mahler et al '95: 3, 6).

Exercise is necessary to burn off excess calories and to keep the body fit. Most exercise routines involve strength exercises such as push up and sit ups as well as cardiovascular exercise. Cardiovascular exercise is by far the most important part of an exercise routine. Being physically active is one of the most important steps that Americans of all ages can take to improve their health. The *2008 Physical Activity Guidelines for Americans* provides science-based guidance to help Americans aged 6 and older improve their health through appropriate physical activity. Children and adolescents should do 60 minutes (1 hour) or more of physical activity daily. All adults should avoid inactivity. Some physical activity is better than none, and adults who participate in any amount of physical activity gain some health benefits. For substantial health benefits, adults should do at least 150 minutes (2 hours and 30 minutes) a week of moderate-intensity, or 75 minutes (1 hour and 15 minutes) a week of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous intensity aerobic activity. Aerobic activity should be performed in episodes of at least 10 minutes, long enough to break a sweat and increase heart beat and respiration, and, it should be spread throughout the week. For additional and more extensive health benefits, adults should increase their aerobic physical activity to 300 minutes (5 hours) a week of moderate intensity, or 150 minutes a week of vigorous intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity activity. Additional health benefits are gained by engaging in physical activity beyond this amount. Ideally an adult would exercise for at least an hour, seven days a week, just like children.

The **Marine Corp** Physical Fitness Test (PFT) Requirements for men are three pull-ups, 50 crunches diminishing with age to 40 and 3-mile run in 28:00 minutes diminishing with age to 33:00. For women it is a 15 second flexed arm hang and 50 crunches diminishing to 40 with age and 3-mile run in 31:00 minutes diminishing to 36:00 minutes with age. To enter Marine Corp basic training men have to do 2 pull-ups, 44 sit-ups in two minutes and 1.5 mile run in 13:30 minutes; women do a flexed arm hang for 12 seconds, 44 sit-ups in two minutes and one mile run in 10:30 minutes. The Boston marathon is one of the last marathons in the United States to require qualifying times be run before the race which are 3:05 for men and 3:35 for women between the ages of 18-34, rising five minutes every four year increments to 80+ times of 4:55 for men and 5:25 for women. Racing wheelchairs, that don't tip over backwards, are so much faster than top marathon runners, they are disqualified. Cardiologists agree with the Marine Corp on the three mile minimum daily run. Army brats, running only 1 ½ miles a day, tend to be germy.

Marine Corp Age Adjusted Physical Fitness Requirements

Age	Push-ups 1 minute	Crunches 3 minutes	Pull-ups	3-Mile Run
Goal	Sets of 50-100	Sets of 50-100	**Sets of 10-20**	25:00
Male 17-26	50	50	3	28:00
27-39	45	45	3	29:00
40-45	45	45	3	30:00
46+	40	40	3	33:00
Females 17-26	50	50	Flexed Armed Hang 15 seconds	31:00
27-39	45	45	15 seconds	32:00
40-45	45	45	15 seconds	33:00

46+	40	40	15 seconds	36:00

Source: Army Study Guide

The **Physical Fitness Test** measures muscular strength and endurance (sit-ups, push-ups & pull-ups), anaerobic power (300-meter sprint), and aerobic power (1.5 - 3 mile run) with limited amounts of recovery between events. There are two general goals of fitness programs identified in the literature. The first general goal is to get officers fit. Secondly, officers should be taught skills to maintain desired fitness levels. Employees should be prepared to stay active throughout their lives There are two important issues to be considered in measuring the effectiveness of fitness programs. The first and most important is whether the program is improving the health and fitness scores of the officers. The evaluator should determine if officers' cholesterol and blood pressure levels, dietary trends, tobacco habits, and levels of obesity are improving. The second is whether the program is saving money in health-care costs. Officers' fitness levels diminished significantly after the academy. Therefore, police administrators should consider fitness maintenance programs (Gaines, Falkenberg & Gambino '93). As competitive as it is to enter the FBI Academy, it is highly recommended to achieve maximum scores on the above test. A sample above average highly competitive score would be the following: Pushups - 50-70; Situps - 50-60; 300m Run-Men 40-45 seconds; Women 50-55 seconds; 1.5 mile run - Men 9:00 -10:30; Women 10:30 - 12:00. Achieving the above scores may take at least six weeks or more even if fairly active and workout regularly.

The **military physical training prescription** takes approximately 45 minutes per day, and should be done everyday. Whether following walk-to-run guidelines or training at a higher level, the military program will help to ensure minimal standards of physical fitness. Training does not require a gym or expensive equipment. It is best to start with just the resistance of the body to develop proper form. Each standardized physical training session expends approximately 300-400 kilocalories found in a ½ cup of cooked rice, cereal, or pasta about the same size as your fist. Do not perform exercises that cause indigestion that could lead to ulceration such as running, or sit-ups, immediately after a large meal, although push-ups may not cause discomfort and other slower exercises can actually aid digestion (TRADOC '03). A review of 3,832 autopsies done on troops who died in combat or of unintentional injuries in the Iraq and Afghanistan wars found that 9 percent had atherosclerosis in the coronaries. That's a dramatic drop from the prevalence found in autopsies of casualties of the Korean (77 percent) and Vietnam (45 percent) wars (Brown '13). Food is believed to have improved dramatically and the 45 minute physical training program is minimally sufficient.

The **1-1-1 Physical Fitness Assessment**, consists of one minute of push-ups, one minute of sit-ups, and a timed, one-mile run. Soldiers are allowed a minimum of 5 minutes and a maximum of 10 minutes to recover between events. Clients often start out doing push-ups on their knees and work up to 40 to 50 regular push-ups without stopping to rest. The Walk-to-Run Program is for people whose 1-mile time was slower than 8:30 or a female with a 1-mile time slower than 10:30 minutes. During the first four weeks alternate walking and running for 10:30 minutes and repeat the walk-run routine five times in each training session. At week five run continuously for the time period listed on the training schedule. Run at a pace that can be maintained for the entire time or distance without feeling out of breath. The ability to carry on a conversation while running (the talk test), indicates the right pace. Males with 1-mile times 8:30 or faster or a female 10:30 or faster should practice speed running or carry a backpack if they don't increase the distance to the minimal daily distance of 10 km to 10 miles, twice a day, used by most athletes trying to stay healthy and keep the marathon within reach. A standardized physical training

session consists of three essential elements: warm-up, activity, and cool-down. A mat may be necessary to avoid injury doing crunches. Socks must not make running shoes tight, flat soled cross-trainers make calf muscles stronger and are best for troublesome weather and conditions of the foot. A ripped pectoral muscle, possibly from doing excessive pull-ups beyond the point of flopping, might lead to an aortic aneurysm and causes pain that is indistinguishable from angina pectoris.

Army warm up and cool down exercises

1. The Bend and Reach (5 repetitions - slow)
2. The Rear Lunge (5 repetitions - slow)
3. The High Jumper (5 repetitions - moderate)
4. The Rower (5 repetitions - slow)
5. The Squat Bender (5 repetitions - slow)
6. The Windmill (5 repetitions - slow)
7. The Forward Lunge (5 repetitions - slow)
8. The Prone Row (5 repetitions - slow)
9. The Bent-leg Body Twist (5 repetitions - slow)
10. The Push-up (5 repetitions - moderate)

Military Movement Drill for warming up

1. Verticals (1 repetition)
2. Laterals (1 repetition)
3. The Shuttle Sprint (1 repetition)

The Stretch Drill for cooling down

1. The Overhead Arm Pull (hold 20 seconds)
2. The Rear Lunge (hold 20 seconds)
3. The Extend and Flex (hold 20 seconds)
4. The Thigh Stretch (hold 20 seconds)
5. The Single-leg Over (hold 20 seconds)

Source: Training and Doctrine Command (TRADOC) Standardized Physical Training Guide. United States Army Physical Fitness School. 5 November 2003

A standardized **physical training** session consists of three essential elements: warm-up, activity, and cool-down. Although any physical activity burns calories and increases a person's caloric needs above the sedentary, it is always advised to warm-up with PFT, to protect the chest and abdomen and verify adequate digestion before running or engaging in the lengthier and more demanding athletic activity. Stretches after running help to eliminate any residual cramps, weariness and woodiness. The recommended rate of progression in an **exercise conditioning program** has three stages, the initial conditioning stage, improvement stage and maintenance stage. The initial conditioning stage includes light muscular endurance activities and moderate-level cardio respirator endurance activities that produce minimal muscle soreness and control injuries. This stage usually lasts up to four weeks and is dependent upon the individual's adaptation to exercise. The duration of the main activity during the initial stage will begin with approximately fifteen to twenty minutes and may progress to thirty minutes or more. The goal of

the improvement stage is to provide a gradual increase in the overall exercise stimulus to allow for more significant improvements in your fitness level. The goal of the maintenance stage is the long-term maintenance of the cardio-respiratory and muscular strength and endurance fitness developed during the weeks spent in the improvement stage. Exercise must be conducted daily at the proper intensity to bring about the desired changes in the body. Missing a whole week of sessions, will probably set the program back a week. If unable to perform certain exercises perform more of those able to do in order to ensure minimal cardiorespiratory exertion. Adequate nutrition, rest and recovery must be studied to optimize health, physical fitness improvement, and control injuries. The military physical training prescription takes approximately 45 minutes per day, and should be done everyday. Training does not require a gym or expensive equipment. It is best to start with just the resistance of the body to develop proper form. Each standardized physical training session expends approximately 300-400 kilocalories found in a ½ cup of cooked rice, cereal, or pasta about the same size of a fist. Exercising with more than a fistful of food in the stomach is likely to cause indigestion and could lead to ulceration.

To make the leap from 50 consecutive push-ups and/or crunches to over 100 it is advised to perform 5 set of 50 push-ups and/or crunches in quick succession, for a total of 250. In the next session, in a few hours or next morning, see how many consecutive push-up and/or crunches can be done without stopping, with 100 as the arbitrary goal, or 10 more than the previous test. Yoga instructors teach to breath through the nose when doing crunches; lightly inhale on the upward crunch and exhale with the help of gravity on the downward crunch to the ground to forcibly clear nostrils. 50 crunches is not enough to prevent or cure pot-belly. Physical education teachers claim it is minimally necessary to do more than 100 consecutive crunches to enjoy wash-board abs. It is not difficult to do more than 100 consecutive crunches, unless the feet are lodged under a bar stressing the quadriceps. It is enough to protect the back from injury with a doubled over hiking mat, or neatly folded blanket. Immobilize the feet and hips with a bar or raise the feet with hands crossed over the chest or allow the hips to rise with hands behind the head. Intensity is increased by moving hands from crossed over the chest for therapeutic crunches, to behind the head for aerobic crunches. Progress from 50 to 100 push-ups, with 5 sets of 50, or 10 more than the previous session. Trekking poles help long-distance hikers to keep their push-ups and avoid chest pain from upper body muscle wasting.

Exercise Calorie Expenditure Chart, by Hour, Weight and Activity

Activity	90 lbs.	100 lbs.	110 lbs.	120 lbs.	130 lbs.	140 lbs.	150 lbs.	160 lbs.	170 lbs.	180 lbs.	190 lbs.	200 lbs.	220 lbs.	240 lbs.	260 lbs.	280 lbs.	300 lbs.
Aerobic dancing	104	115	127	138	149	161	172	184	195	207	218	230	253	276	299	322	345
Aerobics, 4" step	131	145	160	174	189	203	218	232	247	261	276	290	319	348	377	406	435
Aerobics, slide	135	150	165	180	195	210	225	240	255	270	285	300	330	360	390	420	450
Badminton	135	150	165	180	195	210	225	240	255	270	285	300	330	360	390	420	450
Basketball (game)	198	220	242	264	286	308	330	352	374	396	418	440	484	528	572	616	660
Basketball	117	130	143	156	169	182	195	208	221	234	247	260	286	312	338	364	390

(leisurely)																	
Bicycling, 10 mph	112	125	138	150	162	175	188	200	213	225	237	250	275	300	325	350	375
Bicycling, 13 mph	180	200	220	240	260	280	300	320	340	360	380	400	440	480	520	560	600
Billiards	41	45	49	54	58	63	68	72	76	81	85	90	99	108	117	126	135
Bowling	50	55	60	66	72	77	82	88	94	99	105	110	121	132	143	154	165
Canoeing, 2.5 mph	63	70	77	84	91	98	105	112	119	126	133	140	154	168	182	196	210
Canoeing, 4.0 mph	122	135	149	162	175	189	202	216	230	243	257	270	297	324	351	378	405
Croquet	54	60	66	72	78	84	90	96	102	108	114	120	132	144	156	168	180
Cross country ski, hard	297	330	363	396	429	462	495	528	561	594	627	660	726	792	858	924	990
Cross country ski, easy	140	155	171	186	202	217	232	248	263	279	294	310	341	372	403	434	465
Cross country ski, med	198	220	242	264	286	308	330	352	374	396	418	440	484	528	572	616	660
Dancing (noncontact)	90	100	110	120	130	140	150	160	170	180	190	200	220	240	260	280	300
Dancing (slow)	50	55	60	66	72	77	82	88	94	99	105	110	121	132	143	154	165
Gardening, moderate	81	90	99	108	117	126	135	144	153	162	171	180	198	216	234	252	270
Golfing (walking)	90	100	110	120	130	140	150	160	170	180	190	200	220	240	260	280	300
Golfing (with a cart)	63	70	77	84	91	98	105	112	119	126	133	140	154	168	182	196	210
Handball	207	230	253	276	299	322	345	368	391	414	437	460	506	552	598	644	690
Hiking 10 lb. load	162	180	198	216	234	252	270	288	306	324	342	360	396	432	468	504	540

Hiking 20 lb. load	180	200	220	240	260	280	300	320	340	360	380	400	440	480	520	560	600
Hiking 30 lb. load	211	235	259	282	306	329	352	376	399	423	446	470	517	564	611	658	705
Hiking, no load	140	155	171	186	202	217	232	248	263	279	294	310	341	372	403	434	465
Housework	81	90	99	108	117	126	135	144	153	162	171	180	198	216	234	252	270
Ironing	45	50	55	60	65	70	75	80	85	90	95	100	110	120	130	140	150
Jogging, 5 mph	167	185	203	222	240	259	278	296	315	333	352	370	407	444	481	518	555
Jogging, 6 mph	207	230	253	276	299	322	345	368	391	414	437	460	506	552	598	644	690
Mopping	77	85	94	102	111	119	128	136	144	153	162	170	187	204	221	238	255
Mowing	122	135	149	162	175	189	202	216	230	243	257	270	297	324	351	378	405
Ping Pong	81	90	99	108	117	126	135	144	153	162	171	180	198	216	234	252	270
Raking	68	75	82	90	98	105	112	120	128	135	142	150	165	180	195	210	225
Raquetball	185	205	225	246	266	287	308	328	349	369	389	410	451	492	533	574	615
Rowing (leisurely)	68	75	82	90	98	105	112	120	128	135	142	150	165	180	195	210	225
Rowing machine	162	180	198	216	234	252	270	288	306	324	342	360	396	432	468	504	540
Running, 08 mph	274	305	336	366	396	427	458	488	518	549	579	610	671	732	793	854	915
Running, 09 mph	297	330	363	396	429	462	495	528	561	594	627	660	726	792	858	924	990
Running, 10 mph	315	350	385	420	455	490	525	560	595	630	665	700	770	840	910	980	1050
Scrubbing the floor	126	140	154	168	182	196	210	224	238	252	266	280	308	336	364	392	420
Scuba diving	171	190	209	228	247	266	285	304	323	342	361	380	418	456	494	532	570
Shopping for groceries	54	60	66	72	78	84	90	96	102	108	114	120	132	144	156	168	180
Skipping rope	257	285	313	342	370	399	428	456	484	513	541	570	627	684	741	798	855
Snow shoveling	176	195	215	234	253	273	292	312	332	351	371	390	429	468	507	546	585

Snow skiing, downhill	117	130	143	156	169	182	195	208	221	234	247	260	286	312	338	364	390
Soccer	176	195	215	234	253	273	292	312	332	351	371	390	429	468	507	546	585
Squash	185	205	225	246	266	287	308	328	349	369	389	410	451	492	533	574	615
Stair climber machine	144	160	176	192	208	224	240	256	272	288	304	320	352	384	416	448	480
Stair climbing	126	140	154	168	182	196	210	224	238	252	266	280	308	336	364	392	420
Swimming (25 yrd/min)	108	120	132	144	156	168	180	192	204	216	228	240	264	288	312	336	360
Swimming (50 yrd/min)	202	225	248	270	292	315	338	360	382	405	428	450	495	540	585	630	675
Table Tennis	81	90	99	108	117	126	135	144	153	162	171	180	198	216	234	252	270
Tennis	144	160	176	192	208	224	240	256	272	288	304	320	352	384	416	448	480
Tennis (doubles)	99	110	121	132	143	154	165	176	187	198	209	220	242	264	286	308	330
Trimming hedges	94	105	115	126	136	147	158	168	178	189	199	210	231	252	273	294	315
Vacuuming	68	75	82	90	98	105	112	120	128	135	142	150	165	180	195	210	225
Volleyball (game)	108	120	132	144	156	168	180	192	204	216	228	240	264	288	312	336	360
Volleyball (leisurely)	63	70	77	84	91	98	105	112	119	126	133	140	154	168	182	196	210
Walking, 2 mph	54	60	66	72	78	84	90	96	102	108	114	120	132	144	156	168	180
Walking, 3 mph	72	80	88	96	104	112	120	128	136	144	152	160	176	192	208	224	240
Walking, 4 mph	90	100	110	120	130	140	150	160	170	180	190	200	220	240	260	280	300
Washing the car	68	75	82	90	98	105	112	120	128	135	142	150	165	180	195	210	225
Waterskiing	144	160	176	192	208	224	240	256	272	288	304	320	352	384	416	448	480
Waxing the car	90	100	110	120	130	140	150	160	170	180	190	200	220	240	260	280	300
Weeding	90	100	110	120	130	140	150	160	170	180	190	200	220	240	260	280	300
Weights (40 sec.	230	255	280	306	332	357	382	408	433	459	484	510	561	612	663	714	765

down)																	
Weights (60 sec. down)	171	190	209	228	247	266	285	304	323	342	361	380	418	456	494	532	570
Weights (90 sec. down)	112	125	138	150	162	175	188	200	213	225	237	250	275	300	325	350	375
Window cleaning	68	75	82	90	98	105	112	120	128	135	142	150	165	180	195	210	225

Source: Nutribase Professional Nutrition and Fitness Software.

To count caloric needs, above the sedentary daily recommended allowance, incurred by various forms of exercise the Nutribase Professional Nutrition and Fitness Software estimates of how may calories various forms of physical activity burn every hour for people of different weights. For instance a 150 pound person, hiking with a 30 pound load would burn 352 calories an hour, for 10 hours a day, needs to pack for 3,520 calories plus 2,300 sedentary calories, for a total of 5,820 calories a day, consumed in eight to ten small 500 calories meals of trail mix, jerky, sandwiches, and small portions of cooked food, less with experience. A 150 pound person jogging a marathon at 5 mph to complete a 26.2 mile race would expend 278 calories an hour for 5 hours, 1,390 calories, more than the 2,300 calorie sedentary diet, for a total of 3,690 calories that day. A 150 pound person running to win the same marathon at 10 mph would expend 525 calories over 2 ½ hours for 1,313 extra calories, for a total of 3,613 calories the night before and on race day.

The total **caloric expenditure** of runners completing a marathon, in three to seven hours, is difficult, if not impossible to measure accurately, and in general caloric expenditure from physical activity requires more scientific study. However, using a treadmill it has been shown that the energy expended running is approximately 1.5kcal/kg/mile. Therefore, if a marathon were held on a motor-driven treadmill, a 50kg runner would expend 1,970 kcal, a 60kg runner 2,360 kcal, a 70 kg runner 2,750 kcal, and 80 kg runner 3,140 kcal, and so on. However marathons are not run on a treadmill, and in actual running conditions, the caloric cost is not independent of running velocity. Most marathon runners require approximately 2,400 kcal to finish the 26.2 miles. A comparison of horizontal running and hill running at the moderate velocity of 8 min/mile has been shown that an athlete running up a 6% incline will expend approximately 35% more energy than on a horizontal track, and on the downhill part of this 6% decline hill, the runner only reduces energy expenditure by 24%. The direct solar heat gain of marathon runners has been determined to be 55 kcal/m^2/hr on a sunny day with an ambient temperature of 22-23°C and relative humidity of 52-58%. For comparison, it has been reported that during desert conditions, the solar heat gain will approach 140 kcal/m^2/hr. For thin runners requiring at least 2 ½ hours to finish a marathon, an additional energy expenditure of at least 250 kcal must be utilized to cool the body. For the larger runner, who may require four hours to finish the marathon, solar heat gain may result in an energy expenditure of 400-500 kcal (Taylor '82: 38, 39).

Reduction of body weight is a frequently desired outcome in exercise programs. Obesity may be functionally defined as the percent of body fat at which disease risk increases. Body fat is reduced when a chronic negative caloric balance exists. It is recommended that both an increase in caloric expenditure through exercise and a decrease in caloric intake by used to accomplish

this goal, a vegan diet is useful. Exercise increases energy expenditure and slows the rate of fat-free tissue loss that occurs when a person loses weight by severe caloric restriction. Exercise also helps maintain the resting metabolic rate and thus the rate of weight loss. Obese individuals are invariably sedentary and many have had poor experiences with exercise in the past. The initial exercise prescription should be based on low intensity and progressively longer durations of activity. Central obesity, fat deposited primarily in the trunk or abdominal region is particularly problematic. Obesity often carries a negative social stigma and is associated with a reduced physical working capacity. Reduction of body fatness is a need or a goal of many exercise program participants. One pound of fat is equivalent to approximately 3500 kcal of energy (1kg =7700 kcal). In designing the exercise component of a weight loss program, the balance between intensity and duration of exercise should be manipulated to promote a high total caloric expenditure (300 to 500 kcal per session and 1000 to 2000 kcal per week for adults). Obese individuals are at an increased relative risk for orthopedic injury and thus may require that the intensity of exercise be maintained at or below the intensity recommended for improvement of cardiorespiratory endurance. Non-weight-bearing activity and rotation of exercise modalities may be necessary and frequent modification in frequency and duration may also be required (Mahler et al '95: 216-219).

Height Weight Tables for Prior and Non-Prior Service

Height (inches)	Non-Prior Service Prior Service	Maximum weight by years of age for females (pounds)				Maximum weight by years of age for males (pounds)			
		17-20	21-27	28-39	40 and over	17-20	21-27	28-39	40 and over
58	Non-Prior	112	115	119	122	-	-	-	-
	Prior	109	112	115	119	-	-	-	-
59	Non-Prior	116	119	123	126	-	-	-	-
	Prior	113	116	119	123	-	-	-	-
60	Non-Prior	120	123	127	130	139	141	143	146
	Prior	116	120	123	127	132	136	139	141
61	Non-Prior	124	127	131	135	144	146	148	151
	Prior	120	124	127	131	136	140	144	146
62	Non-Prior	129	132	137	139	148	150	153	156
	Prior	125	129	132	137	141	144	148	150
63	Non-Prior	133	137	141	144	153	155	158	161
	Prior	129	133	137	141	145	149	153	155
64	Non-Prior	137	141	145	148	158	160	163	166
	Prior	133	137	141	145	150	154	158	160
65	Non-Prior	141	145	149	153	163	165	168	171
	Prior	137	141	145	149	155	159	163	165
66	Non-Prior	146	150	154	158	168	170	173	177
	Prior	141	146	150	154	160	163	168	170
67	Non-Prior	149	154	159	162	174	176	179	182

	Prior	145	149	154	159	165	169	174	176
68	Non-Prior	154	159	164	167	179	181	184	187
	Prior	150	154	159	164	170	174	179	181
69	Non-Prior	158	163	168	172	184	186	189	193
	Prior	154	158	163	168	175	179	184	188
70	Non-Prior	163	168	173	177	189	192	195	199
	Prior	159	163	168	173	180	185	189	192
71	Non-Prior	167	172	177	182	194	197	201	204
	Prior	163	167	172	177	185	189	194	197
72	Non-Prior	172	177	183	188	200	203	206	210
	Prior	167	172	177	183	190	195	200	203
73	Non-Prior	177	182	188	193	205	208	212	216
	Prior	172	177	182	188	195	200	205	208
74	Non-Prior	183	189	194	198	211	214	218	222
	Prior	178	183	189	194	201	206	211	214
75	Non-Prior	188	194	200	204	217	220	224	228
	Prior	183	188	194	200	206	212	217	220
76	Non-Prior	194	200	206	209	223	226	230	234
	Prior	189	194	200	206	212	217	223	226
77	Non-Prior	199	205	211	215	229	232	236	240
	Prior	193	199	205	211	218	223	229	232
78	Non-Prior	204	210	216	220	235	238	242	247
	Prior	198	204	210	216	223	229	235	238
79	Non-Prior	209	215	222	226	241	244	248	253
	Prior	203	209	215	222	229	235	241	244
80	Non-Prior	214	220	227	232	247	250	255	259
	Prior	208	214	220	227	234	240	247	250

Height will be measured in stocking feet on a flat surface with the chin parallel to the floor. The body should be straight but not rigid, similar to the position of attention. The measurement will be rounded to the nearest inch with the following guidelines:
If the height fraction is less than 1/2 inch, round down.
If the height fraction is 1/2 inch or greater, round up.
Weight should be measured and recorded to the nearest pound.
All measurements will be taken in the APFT uniform.
Add 6 pounds per inch for males and 5 pounds per inch for females measuring over 80 inches tall.

Source: Army Study Guide

To maintain a competitive civil service capable of redressing the economic depression and Down syndrome evident in the accounting of overweight executives it is essential the heigh-weight chart be reinterpreted. If a person is overweight they must be demoted to bootcamp to get into shape and relearn how to live, before imposing their morbid obesity on others. Weight loss diets for fat people, often involve fasting, and always involve expending more calories than consumed.

The most important dietary issue for all people, especially, sedentary, overweight and obese people is to get sufficient exercise to digest their sedentary ration and work up an **appetite**. For sedentary workers this means scheduling the time, usually in the early morning, to minimally perform or exceed, a formal athletic training program, on a daily basis e.g. Marine Corp physical fitness test (PFT), 50 crunches, 50 push-ups and three mile run; age adjusted down to 40 crunches and push-ups and three-mile run. The ability to perform more than 100 consecutive crunches and push-ups can be achieved, by performing 250 in 5 sets of 50 in quick succession. For obese and crippled people this means a half an hour or more a day of extra-hard labor walking, due to extra weight, pain and difficulty in mobility. Fatty, adipose tissue is a fine source of nutrition, if a little toxic, and slow to metabolize. Fat quickly turns into large muscles. Sedentary obese people must become body builders and open up to outdoor activities and cardiovascular exercise. With a little practice, overweight people are able to hike and perform physical labor longer without eating than thin people. For those who are merely overweight or recovering from injury, a walk to run strategy reduces the amount of time it takes to digest a sedentary diet, and work up a healthy appetite, from two hours of walking to as little as a three mile run in half an hour. Do not exercise, particular do not run, with more than a fist-full of food in the stomach, or without some undigested water, carbohydrates, protein and calcium. Do crunches and push-ups to verify if food is sufficiently digested beyond the stomach and duodenum, before running three miles or other main activity, such as swimming a quarter of a mile. The 1.5 mile run of the army is not considered sufficient to prevent atherosclerosis and protect closely quartered troops from preventable communicable diseases, eg. *S. pyogenes,* better than being too fat to join the army.

In a study of **weight control behavior** in female athletes, it was found that about one-fourth of the 182 varsity-level athletes used diet pills routinely, about 15 percent used laxatives, and a small percentage used self-induced vomiting. The percentage of women who restrained their eating, did binge-purge eating, and used self-induced vomiting varied among different sports where leanness is emphasized very often have eating disorders. Ballet dancers and gymnasts have the most, about 70 percent and track runners, about 30 percent. Among athletes who participate in sports where leanness is not emphasized, including tennis, volleyball and swimming, the proportion of women with eating disorders is about 20 percent. A woman should probably not begin intense physical training until she has had her first menstrual period and should monitor the amount and intensity of the exercise to normalize her menstrual cycle, a few menstrual cycles a year (oligomenorrhea) is not enough. When an amenorrheic woman stops training due to an injury or another problem, she usually gains some weight and regains her menstrual periods. With the return of menses she can regain bone mass, but none of the women studies have gained back all the bone mass they lost. Where emphasis on leanness and asexual solitude, is less important, in tennis, volleyball, and swimming, eating disorders, amenorrhea, delayed menarche and stress fractures seem to be less problematic (Lane ’99: 130, 131).

The **age of menarche** (the start of menstruation) is later in athletes compared to non-athletes and swimmers. Breast and pubic hair development are delayed by about a year. This delay occurs more often in activities in which the athletes are thin, such as ballet dancing, gymnastics, running and figure skating. Some dancers and runner do not have their first menstrual period until their 20s. Scoliosis, or curvature of the spine, is also more frequent in ballet dancers with delayed menarche. The end result of delayed menarche is that these women enter menopause with a substantially lower bone mass than normal women. Normal puberty occurs when gonadoptropin-releasing hormone (GNRH) enters the bloodstream and stimulates luteinizing hormone (LH) secretion form the pituitary. In the late-maturing athlete, lack of GNRH

suppresses LH secretion. Important information for the physician to obtain includes the athlete's training intensity, eating habits, history of growth and development, and the blood levels of hormones, including LH, follicle-stimulating hormone (FSD), estradiol, and thyroid hormones. These young athletes should decrease the intensity of their training and improve nutritional intake (Lane '99: 127, 128).

The rate of bone loss in **amenorrheic women** is similar to that in women who are in early menopause. In general, women tend to lose about 1 percent of their bone mass a year form early in their 30s on, whereas athletes who no longer have menstrual periods appear to lose about 5 percent of their bone mass per year, about the same a post-menopausal woman. Estrogen deficiency, which plays a critical role in the loss of bone mass after menopause, is the main cause of osteopenia in both young women and premenopausal amenorrheic athletes. When these athletes resumed their menstrual cycle the bone mineral density of their lumbar spine increased. The beneficial effects of regular strenuous exercise on heart disease may be reversed by exercise-induced amenorrhea. The estrogen that normally reduces the LDL level is decreased in these women. The increased bone mineral density in weight-bearing bone that is usually seen with exercise is not found in amenorrheic dancers and runners. In fact, amenorrheic athletes lost over 3 percent of their spinal bone mineral density over the 15 months they were followed, despite a regular exercise program, while athletes with a normal menstrual cycle lost no bone mass. The amenorrheic runners who were taking birth control pills had a decreased risk of developing stress fractures, since birth control pills contain both estrogen and progesterone. The young athlete who takes birth control pills appears to be able to prevent some of this bone loss, but she still may not achieve peak bone mass and may never regain the bone mass she has lost (Lane '99: 129, 130).

Basic military training is not very demanding by athletic standards however many recruits become permanently disabled in boot camp and are discharged due to chronic bone disease before having made a significant contribution, possibly due to shortage of highly safe and effective $1 athlete's foot cream (clotrimazole) rather than $1 antifungal foot powder spray (toftate) that causes diffuse pain and angina. Rheumatism that occurs in conjunction with angina pectoris, usually alternating between angina that gets better with exercise and hip pain that gets worse with exercise, known as rheumatic heart disease, is caused by *Streptococcus pyogenes* 50% of the time, which responds best to penicillin but any antibiotic, with probiotic supplementation during and for two weeks after finishing a course, should eliminate rheumatism, helping to achieve minimal athletic standards, which heightens the sensitivity to and hastens treatment of new rheumatic infections so that they do not cripple the work-out. **Drug resistance** is only issue for *Staphylococcus aureus* that infects the heart and vertebrae with large lesions 1 cm in diameter and is effectively treated with doxycycline; infectious diarrhea, abdominal and joint infections are always treated with metronidazole (Flagyl ER) whether or not other drugs have been prescribed. Knee pain is rarely can be caused by human influenza, most cheaply treated with Amantadine (Symmetrel) that is also indicated to cure life-threatening extra-pyramidal side-effects of antipsychotic drugs. In general, to avoid injury, before running 3 miles it is necessary to warm up with a minimum of 100 push-ups, sit-ups and some movement drills and after running 3 miles it is necessary to stretch. All organized exercise programs do yoga to help improve flexibility, balance and strength to prevent injury during and after the high intensity endurance activity of the day. A mat or folded blanket is necessary to avoid injuring the back doing crunches. Socks must not make running shoes tight in the winter or the foot bones will be painfully crunched. A ripped pectoral muscle, possibly from doing excessive pull-ups, might lead to an aortic aneurysm and causes pain that is indistinguishable from *angina pectoris*. Do

not run so fast that breathing and/or heart beat is anywhere near painful, slow down, one should be able to talk unless a competitive athlete knows they can tolerate the chest pain needed to win.

Exercise is the cure for **atherosclerosis**, 90% of heart disease. One of the first studies to suggest the benefits of exercise was the London bus drivers' study about thirty-five years ago. The investigators compared the drivers and conductors on the big red double-decker buses in London, England. They found that, in comparison to bus conductors, drivers had more heart attacks and died younger; they concluded that the reason was probably that the driver sat behind the wheel all day, while the conductor ran up and down the stairs taking tickets (Spence '06: 94). **Congestive heart failure** is a constellation of symptoms with a poor prognosis of about 3 years, from onset, whose primary diagnostic criteria is an inability to exercise because angina pectoris becomes worse with exertion and this inability to exercise is ultimately invariably lethal to the heart patient. Carbon monoxide must be avoided. The herb Hawthorne is the only medicine that treats all the symptoms and without any known side-effects is highly recommended for the treatment of congestive heart failure by naturopaths with cures in 6 months to a year. Exercise is generally contraindicated in acute inflammatory cardiac disease, uncontrolled congestive heart failure, acute myocardial infarction, acute pulmonary disease, severe systemic hypertension, acute renal disease, acute hepatitis or drug overdose affecting cardiorespiratory response to exercise (Mahler et al '95: 222).

Patients with COPD often breathe in a rapid, inefficient fashion. They tend to hyper-inflate the chest with their accessory muscles and try to force air in with their abdominal muscles. The patient needs to learn **pursed lip breathing**, relax the abdomen and lower chest encouraging the abdomen to protrude on inspiration, thus allowing maximum descent of the diaphragm. Exhalation against pursed kips, as in whistling, also promotes more complete emptying of the lungs and improved gas transport across the alveolar membrane. Many patients gain immense relief employing this careful breathing pattern during exercise; some patients even learn to follow this pattern while at rest and during sleep. General muscular reconditioning is also important. Patients with severe COPD become progressively unfit, do fewer tasks, and therefore find themselves in a downhill spiral of dyspnea, muscular impairment, progressive disability and weight loss. Patients with marked hypoxemia, often associated with cor pulmonale, benefit from long-term use of oxygen. The knowledge that oxygen can reverse pulmonary hypertension is fundamental to the management of cor pulmonale; oxygen may also improve myocardial function in patients with severe hypoxemia. However, the most important effects of oxygen are improved brain function, improved exercise tolerance, and overall improved quality of life in patients with advanced COPD and sustained severe hypoxemia. Not all patients with advanced COPD require oxygen. A Pa_{O_2} under 55 mm Hg is generally a sign that oxygen may be necessary (Mitchell & Petty '89: 158, 159).

Exceeding 300,000 cases annually, **sudden cardiac death** (SCD) is the leading cause of death in the U.S. Studies of exercise by apparently healthy adults report an acute event rate of 1 per 187,500 person-hours of exercise and death rate of male joggers of 1 per 396,000 man-hours of jogging. The incidence of cardiac arrest while jogging is approximately 1 episode per year for every 18,000 healthy men, by appears to be lower for men with higher levels of habitual physical activity. While the risk of sudden cardiac death is increased during vigorous exercise, this risk is lower among those habitually active. There are no scientific studies on exercise-related cardiac events in women. The major cause of cardiovascular complications during exercise is coronary artery disease (CAD). During medically supervised cardiac rehabilitation exercise programs , the risk of death in the U.S. is approximately 1 per 60,000 participant hours, maybe one death

every four years per program (Mahler et al '95: 8, 9). The risk of SCD in joggers and marathon participants is estimated to 1/15,000 and 1/50,000 respectively. Preparticipation exercise testing should be reserved for men >40-45 years of age and women>50-55 year with moderate to high cardiovascular risk. The probability of an exercise induced cardiac event is greater in athletes with atherosclerotic coronary disease and left ventricular dysfunction and older athletes should be discouraged from participation in high intensity sports if they have left ventricular ejection fraction <50% or evidence of exercise-induced ischemic, ventricular arrhythmia or systolic hypotension (Lawless '11: 391). Make sure exercise clothes are cardiac glycoside free.

SCD is also the leading cause of death in athletes. Exercise-related SCD occurs in one to five cases per one million athletes per year. Of the approximately 25 million competitive athletes in the U.S. there are 25-125 document cases of SCD per year, this is likely a significant underestimation because vigorous exercise does not require participation in organized athletics and independent athletes must guard their heart in certain cardiac conditions. It is estimated that there are 10-25 cases of SCD per year in individuals younger than 30 years. The overall occurrence rate of SCD in high school athletes is estimated to be 1: 100,000-1:300,000 athletes/year. SCD in older athletes (>35 years of age) is most often related to atherosclerotic coronary arterial disease with myocardial infarction. However, in younger athletes (<35 years of age) the majority of these cases are caused by defined and hereditary cardiovascular disorders. Cardiac electrical instability, due to an underlying pathology, deteriorating into fatal ventricular tachycardia or ventricular fibrillation appears to be the most common immediate cause of death. In one study of SCD in competitive athletes from 1985 to 1995 it was found that the majority of these athletes were involved in high school sports (62%) with collegiate athletes in a distant second (22%) and professional athletes ranking third (7%). 90% of athletes suffering SCD were male. 68% of these deaths occurred during football and basketball. Ninety percent of athletes collapsed during or immediately after a training session or competition. Although symptoms or a family history may of SCD may precede the event, most episodes of cardiac arrest are the first manifestation of disease in an "apparently healthy" individual. Many athletes are capable of exceptionally high levels of performance for long periods of time, even while harboring occult and potentially lethal cardiovascular malformations.

More than 20 cardiac pathologies have been identified as causes of SCD in athletes. Findings at autopsy reveal a predominance of an enlarged heart, hypertrophic cardiomyopathy (HCM) (26%), commotion cordia (20%) and aberrant coronary arteries (13%) as the underlying cause of death. Responsible for 20% o SCD in U.S. athletes commotion cordis can be caused by a sudden forceful impact to the chest wall that can elicit electrical instability leading to asystole or ventricular fibrillation, the mean age of victims is 13 years, and the resuscitation rate is only 15%. Only 18% of fatalities had symptoms attributed to the cardiovascular system in the preceding 36 months prior to death, although as many as 10 of 12 older athletes had symptoms prior to death although all had normal ECG findings. SCD in older athletes (<35 years old) is most often related to coronary artery disease with the incidence of SCD increasing with age, including older populations of vigorous exercisers, estimates of SCD incidence approach 1:15,000-1:18,000. Most of these deaths, of young and old athletes, are thought to be related to electrical instability leading to ventricular tachycardia and eventually, ventricular fibrillation. Inflammation, typically related to **Coxsackie B virus** in 50% of cases, or bacterial infection in the myocardial tissue can lead to electrical instability leading to fatal complete heart block after considerable chest pain and dizziness.

Accounting for only 2% of SCD in U.S. athletes, **Marfan's syndrome** is an autosomal dominant inherited connective tissue disorder cocurring in approximately one in 10,000 individuals, who are characteristically very tall and thin, often with disproportionately long limbs, with an arm span greater than their height and have an increased risk of progressive dilation or the aortic root, potentially leading to dissection or rupture, that should monitored every 6 months by ECG. Approximately one in 10,000 Americans have **prolonged QT syndrome** exhibited by an abnormal ECG, 60% have a family history of long QT or SCD, one-third of patients present with palpitations, seizures and syncope. The trigger depends on the mutation, that can be detected by genetic testing, in QT1, the common trigger is swimming, in QT2 it is extreme emotion, in QT3 it is inactivity, in QT4 it is a loud noise, such a an alarm clock. Treatment often involves therapy with Beta-blockers, a pacemaker or ICD, typically then refraining from activity although 70% of athletes with ICDs make a return to play. In one study of an athletic department on the use of automated external defribulators (AEDs) found it has been used on 20% for student athletes, 33% for athletic department staff and 47% for fans, with survival rates of 0% for students, 75% for staff, 57% for fans, and 61% overall (Lawless '11: 3-17).

Arrhythmogenic right ventricular dysplasia or **cardiomyopathy** (ARVD or ARVC) is characterized by fibrofatty infiltration of the myocardium, estimates range from 2.8% of SCD in athletes in the U.S. to as high as 22% in Europe. Athletes with this condition are disqualified from sports and must investigate the benefits of moderate levels of exercise. A rest period of approximately 6 months is recommended following the onset of myocarditis, an inflammatory disease of the myocardium. Similarly a diagnosis of **acute pericarditis** disqualifies athletes from participation in competitive sports, however, once the condition is resolved, sports may be allowed. Sinus bradycardias, sinus tachycardia, premature atrial contraction and nonsustained supraventricular **arrhythmias** are generally manageable non-lethal rhythm disturbances and for symptomatic athletes with no evidence of underlying high-risk disease, all sports are allowed. Athletes with pacemakers however should not participate in collision sports. Sports participation for athletes with **aortic stenosis** depends on the severity of the stenosis. All sports are allowed for athletes with mild aortic stenosis and moderate and low intensity sports are allowed for athletes with moderate aortic stenosis. However play is not allowed for athletes with severe aortic stenosis or occlusion. Mitral valve prolapse accounts for 2% of SCD in athletes (Lawless '11: 394-396, 398, 399).

Activities during the first 48 hours following **cardiac surgery** or acute heart attack that gets worse with exertion, should be restricted to self-care activities, arm and leg range of motion movement, and other low-resistance activities. The posture should progress from lying, to sitting, to standing. Treadmills are highly recommended for uncomplicated patients, about 3 to 5 days post-event. Prior to discharge the patient should be able to perform such activities as stair climbing and most home activities and should demonstrate a knowledge of those activities that are inappropriate or excessive and a safe, progressive plan of exercise and optimal risk reduction should be formulated for patients to take home. Patients should be able to manage their rehabilitation independently and report cardiovascular symptoms promptly. The goals of **outpatient programs** are to provide appropriate patient supervision to ensure detection of problems and potential complications and provide timely feedback to the referring physician in order to enhance effective medical management, vocational and athletic rehabilitation. General principles for progressing the patient include an increase in exercise, as tolerated by the patient, every 1 to 3 weeks, with a goal of achieving 20 to 30 minutes of continuous exercise before prescribing additional increases in intensity. Patients with higher functional capacities respond well to more rapid progression. Patients with low functional capacity respond favorably to lower

intensity activity emphasizing frequent short bouts of exercise with intermittent rest periods, progressing from intermittent to continuous exercise. For most patients progression toward an independent self-management program is desirable but some patients may need to remain in a clinically supervised program (Mahler et al '95: 177-187).

Over 50 million Americans are hypertensive with a resting BP>140/90 mm Hg and/or currently use anti-hypertensive medication. The prevalence of **hypertension** rises sharply with age and is higher in men than in women and in blacks compared with whites, all stages are associated with increased risk of nonfatal cardiovascular events and renal disease. **Endurance exercise training** will elicit an average reduction of 10 mm Hg for both systolic and diastolic blood pressures in individuals with mild essential hypertension (blood pressures in the range of 140 to 180/90 to 105 mm Hg) and eve greater reduction in blood pressure in patients with secondary hypertension due to renal dysfunction. The recommended mode, frequency, duration and intensity of exercise is generally the same as those for apparently healthy individuals. Exercise at somewhat lower intensities (e.g. 40 to 70% VO_{2max}) appears to lower blood pressure as much, or more, than exercise at higher intensities, which may be especially important in specific hypertensive populations, such as the elderly. Individuals with marked elevations in blood pressure should add endurance training to their treatment regimen only after initiating pharmacologic therapy; exercise may reduce their blood pressure further, allow them to decrease their antihypertensive medications, and attenuate their risk for premature mortality. Resistance training is not recommended as the primary form of exercise training for hypertensive or manic individuals. With the exception of circuit weight training resistance training has not consistently been shown to lower blood pressure and upper body strength has a tendency to incite belligerence the more balanced athlete would run away from. Thus resistance training is recommended as a component of a well-rounded fitness program (Mahler et al '95: 207, 208).

Patients with **peripheral vascular disease** such as arteriosclerosis, often associated with hyperlipidemia, hypertension and diabetes, arterial stenosis, Raynaud's phenomenon (an abnormal vasomotor tone exacerbated by cold exposure) and Buerger's disease (an inflammation of the sheath encapsulating the neurovascular bundle in the extremities) experience ischemic pain (claudication) during physical activity as a result of a mismatch between active muscle oxygen supply and demand. The various manifestations of the symptoms may be described as burning, searing, aching, tightness, or cramping. The pain is most often experienced in the calf of the leg but can begin in the buttock region and radiate down the leg. The symptoms typically disappear upon cessation of exercise. Severe occlusive disease is treated initially with exercise and medication that decrease blood viscosity. **Weight bearing and repetitive non-weight bearing exercise** is preferred because of four grades of crippling pain. Daily exercise to maximum tolerable pain with intermittent rest periods is advised. Multi-stage discontinuous protocol may be necessary to achieve necessary O_2 consumption (Mahler '95: 209-213).

There are two major types of **diabetes mellitus**, juvenile onset Insulin dependent diabetes mellitus (IDDM) and maturity onset non-insulin dependent diabetes mellitus (NIDDM). The response to exercise in juvenile onset insulin dependent diabetes (IDDM) varies. If the diabetic is under appropriate control or only slightly hyperglycemic without ketosis, exercise decreases blood glucose concentration and a **lower insulin dosage may be required**. However, a lack of sufficient insulin prior to exercise may impair glucose transport into the muscles limiting the availability of glucose as an energy substrate leading to ketosis, resulting in greater glucose production further exacerbating the hyperglycemic state. Serum glucose concentrations in the general range of 200 to 400 mg/dL require medical supervision during exercise, while exercise is

contraindicated for those with fasting serum values >400 mg/dL pending medical follow-up. Exercise induced hypoglycemia is the most common problem experience by exercising diabetics. **Hypoglycemia** not only occurs during exercise, but may occur up to 4 to 6 hours following an exercise bout. To counteract this response, the diabetic may need to reduce insulin dosage or increase carbohydrate intake prior to exercising. Proper footwear and good foot hygiene is important. Beta-blockers and other medication may interfere with the ability to discern hypoglycemic symptoms and/or angina. Exercise in excessive heat may cause probles in diabetic with peripheral neuropathy. Patients with advanced retinopathy should not perform activities which cause excessive jarring or marked increases in blood pressure. NIDDM diabetic may benefit from oral hypoglycemic agents rather than injections of insulin, although exogenous insulin is sometimes used. Since insulin facilitate the cellular absorption of glucose a lack of sufficiently circulating insulin usually results in hyperglycemia (Mahler et al '95: 213-215).

Metabolic and cardiorespiratory adaptations to **pregnancy** may alter the responses to acute exercise and the adaptations that result from exercise training. Benefits of a properly designed prenatal exercise program include improved aerobic and muscular fitness, facilitation of recovery form labor, enhanced maternal psychological well-being, and establishment of permanent healthy lifestyle habits. There is no data indicating that pregnant women whould limit exercise intensity because of potential adverse effects. Women should **avoid exercise in a supine position after the first trimester**. Pregnant women should stop exercising when fatigued, not exercise to exhaustion and discontinue exercising and seek medical advice at any signs of bloody or fluid discharge form the vagina, swelling of hands, feet, or face, persistent headaches, elevation of pulse or blood pressure that persists after exercise, chest pain, contractions that may suggest onset of premature labor, unexplained abdominal pain or insufficient weight gain (<1.0 kg/month during last two trimesters. Any type of exercise involving the potential for even mild abdominal trauma should be avoided. Pregnancy requires an **extra 300 kcal/day** in order to maintain metabolic homeostasis. There is no objective evidence that woman who exercises has shorter or less complicated labor and delivery. However, studies have shown that women who exercise regularly return to their pre-pregnancy weight, strength and flexibility levels faster than their sedentary counterparts (Mahler et al '95: 235-239).

The wide range of health and fitness levels observed among **older adults** make generic exercise prescription difficult. Major objectives in planning exercise for the aging adult and the person with dementing and disabling illness are to increase muscle tone to improve physical functioning, to increase flexibility and balance, to improve physical stamina or endurance, and to reduce stress and promote a feeling well-being. Aerobic activity, at least 3 times a week for 20 minutes, must be spaced throughout the week. If the person cannot tolerate 20 minutes of continual movement, recent research is showing that exercise can be broken into shorter blocks which total 20 to 30 minutes for the day. Usually walking, even slow walking, is aerobic for many aging adults. As age increases, the heart rate needed to perform aerobically decreases. A 10 second pulse rate between 15 and 19 will be more than adequate to sustain aerobic functioning in an adult between the ages of 70 and 90. Exercises designed to promote flexibility, range of motion and balance daily. Without stretching and utilizing all muscles, some will become stretched and others contracted, resulting in inability to utilize some muscles altogether. Typically, problems occur in the shoulders, arms, and legs. Caregivers must realize how extremely painful it is when muscles become weak, contracted, and out of alignment from lack of use (Bridges '98: 91-92). **Resistance training** to improve muscular strength and endurance offer considerable benefit to older adults enabling them to perform activities of daily living with greater ease and counteract muscle weakness and frailty in very old persons. Some minimal

level of muscular fitness is critical for individuals to retain their independence. It is believed that resistance training provides significant musculoskeletal benefits for men and women of all ages, and an appropriate level of muscular fitness is integral to ensuring that individuals are able to spend their latter years in a self-sufficient, dignified manner. Sessions lasting longer than 60 minutes may have a detrimental effect on exercise adherence and sessions should probably be limited to 20 to 30 minutes. An adequate range of motion in all the joints of the body is important and stretching helps to reduce injury (Mahler '95: 228-234).

The principles of **skeletal muscle training** have been applied to the respiratory muscles. First, in order to increase the functional capability of the skeletal muscles, the muscle must be taxed beyond some critical level. Second, conditioning programs for strength training are different than those for endurance training. Finally, the effects of conditioning are lost after conditioning exercise is stopped. An endurance training program where patients increase ventilation for 30 seconds to 15 minutes over 6 weeks is often used. Inspiratory resistive load training has been used in patients with quadriplegia, in whom the diaphragm and sternocleidomastoid muscles are the only functioning respiratory muscles, as well as patients with acute respiratory distress, cystic fibrosisa and muscular dystrophy. In patients with chronic obstructive pulmonary disease, **inspiratory resistance training** improved exercise performance in 60 percent. The patients whose exercise performance improved after training had electromyographic evidence of inspiratory muscle fatigue with exercise prior to training. Respiratory muscle training may also be beneficial in acute respiratory failure (Cherniak '89: 94).

Special consideration must be given **endurance** exercise, e.g. cross-country running, in the treatment and limitations of respiratory disease, because, first, as a component of physical fitness endurance optimizes utilization of oxygen and, second, respiratory disease does not tolerate weight loss. There are thus three points of knowledge regarding endurance exercise, e.g. cross-country running, that are particularly important for respiratory health. One, maintain a positive caloric balance so as not to lose weight, eating more calories than are expended in exercise, keeping in mind that one cannot run well with more than a fist of food in the stomach, thus snacking frequently and eating regular large meals. Two, those are out of shape or acutely sick may injure their lungs if they perform Marine PFT 3 mile run, and must therefore set a lower par for starting their training. The 1.5 mile run, pushup test, and sit-ups test are nearly universally used as a basis for testing fitness levels. The groups who use this "Common PFT" as a minimum standard for physical testing are the Navy, Air Force, Coast Guard, and more than 50% of federal, state, and local police agencies. Three, the lung has a high threshold for endurance and it is necessary for lung health to return to the levels of exercise enjoyed before illness and to truly enjoy minimal lung health.

The aging adult, and particularly a person with dementing illness, has increasing difficulties with maintaining physical fitness. The person with good muscle tone and endurance prior to illness or injury will recover much more quickly than the person without. Good **muscle tone** is essential for maintaining normal body functions such as evacuating bowel movements, and for maintaining posture and mobility. There are three aspects of maintaining muscle tone that are important to the caregiver. One is that utilizing all possible muscles while performing every day activities, the second is in encouraging muscle usage when the person is relaxing, and the third is initiation of a more formal exercise program. It is extremely important that the patient perform any and all activities independently, if possible. Independent performance of activities will increase feelings of achievement and accomplishment, and serve to enhance the quality of life

for the person with dementing illness. There are many times during the day when caregivers can encourage persons to strengthen muscles by being a little more creative (Bridges '98: 88-90).

Exercises designed to **tone all body muscles**, including work with light weights, should be done no less than three times per week. At the beginning stages of weight exercises, it is best to perform the motions without weights for at least two weeks. Gradually add weights at monthly intervals starting with one pound and increase as tolerated up to a maximum of three pounds. Most older women can improve muscle performance with continuous work with one pound weights. Men may require more. The numbers of repetitions should be no more than eight to ten. With any complaints of pain, muscle tenderness, or soreness, weight activities should be stopped. Exercise bicycles can be utilized with ease. Stair climbers and treadmills may be too vigorous for most older people to utilize for cardiovascular conditioning (Bridges '98: 93, 94). In children under no circumstances should a weight be used that allows for less than eight repetitions to be completed per set, since heavy weight can be potentially dangerous and damaging to developing skeletal and joint structures. Resistance exercise may not be appropriate for some patients, including those with congestive heart failure (CHF), severe valvular disease, uncontrolled arrhythmias, or significant left ventricular dysfunction. Resistance training should generally be deferred until 4 to 6 weeks of supervised cardiorespiratory endurance exercise have been completed. Less myocardial ischemia and fewer arrhythmias occur with resistance exercise compared with endurance (Mahler et al '95: 225, 189).

Exercise testing is performed in many setting for nondiagnositic purposes, such as worksite health promotion programs, YMCAs and YWCAs, health clubs and other community exercise programs. This testing tends to be functional, in many the ECG is not monitored, and is aimed at assessment of physical fitness, providing a basis for exercise prescription, or monitoring of progress in an exercise program (Mahler et al '95: 10). In a **stress test**, one exercises on a treadmill while the ECG is monitored. Walking or running speed is progressively increased along with the grade (or slope) as the doctor continuously analyzes blood pressure as well as the ECG. The doctor may perform a **nuclear stress test** in which a nuclear agent (radioisotope) is injected into your vein and images of your heart are acquired to identify whether areas in the heart muscle are receiving enough blood. Stress tests are useful for sedentary patients before they begin an exercise regimen, to evaluate whether exercise is safe for them. For all stress tests and invasive procedures the patient must have nothing by mouth (NPO) for at least 6 hours prior to the procedure. In addition, the doctor may ask the patient to stop taking blood thinners, such as warfarin (Coumadin) and antiplatelet medications, such as acetylsalicylic acid (aspirin) and clopidogrel (Plavix), before a procedure (Cohen ’10: 63, 64, 65).

Exercise testing is used to determine whether exercise limitation is present if so to delineate the underlying mechanism of the reduced exercise tolerance. Exercise limitation may be caused by a ventilator defect, a cardiovascular defect, impaired physical fitness, or exercise-induced bronchospasm. Analysis of expired gas, heart rate and blood pressure simultaneously with arterial blood allows calculation of the cardiovascular response, the ventilator response (tidal volume and respiratory frequency), respiratory quotient (oxygen consumption and carbon dioxide production) the $P(A\text{-}a)O_2$, and the dead space tidal volume (VD/Vt) ratio. A change in the FEV_1 is used to assess whether exercise induced bronchospasm is present after an exercise load, which results in an increase in heart rate greater than 80% of the predicted maximum. Exercise tolerance and the cardiopulmonary response to exercise can be assessed using either multistage testing or steady-state testing. Multistage testing is preferable in that it evaluates the patient's ability to adapt to exercise. Starting with a small workload the workload is increased by

increments at 1-minutes, 5-minutes- 10 minutes, 30 minutes or longer. A rise in $PaCO_2$ and a fall in PaO_2 during the exercise indicates that the patient is unable to increase alveolar ventilation sufficiently to cope with the increased metabolic production of CO_2 during the exercise load. Thus these findings indicate that the patient has exercise limitation because of mechanical impairment. In patients with restrictive disorders, ventilation increases predominately by increases in respiratory rate. A greater than expected heart rate and ventilation and an increase in respiratory quotient, as well as a fall in pH at a given workload, indicate oxygen delivery is inadequate to meet the energy demands of the exercising muscles. This occurs if the cardiovascular system is unable to cope with the increased tissue demands during exercise or if the individual is physically unfit (Cherniak '89: 54-58).

At sea level the air surrounding us and pushing down on us is at a pressure of one atmosphere, or 760 mm Hg. This is the pressure that can support a column of mercury (Hg) to a height of 760 mm. Weather patterns are associated with small changes in barometric or atmospheric pressure. At a higher altitude air becomes thinner and barometric pressure is lower, even though there is the same percentage of oxygen in the air. When the pressure is lower there are fewer particles of air, so there are fewer particles of oxygen available. This is why with mild or moderate lung disease, shortness of breath may not occur or is less at sea level when resting than in the mountains or when flying. Therefore to survive at higher altitudes extra oxygen is needed (Tucker et al '01: 39). The amount of oxygen in the blood is measured as the oxygen partial pressure. Normal value depends on the altitude, but at sea level in an older person the blood oxygen value is typically above 80 millimeters of mercury. In a person with COPD, an oxygen pressure below 55 is abnormal enough that extra oxygen is usually prescribed. The amount of oxygen which is bound to hemoglobin, the red pigment in the blood, is called the oxygen saturation or saturation. A normal level is above 96%. Saturation values at or below 87% are abnormal and enough extra oxygen is prescribed to get the saturation level above 90%. People who overexert themselves, hyperventilating at high altitudes above 8,000 ft. often develop severe respiratory complications, atelactactis and must descend to a lower altitude. At the peak of Mt. Everest oxygen is necessary and on an average day of 250 climbers 4 die. Usually, it takes 14 days to get acclimatized to a higher elevation, and re-acclimitization is necessary high elevations are left for an extended period and returned to. The summer heat also requires 14 days to become acclimatized to.

The essential components of a systematic, individualized **exercise prescription** include the appropriate mode(s), intensity, duration, frequency, and progression of physical activity. Improvement of the ability of the body to utilize oxygen efficiently, resulting in improved endurance, is one component of physical fitness. The increase in maximal oxygen intake (VO_{2max}) may range from 5 to 30% and is most dramatic in people with low initial levels of fitness, cardiac patients and those exhibiting weight loss. The greatest improvement VO_{2max} occurs when exercise involves the use of large muscle groups over prolonged periods and is rhythmic and aerobic in nature (e.g. walking, hiking, running, stair climbing, swimming, cycling, rowing, dancing, skating, skiing, rope skipping, or endurance game activities). Circuit weight training, which involves 10 to 15 repetitions with 15 to 30 seconds rest between weight stations results in an average improvement of about 5% and is not generally recommended as an activity for improving cardiorespiratory endurance. Intensity and duration of exercise determine the total caloric expenditure during a training session. To reduce the risk of orthopedic injury progams emphasizing low- to moderate-intensity exercise with a longer training duration are recommended for most individuals. The recommended intensity of exercise should be prescribed as 60 to 90% of maximum heart rate, or 50 to 85% of $VO_{2max.}$ However individuals

with a very low initial level of fitness respond to a low exercise intensity, for example, 40 to 50% of VO_{2max}. Although improvement in cardiorespiratory endurance have ben demonstrated with 5 to 10 minutes of very high intensity (>90% VO_{2max}) exercise, at least 20 to 60 minutes of continuous aerobic activity is recommended (Mahler et al '95: 153, 155, 156, 157, 165).

IV.2 Diet

Diet, in the sense of Hippocrates, is a complete regime. Nutrition should be regarded as a remedy, prescribed as to kind and quantity or items to be forbidden (Gerson '90: 139). There are diets for weight loss, idiopathic bowel disease, heart health and cancer. The dietary response to chest pain is a vegan diet for heart disease, with absolutely no fat or animal products, and better than minimal nutrition to sustain adipose tissue to seal the lungs against respiratory ailments. A **calorie** is the heat required to raise the temperature of 1 gram of water 1ºC. The energy value of food and human energy requirements are expressed as caloric equivalents. Good nutrition is the foundation of health and well-being for all (Balch '00: 3)(WHO '19: 6). Everyone needs a balanced diet, containing adequate, but no too much calories, in the right proportion of four basic nutrients – water carbohydrates, proteins and fats – as well as vitamins, minerals and other micronutrients, on a daily basis. The human body is two-thirds water (Balch '00: 3). Total fat intake should be less than 30 percent of total energy intake. Saturated fatty acid intake should be less than 10 percent of total energy intake. Trans-fatty acid intake should be less than 1% of total energy intake (WHO '19: 24). There is not really a well-established rule regarding the minimum intake of fat, but some fat, as well as fiber, is essential for stool quality; ie. bread and butter with vegetable soup; avocado, olive and coconut oil are fine sources of small quantities fat, greater than 1 percent but less than 5 percent of caloric intake. The amount of protein in a mother's breast milk is 5 percent of calories. According to the World Health Organization (WHO) the human minimum protein requirement is 5 percent of total calories, according to the US Recommended Dietary Allowance for adults 10 percent of total calories. Legumes and peanut butter contain more protein per gram than steak. For optimum protein intake WHO recommends 10-15 percent of calories (Robbins '01: 71, 67). Therefore, 55-75 percent to 90-94 percent of calories in the diet should come from carbohydrates.

Carbohydrates always contain some protein, wheat contains too much protein, rice and other grains are reliable carbohydrates, that can be eaten in proportionally large quantities, all the time. Rice and beans make a complete protein; amaranth and quinoa provide all the essential amino acids needed to make all proteinaceous enzymes. Potatoes, sweet potatoes and bananas are also carbohydrates. Having minimally treated calorie and protein deficiency, with sufficient carbohydrates, flavor, balance and fullness, is best achieved with trace amounts of calorie rich fatty acids and large servings of light vegetables to treat micronutrient deficiency, especially oft-excreted calcium, found in leafy green and cruciferous vegetables, meat and dairy. Potatoes and milk, or milk and grain such as granola, oats or cereal, are the simplest balanced meals. Animal foods would provide a balanced diet, because they are composed of all the same elements, in nearly exactly the same proportion, as in the human body, but the consumer gets atherosclerosis before they can eat enough calories, because there is too much protein and the human lymphatic system that digests fat, is not detoxified by the liver, like protein and carbohydrates. The limit for empty calories, found swiftly in excessive amounts of animal products, protein, breads and sweets, is based on estimated calorie needs by age/gender group. Physical activity increases caloric needs, so those who are more physically active need more total calories and have a larger limit for empty calories.

Age and gender	Estimated calories for those who are not physically active	
	Total daily calorie needs*	**Daily limit for empty calories**
Children 2-3 yrs	1000 cals	135
Children 4-8 yrs	1200-1400 cals	120
Girls 9-13 yrs	1600 cals	120
Boys 9-13 yrs	1800 cals	160
Girls 14-18 yrs	1800 cals	160
Boys 14-18 yrs	2200 cals	265
Females 19-30 yrs	2000 cals	260
Males 19-30 yrs	2400 cals	330
Females 31-50 yrs	1800 cals	160
Males 31-50 yrs	2200 cals	265
Females 51+ yrs	1600 cals	120
Males 51+ yrs	2000 cals	260

Source: Choosemyplate.gov * calories estimate for sedentary lifestyle, double for full-time physical labor.

The **sedentary calorie requirement** can be misleading to active pregnant and lactating women, males age 14-30, physical laborers, alcoholics and athletes, especially female athletes; who if undernourished, require up to double the normal calorie estimate, and can often eat more without ill-effect, and are due extra-rations, as a matter of law. As a rule the larger a person is the more that person needs to eat to sustain their metabolism. Conversely smaller people and children need fewer calories. Although the portions may be small, children require about 25% more food that their relative size would indicate, because they are growing. Pregnant and lactating women require about 25 percent more calories than normal. Hikers, with a heavy backpack who walk for more than eight hours a day, are hungry, they initially require more than 5,000 kcal per day before they adapt and merely consume 1 ½ to 2 times the sedentary rate, up to 5,000 kcal. 19th century loggers are said to have consumed 12,000 kcal/day. Most long distance runners eat enough additional foodstuffs to more than double their body weight during the course of only a single year of training. When the demands of the body require repletion of the muscle and liver glycogen, carbohydrates and excess protein molecules are the only source from which the body's mechanisms can manufacture glycogen. Fat can never be converted to **glycogen**. For an endurance runner in training a proper diet should include at least 1 gm/kg/day of protein, a limitation of fat intake to no more than 20% of the caloric intake, a high percentage of the daily

calories from complete carbohydrates, and an alcohol consumption that is no more than 10% of the daily caloric intake. Alcohol has a caloric index of 7 kcal/gram in comparison to 4 kcal/gram for both carbohydrates, 5 kcal for proteins and 9 kcal/gram for fats. Top men marathon runners have a percentage of body fat in the range of approximately 2% to 8%, while the top women marathon runners generally have a range of 9% to 12%. Normal hemoglobin concentrations are nearly 10% lower for women than men of the same age (Taylor '82: 60, 71, 72).

Recommendations for **total weight gain during pregnancy** and the rate of weight gain per month appropriate to achieve it may be made based on a body mass index (BMI) calculated for the pre-pregnancy rate. Underweight mothers with a BMI <19.8 should gain a total of 12.7-18.2 kg (28-40 lb) at a rate of 2.3 kg (5.0 lb) every 4 weeks. Normal weight mothers with a BMI 19.8-26.9 should gain a total of 11.4-15.9 kg (25-35 lb) at a rate of 1.8 kg (4.0 lb) every 4 weeks. Overweight mothers with a BMI of 26.1-29.0 should gain a total of 6.8-11.4 kg (15-25 lb) at a rate of 1.2 kg (2.5 lb) every 4 weeks. Obese mothers with a BMI >29.0 should gain 68 kg (15 lb) at a rate of 0.9 kg (2.0 lb) every 4 weeks. Twin gestation by a normal mother requires a weight gain of 15.9-20.4 kg (35-40 lb) at a rate of 2.7 kg (6.0 lb) every 4 weeks (Beckmann et al '02: 91, 92). Pregnant and lactating women in emergency settings should be provided with an extra liter of water and fortified blended food commodities, in addition to the basic general ration, that are designed to provide 10–12% (up to 15%) of energy from protein and 20–25% of energy from fat. The fortified blended food should be fortified to meet two thirds of the daily requirements for all micronutrients (WHO '19: 145).

The documentary *Game Changers* (2018) explains that **plant based diets** do not pollute blood plasma and harden artery endothelium. Plant foods provide more than enough protein. Plant based, vegan diets have been proven by many winning world class athletes to improve performance. Pound for pound, many vegetarian foods are better sources of protein than meat. A hundred-gram portion of meat contains only twenty grams of protein. In comparison, a 100-gram portion of cheese or lentils yields twenty-five grams of protein, while a hundred grams of soybeans yields thirty-four grams of protein. Although meat provides less protein, it costs much more. A spot check in Florida in August 2005 showed sirloin steak costing $7.87 a pound, while staple ingredients for vegetarian meals averaged less than $1.50 a pound. An eight-ounce container of cottage cheese costing $1.59 provides 60 percent of the minimum daily requirement of protein. A study by Dr. Fred State of Harvard and Dr. Mervyn Hording of Loma Linda University made extensive comparisons between the protein intake of vegetarians and that of flesh-eaters. The concluded that “each group exceeded twice its requirement for every essential amino acid and surpassed this amount by a large margins for most of them. For many Americans and Europeans, protein makes up more than 20 percent of their diet, nearly twice the quantity recommended by the WHO. Although inadequate amounts of protein will cause loss of strength, the body cannot use excess protein, rather, it is converted into nitrogenous wastes that burden the kidneys and is eventually passed from the body, taking calcium with it. A number of studies have linked the overeating of protein to the rise in osteoporosis. Although scientists have long known that osteoporosis results from reduced calcium in the bones, they are now coming understand that one of the main causes of calcium deficiency is too much protein in the diet. Carbohydrates are the body's primary source of energy. Only as a last resort does the body use protein to produce energy. Too much protein actually reduces the body's energy capacity. In a series of comparative endurance tests conducted by Dr. Irving Fisher of Yale, vegetarians performed twice as well as meat-eaters. By reducing the non-vegetarians protein consumption by 20 percent, their efficiency improved by 33 percent. A study by Dr. J. Iotekyo and V. Kipan at Brussels University showed that vegetarians were able to perform physical tests two to three

times longer than meat-eaters before exhaustion, and were fully recovered from fatigue in one-fifth the time needed by meat-eaters (Swami '06: 11- 12, 21 – 22). The only challenge with a vegetarian diet is to get enough iron, calcium, vitamin D and phosphorus.

A vegan diet is necessary to recover from heart disease, to lose weight more reliably than any fad diet and particularly to avoid excessive atherosclerotic accumulation when exposed to a cardiac glycoside or natural hyperlipidemia from the overconsumption of fatty foods. Anyone who senses angina pectoris should keep a strictly vegan diet – brown rice and vegetables boiled in water is a nutritious staple that can be eaten twice a day perhaps with green salad with vinaigrette dressing, and a large fruit salad for breakfast. A vegan is someone who avoids all animal products; milk, eggs and all dairy products and by-products as well as all foods that contain these ingredients. The vegetable protein tolerance for heart disease is much higher than for cancer but complete vegetable proteins found in wheat gluten and vegetable combinations such as rice and beans and beans and corn can be cardiotoxic and should be avoided or minimized to less than 10% of meal mass. Careful attention must be paid to maintaining levels of caloric intake expended by exercise and vegans tend to have better appetites than the obese people. A vegetarian is someone who does not eat meat. A lacto-ova vegetarian is someone whose diet includes milk and eggs. This type of vegetarian diet is well accepted and proven to be healthy in children, heart patients should however not eat eggs that are high in cholesterol, much lower in egg whites. Eggs are as good as meat as a source of vitamins and minerals found only in animal products and are a fairly powerful medicine for the reversal of vegan diet induced diarrhea, anemia, osteoporosis and dental cavities, not to be taken daily if there is any cardiac intolerance. A lacto-vegetarian is someone who includes milk and milk products in their diet but not eggs or foods that have eggs in them. This diet is a healthy diet for children and because a long term vegan diet requires supplementation to keep the stool firm and prevent cavities a lacto-vegetarian diet provides the minimal amounts of animal product nutrition necessary to sustain gastrointestinal health in vegans over the long term. Two dairy products are particularly safe and effective source of animal nutrition, cheese aged over two months does not tend to cause intolerance because the lactose has converted to lactic acid, and probiotioc yoghurt and drinks supply the gut with friendly bacterial cultures that comprise 30% of healthy fecal volume and protect against dominating proliferations of fast growing bad bacteria. Vegetarian cultures, including the Hunza, Seventh Day Adventists, and various Indian sects, have a long history. Among these communities, vegetarianism is firmly grounded in a cultural setting, sufficient nutritional knowledge is embedded in daily and yearly rituals, ensuring continued health. In the United States, the Seventh Day Adventists were the first large group to develop and maintain a healthy vegetarian lifestyle (Yntema ’95: 40, 41, 68).

Vegetable Calories and Macro-Nutrients

Vegetable	Serving	Calories	Carbs (g)	Protein (g)	Fat (g)
Asparagus	raw, 4 medium spears, 2oz	11	2.2	1.3	0.1
Beans, Kidney	boiled, 1/2 cup, 3oz	108	19.4	7.2	0.4
Broccoli	1 cup chopped, 3oz	35	5.6	2.4	0.3
Cabbage	1 cup shredded, 5oz	41	9.8	2.1	0.1
Carrots	1 cup chopped	52	12.3	1.3	0.3
Cauliflower	1 cup chopped, 3.5oz	23	4.1	1.8	0.4
Celery	1 cup chopped, 3.5oz	14	3.6	0.7	0.2
Corn (kernels)	1/2 cup kernels, 3.5oz	354	82.3	10.8	4.3

Vegetable	Serving	Calories	Carbs (g)	Protein (g)	Fat (g)
Corn on cob	1 large ear, 5.5oz	140	33.3	4.7	1.1
Cucumber	1/2 cup slices (with skin), 2oz	7	1.3	0.3	0.1
Lentils	1/2 cup boiled, 3.5oz	115	19.9	8.9	0.4
Lettuce (iceberg)	1 cup shredded, 1.9oz	8	1.7	0.5	0.1
Mushrooms	1/2 cup pieces, 2.5oz	20	3.8	1.4	0.4
Onion	1/2 cup chopped, 3oz	36	8.6	0.8	0.1
Rice, Brown	½ cup boiled, 3.5 oz	321	142.9	14.7	5.4
Peas	1/4 cup, 1.5oz	36	6.7	2.3	0.1
Peppers (bell or sweet)	1 cup sliced, 3.2oz	18	4.2	0.8	0.2
Potatoes	1 potato, baked with skin, 7oz	255	58.1	7.0	0.4
Pumpkin	1/2 cup mashed, 4oz	23	5.6	0.8	0.1
Spinach	1/2 cup, 3oz	20	3.2	2.6	0.3
Sweet potato	1 cup, baked, with skin, 7oz	180	41.4	4.0	0.4
Tomato	1 tomato, raw, 2.2oz	11	2.4	0.6	0

Source: Freedieting.com calories from rice and vegetables

An important way of looking at foods made from grains involves the glycemic index, which deals with how quickly foods are converted to sugar. On a scale of 0 to 100, table sugar is 100; white bread, white rice, and potatoes are about 80; brown rice about 60; and whole-grain pasta about 20. Learning to prepare vegetable dishes make it easier to reduce the intake of meat and other animal products or highly processed sugary foods. When selecting margarine and cooking oils it is important to choose a non-hydrogenated margarine or oil high in polyunsaturated and monounsaturated fats, and low in saturated fats (Spence '06: 108, 109, 111, 110). Omega-3 fats, can also be an issue. You have to eat twenty of today's supermarket eggs to get as much Omega-3s as are provided by a single egg from a free range chicken. Omega 3s are plentiful in flax seeds and oil, in fatty fish such as salmon, herring, mackerel and sardines, and can be found in lesser amounts in walnuts, hemp seeds, green leafy vegetables and in canola oil (Robbins '01: 91). To the heart patient fish are Japanese junk food. Conventional wisdom tends to recommend olive oil as the heart friendly oil and categorizes coconut oil as a saturated fat but coconut oil is easy on the heart and has antifungal properties. Garlic also has antibiotic, antifungal and antiviral properties that make it a useful seasoning with or, preferably for the heart patient, without any oil.

Obesity is certainly a factor in shortening the life span and increasing the incidence of diabetes, cholelithiasis, hypertension, gallbladder disease, and vascular disorders including atherosclerosis. In 1862 the famous Dr. William Harvey imposed the then radical carbohydrate restrictive diet on his obese patient and friend, William Banting, an overweight London cabinet maker and undertaker to royalty, after diet and exercise failed to help with Banting's problem. The regiment was so successful that in 1864 Banting published a booklet "A Letter on Corpulence Addressed to the Public" extolling its virtues. The booklet sold over 60,000 copies and his diet became as widely known and controversial in Britain and Later America. Banting maintained his normal weight on his low carbohydrate diet until his death at 81. Atkins, a young cardiologist in 1963 found that for him a low carbohydrate diet worked to assuage his hunger and control his tendency to gain weight. In 1972 just as the American Medical Association and the American Heart Association started the low cholesterol/low fat juggernaut a little-known doctor by the

name of Robert Atkins started his own trajectory, named Diet Revolution. He sold millions of copies of his book promising that a diet completely contradictory to the medical establishment recommendations was the way to go. He promised the public they would lose weight by eating steak, eggs and butter to their heart's desire because fat was harmless. It was the carbohydrates, the pasta, rice, bagels and sugar that caused obesity and heart disease. The result is our present obesity epidemic (Graveline '04: 86, 76).

Changing one's diet, even to save one's life, is very similar to weaning a baby and probably doesn't happen overnight resulting in chronic atherosclerotic illness reversible with a vegan diet but for a long time. Nursing babies under eight or nine months, that derive all their nutrition from mother's milk, cannot tolerate it if she eats an unhealthy diet. When a child is weaned, his eating schedule is usually adapted to that of the rest of the family. By 1 ½ years most children can eat by themselves. By 2 years the child continues to need help feeding and likes to play with the food at meals. Three year olds can feed themselves and food dislikes are rarer, and most children will choose food based upon familiarity with it. At 3 ½ they like to complain about their food. By four years, sweetness is the most important factor determining food preference. By 5 years they have basically a normal adult eating pattern. It is important introduce a wide variety of foods. Bear in mind that hunger and fatigue can affect mealtime behavior. Remember young children usually prefer unmixed foods. Remember that socially determined habits may not work for all people. Remember that everyone has food likes and dislikes (Yntema '95: 28-30). The diet for the heart patient is limited to the vegan diet of fruits, vegetables and whole grains. The diet for the anemic, diarrheal and tooth decaying vegan heart patient is vegetarian.

Food of high fat, sugar and protein content should be avoided. Cholesterol comes from eating food of animal origin, when ingested in the form of fat, this substance is absorbed from the intestinal tract, by the lymphatic system directly to the heart. When the amount of cholesterol becomes high, arteries begin to show an increase in fatty deposits. A healthy person can tolerate 6 ounces of liquor over a one hour period, but more than this amount rapidly weakens muscle contraction and can lead to alcoholic myocarditis. The risk of developing myocardial infarction is about twice as great for heavy coffee drinkers as it is for individuals who drink no coffee at all. Elevated blood pressure, stress may increase serum cholesterol thereby causing atherosclerosis. The use of oral contraceptives involves an increased risk of clotting disorders, increases hypertension and thrombotic strokes and sharply increases the risk of stroke when cigarette smoking is also practiced. Excessive licorice (*Glycyrrhiza glabra*) ingestion for example can lead to cardiac dysfunction and severe hypertension. Vitamin E deficiency is also implicated in heart disease, and homogenized milk may be involved in atherosclerosis and other cardiovascular disease. "Everything I enjoy in life" runs the ancient lament, "is either illegal, immoral or fattening" (Elvin-Lewis '77: 181, 182). To make the elimination diet for heart disease as simple as possible - no animal products, no angina pectoris.

Eating the standard American diet that's based on meat and dairy products, with plenty of white flour and white sugar, one-third of the women and one-half of the men in the US population die of heart disease. Meanwhile, vegetarians and vegans (vegetarians who consume no dairy products or eggs) not only have far less heart disease, but also have lower rates of cancer, hypertension, diabetes, gallstones, kidney disease and obesity. Not only is mortality from coronary artery disease lower in vegetarians than non-vegetarians, but vegetarian diets have been successful in arresting coronary artery disease. The daily intake of cholesterol by non-vegetarians is 300-500 mg/daily, lacto-ovo-vegetarians 150-300 mg/ daily and vegans zero, their cholesterol levels were 210, 161 and 133 respectively, safe levels of cholesterol are less than

150. The ideal ratio of total cholesterol to HDL (high-density lipoproteins) is 3.0 to 1 or lower, the average American male's ratio is 5.1 to 1 and the average vegetarian's ratio, on the other hand, is 2.9 to 1. When it comes to heart disease the evidence is against animal products. Vegans live on average six to ten years longer than the rest of the population and in fact seem to be healthier on every measurement we have of assessing health outcomes. A low-fat plant based diet would lower the heart attack rate about 85 percent, and cancer rate 60 percent (Robbins '01: 14 , 15, 21, 22, 47).

The cardinal risk factors for coronary artery disease in the United States are hypercholesterolemia, hypertension, inactivity and smoking. Modified nutritional habits of high-risk American men, substituting diets moderate in calories, total fat, and carbohydrate, low in saturated fat, cholesterol, and simple sugars reduced heart disease mortality by about one-half and the sudden death rate was only one-fourth as great, and total mortality was lower by 40%. In a study of coronary heart disease in seven countries only the concentration of cholesterol in the blood proved to be the outstanding risk factor within and between national groups. As these data indicate, Japanese men have the lowest incidence of coronary heart disease of any industrialized nation, they smoke heavily and they have high blood pressure, but they eat a low cholesterol diet (Elvin-Lewis '77: 201, 202, 182-183). In North America there are about six hundred heart attacks per 100,000 population annually, compared with 60 per 100,000 in China. People of Chinese origin who live in North America; however, have just as many heart attacks as do other Americans. This means the major difference is environmental, not genetic, the main difference is diet. The typical North American diet tends to be too high in total fats (approximately 39 percent of total calories consumed) (Spence '06: 108, 109, 111, 110).

A new study of 137 mummified bodies, some as old as 3,500 years, found a high prevalence of hardening of the arteries, which often presages heart attack or stroke. The researchers used computer tomography (CT) scanners to detect calcium in arteries. They looked in the aorta, which is the body's main arterial trunk; the coronary arteries of the heart; the carotid arteries of the neck; and the arteries of the thigh and the lower leg. When calcium was present, they concluded the person had atherosclerosis — a diagnosis supported by studies of living patients. Probable or definite" atherosclerosis was evident in 34 percent of the mummies. Only 4 percent, however, had atherosclerosis in the coronary arteries, where it can cause heart attacks. The condition was more common in people who died in middle and old age, but was also seen frequently in those dying in their 30s. The 51 ancient Peruvians, who in life presumably ate a lot of beans and complex carbohydrates such as sweet potatoes and manioc, had atherosclerosis in 25 percent of their mummies. Three of the five Aleutian hunter-gatherers who ate a "paleo diet" high in meat and devoid of sweets and grains, showed atherosclerosis and one woman who died in her late 40s had the kind of disease seen in people with bypass surgery (Brown '13).

Around 75 percent of the day's exposure to cholesterol and harmful fat is determined by diet. The Lyon Diet Heart Study showed that a Mediterranean diet from Crete reduced heart attacks and death by 60 percent in four years, compared to the diet usually prescribed in North American coronary care units. A Cretan Mediterranean diet is low in cholesterol and animal fat, high in beneficial oils such as olive and canola, and high in fruit vegetables and whole-grain fiber. Never eat an egg yolk (use whites or egg substitutes or organic tofu). Avoid trans-fats and fried foods such as chips and fries. Heart patients who eat meat at all should keep meat intake to two ounces per day, or one serving of animal flesh every other day. Use a non-hydrogenated canola margarine, preferably one that also contains olive oil, or coconut oil. Have fun making vegetarian meals delicious (Spence '06: 164). The National Academy of Science recommends a

2,000 calories diet for 128 pound woman, and 2,900 for a 175 pound man. One pound of fat consists of 3,500 calories stored. One serving of anything fat-based, such as meat, cake, pie, ice cream, nuts, chips or fries, is about 400 calories, a serving of starches such as potatoes, pasta, rice, bread, juice, fruit, four crackers, half a bagel , or a can of pop is 100 calories. Avoid cake, pie, ice cream (except on your birthday), nuts, chips and fries. The trick is finding tasty alternatives (Spence '06: 165).

Stuff a cold, starve a fever. Although not exactly starving, coronary artery disease calls for a completely vegan diet to metabolize atherosclerotic plaques through osmotic power of low lipid levels in the blood stream. Fat causes chest pain in heart patients. Weight loss is often an objective in a heart healthy vegan diet, but the primary purpose is to eat enough fruit, vegetables and whole grains, to maintain body weight without any dietary intake of fat, whatsoever. The limits on fat provided by the American Heart Association are addressed to healthy people and tend to prolong a mild survivable form of heart disease when a completely fat-free vegan diet is wanted to respond to chest pain. Weight loss can be a sign of impending doom in cancer and serious respiratory conditions that "get worse with exercise" and comes with a grim prognosis. Little however has been written on the topic of diet and exercise for pulmonary patients. They tend to overeat and under-exercise. **Animal products** and particularly meat are very high in calories that are released in satisfactory amounts over an extended period, after other foods have been digested and cease to provide the body with energy. Animal products must be avoided with heart disease. Sugar and lactose are slightly frowned upon. **Sugar** invariably causes infections of the oral cavity which complicate and aggravate respiratory infections and brushing within 5 minutes of ingestion does little to correct the blood glucose levels in the lung. **Lactose** has been implicated in infiltration of parenchymal tissue from sputum samples and a majority of people are intolerant. In cheese aged longer than 2 months all the lactose has been converted lactic acid. Cheese is a bountiful source of calories that can be added to almost any meal. Many people are gluten intolerant and allergic to bread. The unceasing demand for calories of pulmonary patients with cor pulmonale or cancer must be met by consuming extremely large quantities of fruits, vegetables and whole grains, at least a kilogram a day.

There is considerable evidence that heavy doses of **vitamin C**, 200 – 1,000 mg may reduce the length of colds. Oranges provide about 100 mg of vitamin C and are at the peak of their medicinal effectiveness at around 200mg a day. There are other natural sources of vitamin C many of which also have medicinal qualities that are also useful for the treatment of colds and flu-like symptoms. At the first sign of a runny nose swiftly take vitamin C and available medicines to avoid a diagnosis of allergic rhinitis if the symptoms do not stop within a week. **Vitamin D** deficiency may hamper lung function, affect human's lung structure and function, according to a new study conducted on mice by scientists from Australia. Vitamin D has already been found associated with severity of asthma and chronic obstructive pulmonary disease (COPD). The Australian researchers compared two groups of two-week-old mice, one with vitamin D deficiency and the other without, for the lung volume and lung function. The study published in the American Journal of Respiratory and Critical Care Medicine showed the mice with Vitamin D deficiency had reduced the lung function and volume, compared with the control mice. The results of this study clearly demonstrate that vitamin D deficiency alters lung growth, resulting in lower lung volume and decrements in lung function. This is the first direct mechanistic evidence showing that vitamin D deficiency alters lung development, which may explain the association between obstructive lung disease and levels of vitamin D. Vitamin D deficiency is associated with higher risk of rickets, osteomalacia, osteoporosis, cancer, heart disease, diabetes, depression, and autism among other things. In 2010, The Food and Nutrition

Board slightly increased its Recommended Dietary Allowances for vitamin D for people at various ages. Exposure of the bare bands and the face to the sun at the hottest time in the summer is believed to help make more than 10,000 IUs of vitamin D. Healthy adults can tolerate intake of up to 10,000 IUs of vitamin D per day while the Institute of Medicine suggests that the up tolerable limit is 4000 IUs for adults. Only a few foods contain low levels of vitamin D, which are not enough for most people to use to maintain a healthy serum level. They include salmon, sardines, mackerel, fortified cow's milk, soy milk, fortified orange juice, fortified cereal, egg yolk and mushroom. Adults are recommended to use about 4000 to 5000 IUs daily to prevent diseases.

Vitamin, Mineral and Herbal Remedies for Respiratory Ailments

Vitamin	**Indication**
Vitamin C ascorbic acid	Take 200-1,000 mg daily to shorten duration of cold. Collagen synthesis, amino acid metabolism, helps iron absorption, immunity, antioxidant. Found in spinach, broccoli, red bell peppers, snow peas, tomato juice, kiwi, mango, orange, grapefruit juice, strawberries, rosehips.
Essential Oil	**Indication**
Peppermint, Lavender and Lemonbalm	These safe essential oils are effective for use in the treatment of allergic rhinitis, with direct and/or repeated application to the affected nostril(s) by aromatherapy or leaf
Culinary Herb	**Indication**
Black Pepper, Horseradish,	Black pepper is warming, energizing and stimulating. It is indicated for "cold-type" problems such as flus, coughs, colds, poor circulation, and poor digestion. Horseradish is good for sinus congestion and head colds.
Cinnamon *Cinnamomum* spp.	Powerful antiseptic, with antiviral and antifungal properties. Often indicated in cases of viral infections, fungal infections, and colds and flus.
Elder *Sambucus nigra*	Elderberry and elder flower are among Europe's most esteemed remedies for cold and flus, where they line pharmacy shelves. Elder's beautiful lacy flowers are diaphoretic, meaning they induce sweating, thereby helping to lower fevers. Elderberry has immune-enhancing properties and are often combined with Echinacea in immune-stimulating remedies for colds with powerful antiviral properties and are helpful in treating viral infections including flus, URI, herpes and shingles. Elderberries make some of the best syrup, wine, jams, jellies and pies. The flowers are also edible, making nice fritters dipped in a light batter. Do not eat the raw uncooked berries in any great quantity as they can cause digestive upset and diarrhea in some people.
Garlic *Allium sativum*	Herb of choice for treating colds, flus, sore throats and poor or sluggish digestion. It stimulates the production of white blood cells, boosting immune function and is a potent internal and external antiseptic,
Ginger *Zingiber officinale*	Popular warming, decongesting herb for cold-type imbalances such as poor circulation, colds and flues, respiratory congestion and sore throat. Safe.
Sage	Astringent, antiseptic and relaxing action on the mucous membranes,

Salvia officinalis	sage is the classic remedy for inflammation of the mouth, throat, tonsils and laryngitis. It can be used as a mouthwash or swab to treat infected or sore gums and canker sores.
Thyme *Thymus* spp.	Fine tea for treating coughs and chest complaints. Rich in anti-oxidants and has a markedly tonic effect, supporting normal body function. It seems to have a positive effect on the glandular system as a whole and especially the thymus gland.
Herbal Teas	
Cordyceps sinensis	Enhances physical strength and endurance, treats pneumonia, respiratory infections
Green or Black Tea *Camellia sinensis*	A pleasant stimulant containing theophylline, a substance with powerful lung healing qualities. Can be drunken in great quantities by people with lung disease.
Echinacea *Echinacea* spp.	Echinacea can be taken, as a tea or tincture, at the first sign of a cold or flu to boost immune system function. Increasing macrophage and T-cell activity. Rich in vitamin C and polysaccharides, which have antifungal, antiviral, antibacterial properties. Particularly effective against bronchial and respiratory infections, sore throat, and oral infections.
Lavender *Lavandula* spp.	Lavender is an antibacterial, antifungal and antiseptic agent. More used in washing, fresh can be made into a tea. Useful in treating a host of infections, including staph, strep, colds and flus.
Licorice *Glycyrrhiza glabra*	Herb of choice for soothing irritated and inflamed tissue such as in cases of sore throat, bronchial inflammation and stomach and bowel irritation. Licorice has a long history of use relieving throat inflammation and for strengthening the vocal cords. Licorice gently supports the adrenal glands ability to produce hormones and aids in the breakdown and elimination of excess or "worn-out" hormones via the liver and kidneys. It has a thick, sweet flavor, which makes it a nice addition to tea in small amounts. The root can be almost too sweet, and some people find its flavor rather offensive when brewed by itself. To increase its palatability blend it with other herbs in syrups, teas and tinctures. You can also eat the licorice root dried or fresh whole root.
Spearmint *Mentha spicata*	Spearmint is sweeter, milder and less pungent than peppermint and tends to be better for children. Combined with catnip, it's an excellent herb for children with a fever.
Probiotics	
Lactobacillus reuteri	Cold and respiratory virus
Lactobacillus plantarum 299v	Cold and respiratory virus

Source: Gladstar '12; Brown '04: 82, 83; Huffnagle '07: 263;

Green or Black Tea (*Camellia sinensis)* A pleasant stimulant containing theophylline, a substance with powerful lung healing qualities. Can be drunken in great quantities by people with lung disease. Garlic is both an antibacterial, antiviral and antifungal agent, helping to rid the body of harmful invaders. *Echinacea purpurea* is a wild American herb that is believed to increase the body's white blood cells, which fight infection. Goldenseal is another herb believed to help with colds by strengthening weakened nasal membranes and increasing the liver's ability to filter our infectious wastes. Most colds last for a week, while some take several days to run

their course. Fortunately, most colds clear without complications. But sometimes what begins as the typical viral nasal infection of a cold progresses to a similar infection of an adjacent area, such as the ears, sinuses, throat, voice box (causing laryngitis) or bronchial tubes (leading to bronchitis or even pneumonia). At this point, the infection often becomes bacterial. Penicillin is usually the most effective antibiotic for the treatment of sinusitis, pneumonia, meningitis or rheumatic heart disease, however, any antibiotic (other than Bactrim) should treat most respiratory infections. Infections causing stenosis of the airways in the throat, should however be treated with azythromycin, or doxycycline (over age 8), in case a hypersensitivity to yeast and mold has manifested an anaphylactic reaction to the penicillin mold.

Plants trusted in domestic and aboriginal medicine as efficacious for respiratory disease are Gymnopserms *Ephedra gerardiana* (Ephedraceae), Angiosperms, Asclepiadaceae, *Tylophora indica*, Asteraceae, *Saussurea lapp* (costus), Campanulacea, *Lobelia inflate* (Indian tobacco), Euphorbiaceae, *Euphorbia hirta*, Fabaceae, *Glycyrrhiza glabra* (licorice), Lamiaceae, *Monardo fistulosa* (wild bergamot or horsemint), Scrophulariaceae, *Verbascum Thapsus* (mullein), Solanaceae, *Datura stramonium*, Zingiberaceae, *Alpinia galangal* (greater galangal), *Rhododendron anthopogonoides* (Ericaceae). Cold remedies include Gymnosperms *Abies balsamea* (balsam fir), *Juniperus virginiana* (juniper or red cedar), *Tsuga Canadensis* (hemlock), Angiosperms, Araceae, *Acorus clamus* (sweet flag), Asteraceae, *Achillea milefolium* (yarrow), Cucurbitaceae, *momordica charantia* (whild balsam apple), Betulaceae, *Betula occidentalis* (western red birch), Lamieaceae, *Hedeoma pulegioides* (American pennyroyal), *Marrubium vulate* (horehound), *Nepeta cataria* (catnip) Salicaceae, *Populus balsamifera* (balsam poplar) and *P. candicans* (balm of Gilead), Scrophulariaceae, *Verbascum Thapsus* (mullein), Solanaceae, *Withania somnifera* . *Cornus florida* (dogwood) was prescribed by pioneer doctors as a bitter drink made by steeping dogwood flowers, fruit and bark in water for fevers and chills. *Myrica cerifera* (bayberry) *Oldenlandia corymboso*, and *Salix* spp. and *Populus* spp. (willow and poplar) were also used to treat fever. (Elvin-Lewis ’77: 306-308).

Antitussive (anticough) agents are sometimes needed to suppress coughing to facilitate rest and sleep and to reduce irritation of the respiratory tract. Acting centrally by depressing the cough reflex of the central nervous system, codeine, and to some extent other opium alkaloids, are probably the most widely used compounds with nethol (peppermint oil) and eucalyptol. A number of plants have been used to stop coughing and soothe sore throats, Anacardiaceae, *Rhus glabra* (sumac), Araliaceae, *Aralia nudicaulis* (wild sarsaparilla), *Aralia racemosa* (spikenard), Fabaceae, *Prosopis julifora* (mesquite), Myrtaceae, *Syzgium cumini*, Ranunculaceae, *Xanthorhiza simplicissima* (shrub yellowroot), Rosaceae, *Prunus serotina* (wild black cherry), *P. virginiana* (choke cherry), Solanaceae, *Solanum surattense*. Many individuals who suffer from respiratory disease find it difficult to clear the chest of sputum. Expectorants and mucolytic agents are used to help them. Expectorants and mucolytics such as guafenesin (Humibid, Tussi-ortganidin) or the herb mullein, which may be smoked as a tobacco substitute help liquefy secretions and allow you to cough up mucus more easily (Tucker et al ’01: 75). Ipecac syrup (*Cephaelus ipecacuanha*) is an expectorant, others are Gymnosperms *Pinus roxburghii*, Angiosperms, Acanthaceae, *Adhatoda vasica,* Apocynaceae, *apocynum androsaemifolium* (spreading dogbane or wild ipecac), *A. cannabinum* (hemp dogbane), Araceae, *Acorus calamus* (sweet flag), Euphorbiaceae, *Acalypha indica,* Hydrophyllaceae, *Eriodictyon californicum* (yerba santa) (Elvin-Lewis ’77: 300). One of the best expectorants is water. Drinking an adequate amount of water, about one quart per day, will make clearing phlegm easier, which may lead to improved breathing (Tucker et al ’01: 75).

Iron deficiency is probably the most common nutritional disorder in the world. Although more common in developing countries this form of anemia is also common in the United States. Normally, the total body iron content is in the range of 2gm in women and up to 6 gm in men. Approximately 80% of the functional iron is found in hemoglobin, myoglobin and iron-containing enzymes such as catalase and the cytochromes contain the rest in pools of hemosiderin and ferritin containing approximately 15 to 20% of total body iron. Because women have substantially smaller stores of iron than males they have a much more precarious iron balance and are vulnerable to excessive loss or increased demands associated with menstruation and pregnancy. In iron deficiency, **serum ferritin** is always below 12 µg/liter, whereas in iron overload very high values approaching 5000 µg/liter may be obtained. With liver damage and inflammatory states, serum ferritin levels may be high despite normal body stores. **Storage iron pool** is readily mobilized in the event of an increase in body iron requirements, as may occur following loss of blood. Iron is transported by **transferrin** which delivers iron to the cells, including erythroid precursors, where iron is required for hemoglobin synthesis. Immature red cells possess high-affinity receptors for transferrin. The most active site of iron absorption is the duodenum, but the stomach, ileum, and colon may also participate to a small degree. Approximately 25% of the **heme iron** derived from hemoglobin, myoglobin, and other animal proteins is absorbed, but only 1 to 2% of nonheme iron found in green leafy vegetables is absorbed. Daily losses of iron range between 1 and 1.5 mg. Thus to maintain a normal iron balance, approximately 1 mg of iron must be absorbed from the diet every day. Because only 10 to 15% of the ingested iron is absorbed, the daily iron requirement for adult males is 5 to 10 mg and for adult females 7 to 20 mg. The average daily dietary intake of iron in the Western World is about 15 to 20 mg. An iron deficiency may result from (1) dietary lack; (2) impaired absorption; (3) increased requirement; or (4) chronic blood loss.

Dietary inadequacy is found in the elderly, very poor, infants because milk contains very small amounts of iron and children who need dietary iron to accommodate growth and expansion of blood volume. Impaired absorption is encountered in sprue, intestinal steatorrhea and chronic diarrhea. Chronic blood loss is the most important cause of iron deficiency in the Western world but is common in vegans complaining of diarrhea. Bleeding within the tissues or cavities of the body may be followed by total recovery and recycling of iron, however, external hemorrhage depletes the reserves of iron. Iron deficiency induces a hypochromic microcytic anemia and may cause other changes, including koilonychias, alopecia, atrophic changes in the tongue and gastric mucosa and intestinal malabsorption. The diagnosis of iron deficiency anemia rests on laboratory studies. Both hemoglobin and hematocrit are depressed, usually to moderate levels, and are associated with hypchromia, microcytosis and some poikilocytosis. The serum iron and serum ferritin are low, and the total plasma iron-binding capacity is high. Low serum iron with increased iron-binding capacity results in a reduction of transferrin saturation levels to below 15%. Reduced heme synthesis leads to elevation of free erythrocyte protoporphyrin. Unexplained iron deficiency anemia can be caused by an occult lesion or cancer (Saunders ’94: 610-613). .

A balanced diet with enough fruits and vegetables to digest some animal products provides sufficient amounts of vitamins and few individuals have deficits. One of the biggest concerns of vegetarians, is providing adequate levels of B_{12} which is almost entirely unavailable in vegetable. There is typically no problems in the growth and development of vegetarian and vegan children who eat varied diets with enough calories and adequate intake of vitamin $B\text{-}_{12}$. The recommended Dietary Allowance for vitamin B-12 is 2 micrograms, 2 millionths of a gram. Because soils have been sprayed with chemical fertilizers and pesticides, they are devoid of the

B-12 that was once abundant in the dirt (Robbins ’01: 85). Vitamin B 12 is found in tempeh, dulse and kombu (two varieties of seaweed), many fortified soy products, meat and dairy products. The recommended daily dietary allowance for B_{12} is Children 1-3 years 0.7 micrograms/day, 4-6 years 1.0 micrograms/day and 7 and up 1.4 micrograms/day. Approximately 13 micrograms of B12 can be derived from 100 grams of dried seaweed (Yntema ’95: 94). A deficit in vitamin B_{12} can result from various causes with disparate results. Vegetarians and the elderly are often deficient in B_{12} because the main dietary source is meat and they should therefore take a **vitamin B_{12} supplement**. An estimated 15-20 percent of the elderly have B_{12} deficiency. Pernicious anemia is a condition in which vitamin B_{12} is not properly absorbed because the stomach does not produce a factor required for its absorption in the distal intestine. Individuals who lack this factor can develop anemia, because we need vitamin B_{12} to make new red blood cells; they can also develop a problem in the spinal cord and peripheral nerves that results in numbness and tingling of the extremities, and if untreated, in paralysis and dementia. Another cause of vitamin B_{12} depletion is long-term use of drugs that suppress the production of acid by the stomach, such as omeprazole. Gastric acid is needed to strip vitamin B_{12} off food so we can absorb it; because crystalline vitamin B_{12} can also be absorbed from tablets without acid, it will be effective. Individuals taking omeprazole or related rugs for longer than a few months should probably take a B_{12} supplement. Folic acid is particularly important for the development of the nervous system of the fetus and the typical North American diet may not provide enough folic acid found in green leafy vegetables for pregnant women, and it is now apparent that folic acid fortification of cereal –grain products (mandated in the U.S. since 1998) has reduced by half abnormalities of the brain and spinal cord that lead to spina bifida and related abnormalities (neural tube defects) (Spence '05: 156, 155).

Megaloblastic anemias constitute a diverse group of entities, having in common impaired DNA synthesis and distinctive morphologic changes in the blood and bone marrow. The erythroid precursors and erythrocytes are abnormally large, thought to be related to impairment of cell maturation and division. Vitamin B_{12} and folic acid are coenzymes in the DNA synthetic pathway. A deficiency of these vitamins or impairment in their utilization results in deranged or inadequate synthesis of DNA that may lead to megaloblastic anemia and usually presents in the form of chronic diarrhea. **Vitamin B_{12}** is a complex organometallic compound known as cobalamin, for the cobalt atom attached to a corrin ring, therapeutically synthesized as stable cyanocobalamin. Vitamin B_{12} is required for methylcobalamin to convert homocysteine to methionine and to metabolize polyglutamate forms of folate. Under normal circumstances, human are totally dependent on dietary animal products for the vitamin B_{12}. Strictly vegan or macrobiotic diets do not provide enough of this essential nutrient. The daily requirement is 2 to 3 µg daily and the normal balanced diet contains significantly larger amounts which takes years of vegan diet to deplete (Saunders ’94: 603-607). The hypothesis that lack of **folate** is the proximate cause of anemia in vitamin B12 deficiency is supported by the observation that the anemia improves with the administration of folic acid. Folate is most necessary for (1) the synthesis of purines.; (2) the synthesis of methionine from monocysteine, a reaction that also requires vitamin B_{12}; and (3) the synthesis of deoxythymidylate monophosphate (dTMP). **Folic acid deficiency** results in megaloblastic anemia without the neurological changes, but is not common, except with a very marginal diet, without adequate green vegetables. Despite their abundance in raw foods folate is sensitive to heat and cooking foods for 5 to 10 minutes destroy up to 95% of the folate. Folic acid antagonist drugs such as methotrexate, 6-mercaptopurine and cyclophosphamide inhibit folate function leading to ulcerative lesions in the gastrointestinal tract as well as megloblastic anemia. Human require 50 to 200 µg of folate daily especially due to the increased demand for folate during pregnancy and dietary inadequacies found in chronic

alcoholics, the indigent and very elderly. Megaloblastic anemia resulting from folic acid and vitamin B_{12} deficiency are identical (Saunders '94: 605-610). **Dark leafy greens and brown rice**, seem to be the most effective vegan staple.

The feature that sets **pernicious anemia** apart from dietary vitamin B_{12} deficiency is that the cause of the malabsorption is atrophic gastritis with failure of the production of intrinsic factor (IF). Chronic atrophic gastritis is marked by a loss of parietal cells, a prominent infiltrate of lymphocytes and plasma cells, and megaloid and atypical changes to the mucosal cells. It is an auto-immune disorder resulting from the presence of blocking, binding and gastric antibodies. Absorption of vitamin B_{12} requires IF, which is secreted by the parietal cells with HCl. Diagnostic features include (1) a marked to severe megalobastic anemia; (2) leukopenia with hypersegmented granulocytes; (3) mild to moderate thrombocytopenia; (4) neurologic changes related to involvement of the posterolateral spinal tracts; (5) achlorhydria even after histamine stimulation; (6) inability to absorb an oral dose of cobalamin (assessed by urinary excretion of radiolabeled cyanocobalamin given orally, called the Schilling test; (7) low serum levels of vitamin B_{12} ; (8) excretion of methymalonic acid in the urine; and (9) a striking reticulocytic response and improvement in hematocrit levels following parenteral administration of vitamin B_{12} (Saunders '94: 605, 608).

The B complex vitamins seem to have the greatest relationship with cardiovascular health. Niacin, also known as vitamin B3, has for years been widely prescribed to lower "bad" LDL cholesterol and raise levels of "good" HDL cholesterol. Niacin -- in doses about 100 times higher than the recommended amount from food -- was thought to be helpful. A combination drug containing these "medicinal" doses of niacin failed to lower the risk of heart attacks or strokes and even proved harmful for some with vascular disease. Indeed, the combination drug used in the study -- made by US pharmaceutical giant Merck and combining extended release niacin with laropiprant -- is already approved in 70 countries, though not the US. But when tested against a placebo in more than 25,000 patients, it failed to reduce the numbers of heart attacks, strokes or other serious cardiovascular problems. Even more worryingly, the study showed unexpectedly higher levels of bleeding and infections in the group taking the drug versus the placebo. And the group taking the study drug also showed higher levels of other side effects, including new cases of diabetes and complications for previously-diagnosed diabetes, as well as rashes and diarrhea. It was unlikely the poor outcome could be linked to the second component of the drug, laropiprant, which was included to reduce the facial flushing caused by niacin. The lack of benefit on heart attacks and strokes is consistent with another recent, smaller-scale study of niacin, which did not use laropiprant, and many of the side effects are known to be due to niacin. Because of the results of this research, Merck has withdrawn its application for FDA approval of the drug and suspended its sale around the world (Armitage '13). Niacin should not be taken in doses many times the Recommended Daily Allowance (RDA) found in multi-vitamins.

Folic acid 2.5 mg daily will normalize blood levels of homocysteine in about half the cases; a combination of folic acid 1 mg, vitamin B_6 10 mg, and vitamin B_{12} 1 mg (1000 mcg) will normalize levels in more than 95 percent of cases. A high dose of B_{12} is needed. Blood levels of B_{12} should be above 300 pmol/L. In some cases it is necessary to add a fourth supplement called betaine, and vitamins are not as effective for individuals with kidney failure. Overnight daily dialysis is more effective at lowering homocysteine than routine dialysis three times a week, and sulfur containing compounds called thiols may be useful (Spence '05: 157, 158). **Vitamin E**, C and beta carotene, which reduce oxidation, may be protective. A Cambridge study showed a

significant reduction in recurrent heart attacks in individuals given vitamin E after a heart attack, but without a reduction in deaths. Vitamin E, when it accepts a free radical, itself becomes a free radical (the tocophyryl radical); it then needs vitamin C to detoxify it. A Finnish study showed that combining vitamin E with 250 mg daily of slow-release vitamin C reduced the progression of artery thickening as measured by ultrasound. It is probably best to get vitamins and antioxidants from food rather than from tablets. Vitamin C in orange or grapefruit juice brings along with it other potentially beneficial antioxidants and bioflavonoids- hesperitin in orange juice and naringin in grapefruit juice are related to genistein in soy beans. These have anticancer and cholesterol-lowering effects. The antioxidant lycopene is what gives the red color in tomatoes, watermelon, and strawberries; blueberries get their color and flavor from another brightly colored antioxidant. Eat fruits and vegetables of all colors to get a variety of antioxidants (Spence '05: 159, 160). **Selenium** is an antioxidant found in grains needed to help the absorption of vitamin E to protect body from oxidation. In general vitamin supplementation is ineffective for the treatment of heart disease and dietary vitamins and minerals should suffice in the absence of bone loss, dental cavities, diarrhea or anemia due to deficiency. If the diet is not nutritious a multivitamin may help, but is poor substitute for a balanced diet.

Vitamins, Minerals and Herbs Essential to Cardiovascular Health

Vitamin	Indication
B1 (thiamin)	Supports energy metabolism and nerve function. Found in spinach, green peas, tomato juice, watermelon, sunflower seeds, lean ham, lean pork chops, soy milk
B2 (riboflavin)	Supports energy metabolism, normal vision and skin health. Found in spinach, broccoli, mushrooms, eggs, milk, liver, oysters, clams
B3 (niacin)	Supports energy metabolism, skin health, nervous system and digestive system. Found in spinach, potatoes, tomato juice, lean ground beef, chicken breast, tuna (canned in water), liver, shrimp
B6 (pyridoxine)	B complex, amino acid and fatty acid metabolism, red blood cell production. Found in bananas, watermelon, tomato juice, broccoli, spinach, acorn squash, potatoes, white rice, chicken breast
B9 (folate)	Supports DNA synthesis and new cell formation. Found in tomato juice, green beans, broccoli, spinach, asparagus, okra, black-eyed peas, lentils, navy, pinto and garbanzo beans
B12	Used in new cell synthesis, helps break down fatty acids and amino acids, supports nerve cell maintenance. Found in meats, poultry, fish, shellfish, milk, eggs
C (ascorbic acid)	Collagen synthesis, amino acid metabolism, helps iron absorption, immunity, antioxidant. Found in spinach, broccoli, red bell peppers, snow peas, tomato juice, kiwi, mango, orange, grapefruit juice and strawberries.
Vitamin E	Antioxidant, regulation of oxidation reactions, supports cell membrane stabilization. Found in polyunsaturated plant oils (soybean, corn and canola oils), wheat germ, sunflower seeds, tofu, avocado and sweet potatoes.
Vitamin K	Synthesis of blood-clotting proteins, regulates blood calcium. Found in Brussels sprouts, leafy green vegetables, spinach, broccoli and cabbage.
Mineral	**Indication**

Selenium	Antioxidant. Works with vitamin E to protect body from oxidation. Found in grains.
Culinary Herb	**Indication**
Cayenne *Capsicum annuum* and related Peppers and Chiles	Warming, improves circulation, is used in heart tonic, lowers cholesterol, analgesic, decongestant. May irritate heart or cause heartburn in some patients.
Garlic *Allium sativum*	Garlic helps to maintain healthy blood cholesterol and prevent blood platelet aggregation, making it the herb of choice for many circulatory issues and lowers blood sugar levels in Type 2 diabetes. Garlic is antibiotic, antiviral and antifungal.
Ginger *Zingiber officinale*	Ginger lowers blood level triglycerides linked to diabetes and heart disease.
Hawthorne *Crataegus laevigata*	Hawthorn is considered the herb supreme for the heart. The berries, leaves and flowers are rich in bioflavonoids, antioxidants, and procanidins, which feed and tone the heart. Hawthorn works in part by dilating the arteries and veins, enabling blood to flow more freely and releasing cardiovascular constrictions and blockages. It strengthens the heart muscle while helping to normalize and regulate blood pressure. It also helps maintain healthy cholesterol levels. Hawthorn is outstanding both to prevent heart problems and to treat high or low blood pressure, heart disease, edema, angina and heart arrhythmia. Hawthorn doesn't store in the body and isn't accumulative in action, it's important to take on a regular basis if using as a heart tonic. Hawthorn also helps to stabilize collagen and support the health and repair of ligaments, tendons and muscles. Hawthorn strengthens capillaries and heals bruises. The berries are tasty and often enjoyed in syrups, jams and jellies or dried infusions.
Lemon balm *Melissa officinalis*	Remedy for heart disease (and heartache), depression and anxiety, nervous disorders and a host of viral and bacterial infections. Lemon balm is considered a thyroid inhibitor, those suffering from hypothyroidism or low thyroid activity should use it only under the guidance of a health care practitioner.
Rhododendrum caucasium	Antioxidant, blocks carcinogen absorption and 20% of fat absorption through intestines. Increases energy in heart muscles and uric acid excretion. Relaxes blood vessels, lowers blood pressure.
Rosemary *Rosmarinus offinalis*	Rosemary is a circulatory stimulant useful for the treatment of poor circulation and low blood pressure.
Sage *Salvia officinalis*	Sage is a superb aid in the digestion of rich, fatty meat. It also lowers cholesterol levels and is a bitter tonic for the liver. It rebuilds vitality and strength during long-term illness. Sage tea is a warming, bracing drink, nice mixed with mint or rosemary and lemon balm.
Valerian *Valeriana officinalis*	Valerian has a tonic effect on the heart and is especially recommended in cases of irregular heartbeat and anxiety that affects the heart. It is often combined infusion with hawthorne berry to treat high blood pressure and irregular heartbeat. For those people for whom valerian works, it works well. Some people find it irritating and stimulating, rather than relaxing.

Source: Sanders '12

Congestive heart failure (CHF) is a constellation of problems rather than a specific disease. It means that the heart is not functioning properly, so that blood is not being pumped around the body efficiently. Digitalis, blood thinners and many high blood pressure medicines are also thought to be ineffective and dangerous alternatives to Hawthorn, the supreme herb for the heart. The end result is that tissues are not receiving adequate blood supply to meet their needs. People with heart failure frequently suffer from fatigue. They also tire easily when exerting themselves, because decreased pumping action form the heart does not deliver enough blood to the leg muscle during walking or other exercise (Wilson '06: 33). Heparin, a natural anticoagulant in blood, is commercially available from animal sources, especially beef lung. Hemorrhage due to overdose of anticoagulants may be controlled quickly by the administration of vitamin K. Red Clover (*Trifolium pretense*) has blood thinning properties and should not be used by those who are taking heart medication or who have any type of blood-thinning problem. Discontinue red clover for 2 weeks before and after surgery (Glastar '12). Coumadin (Warfarin) is another bloodthinner with many contraindications. Prescription cardiac drugs are consistently the second leading cause of fatal drug overdose reported by the annual report of the National Association of Poison Control Centers (2010-11).

The miraculous affects of *Digitalis purpurea* against congestive heart failure and of Rauvolfia against hypertension were among the great medical advances of the eighteenth and twentieth centuries. However both substances had long histories of use in domestic medicine before their rediscovery by researchers and incorporation into orthodox medical practice. While Rauwolfia is now an expensive high blood pressure medicine, Digitalis is a somewhat abusive alternative to Hawthorn. *Digitalis* slows the wildly beating ventricles to a normal level by blocking or delaying the conduction of the electric impulse through the atrioventricular node. By increasing the heart stroke, *Digitalis* increases the amount of blood being oxygenated by the lungs, as well as the blood in general circulation, by as much as 30% with each beat. Because of this improved action of the heart and circulation, the drug tends to improve renal secretion to relieve edema, and to aid the cardiac muscle to compensate for mechanical defects or structural lesions. More than 3 million cardiac sufferers in the United States routinely use the glycoside digoxin from *D. lanata*, and this is but one of six glycosides from *Digitalis* prescribed today. *Digitalis* whole leaf, digitoxin, digoxin, lanatoside C, acetyldigitoxin and deslanoside. Since the effective dose may be as high as 70% of the toxic dose, administration must be done carefully on an individual basis. Various Digitalis glycosides, all taken orally, include *D. purpurea* whole powdered leaf, containing a large number of glycosides of which about 30 are identified besides the medicinally important digitoxin, gitaloxin, and gitoxin. The average concentration of these three glycosides in a leaf is 0.16%. Recently it has been recommended the use of whole leaf preparations over isolated glycosides. Cardiac glycosides bring only temporary relief and must be administered orally during the whole course of the disease. Adverse reactions are found in about 20% of hospitalized patients receiving *Digitalis* preparations. (Elvin-Lewis '77: 183, 184, 186, 187, 189, 193, 194, 190, 191 192).

Hawthorne (*Crataegus laevigata*) is considered the herb supreme for the heart. Hawthorn is outstanding both to prevent heart problems and to treat high or low blood pressure, heart disease, edema, angina and heart arrhythmia. The berries, leaves and flowers are rich in bioflavonoids, antioxidants, and procanidins, which feed and tone the heart. Hawthorn works in part by dilating the arteries and veins, enabling blood to flow more freely and releasing cardiovascular constrictions and blockages. It strengthens the heart muscle while helping to normalize and regulate blood pressure. It also helps maintain healthy cholesterol levels. Hawthorn doesn't store in the body and isn't accumulative in action, it's important to take on a regular basis if

using as a heart tonic. Hawthorn also helps to stabilize collagen and support the health and repair of ligaments, tendons and muscles. Hawthorn strengthens capillaries and heals bruises. The berries are tasty and often enjoyed in syrups, jams and jellies or dried infusions. The best strategy to procure hawthorne involves harvesting some of the flowers and enough berries to make pancakes, syrups and jams with enough left over to dry and make hawthornberry tea infusions year round. Other cardiac stimulants and tonics include *Apocynum cannabinum* (dogbane), *Asarum canadense* (American wild ginger) is however not a highly recommended substitute for *Zingiber officinale, Asclepia spp* (milkweeds), *Crateagus tomoentosa* (hawthorn), *Euonymus atropurpureus* (wahoo or burning bush), *Heuchera* spp. (alum root) Ilex opaca (American Holly), *Ipomoea leptophylla* (bush morning glory), *Monarda* spp. (horsemint), *Veratrum californicum* (hellebore), *Veratrum viride* (green hellebore), and *Viola* spp. (violet) (Elvin-Lewis '77: 192). Sage is a superb aid in the digestion of rich, fatty meat. It also lowers cholesterol levels and is a bitter tonic for the liver. It rebuilds vitality and strength during long-term illness. Sage tea is a warming, bracing drink, nice mixed with mint or rosemary and lemon balm. Rosemary is a circulatory stimulant useful for the treatment of poor circulation and low blood pressure. Lemon balm is a remedy for heart disease (and heartache), depression and anxiety, nervous disorders and a host of viral and bacterial infections. Paralesus called lemon balm the "elixir of life" and Dioscorides used it for "sweetening the spirit". In the 1600s herbalist John Evelyn wrote "balm is sovereign for the brain, strengthening the memory and powerfully chasing away melancholy". Because it's so delicious lemon balm is often prepared as tea, but it is also tasty as a culinary herb. Lemon balm is considered a thyroid inhibitor, those suffering from hypothyroidism or low thyroid activity should use it only under the guidance of a health care practitioner. Garlic helps to maintain healthy blood cholesterol and prevent blood platelet aggregation, making it the herb of choice for many circulatory issues and lowers blood sugar levels in Type 2 diabetes. Garlic is antibiotic, antiviral and anti-fungal.

IV.3 Diagnosis

Chest pain may be caused by diseases of the lungs, heart, pleura, ribcage or pectoral muscle. If chest pain is localized, it usually occurs in the area of the heart cavity because the left lung has only two, rather than three lobes, and not only is the heart vulnerable to ischemia, the left lung is relatively small and is the first to be injured during over-exertion, and/or succumb to opportunistic or environmental infection. Nonetheless, if chest pain is localized to the heart area, coronary artery disease is presumed in 90% of cases, fresh air, fabric and vegan diet are prescribed, antibiotics cure endocarditis and statins reduce cholesterol. Respiratory diseases are much more common because of the nearly constant exposure of the airways to the external environment. Respiratory disease require hygiene and a high calorie diet whereas adipose tissue is needed to seal the lung and must not be depleted. Colds are diagnosed by a runny nose, if it lasts more than a week it is called allergic rhinitis, and may cure instantly with a dab of hydrocortisone crème to the nose. Pertussis also causes a runny nose in the first week, when it can be treated with antibiotics, to prevent the subsequent 6 week cough. Influenza, COVID-19 and many other respiratory viruses and molds cause a cough. A dry cough indicates pneumonia and a wet cough the flu. Flu is treated with Oseltamivir (Tamiflu), Zanamivir (Relenza) o Amantadine (Symmetrel). Allergens are typically mold, fungi are not contagious, molds are environmental in origin, and merely happen to colonize a human test subject. Corticosteroids (hydrocortisone crème, nasal spray or inhaler) diagnostically cure many molds and relieve viral infections. Ampicillin or azithromycin (Zmax) treat the pneumonia that invariably sets in after an epidemic of coughing. Hygiene and self-quarantine are advised.

A **complete blood count** (CBC) test gives a doctor important information about the types and numbers of cells in your blood, especially the red blood cells and their percentage (hematocrit) or protein content (hemoglobin), white blood cells, and platelets. The results of a CBC may diagnose conditions like anemia, infection, and other related disorders such as cancers of the blood. The platelet count and plasma clotting tests (prothombin time, partial thromboplastin time, and thrombin time) may be used to evaluate bleeding and clotting disorders. Complete blood count (CBC) is dome by automated cell counters that measure the hemoglobin, red blood cell count, red blood cell volume distribution, platelet count, and white blood cell count. Blood appears red because of the large number of red blood cells, which get their color from the hemoglobin. The percentage of whole blood volume that is made up of red blood cells is called the **hematocrit** and is a common measure of red blood cell levels, the mean cell volume (MCV) (based on volume distribution), mean cell hemoglobin (MCH) (hemoglobin divided by RBC count), mean cell hemoglobin concentration (MCHC) (hemoglobin divided by hematocrit) and the red cell distribution width (RDW). The red cell indices and RDW are used together with a direct inspection of the Wright-stained blood smear to evaluate red blood cell morphology (Hillman '98: 334-336). To count the specific white blood cells a **CBC with Differential** is ordered.

Complete Blood Count (CBC), Coagulation Tests and White Blood Cell (WBC) Differential

Test	Normal Range	Comments
Complete Blood Count (CBC)		
Red Blood Cell (RBC) count	M 4.7-6.2 million/cu mm F 4.2-5.4 million/cu mm	Low – anemia, hemorrhage High – chronic anoxia
Hemoglobin (Hgb)	M14-18 g/dl F12-16	Same as above
Hematocrit (Hct)	M42-52% F37-47%	Same as above
Mean corpuscular volume (MCV)	80-95 cu/u	High - RBC macrocytic Low –RBC microcotic
Mean corpuscular hemoglobin concentration (MCHC)	32-36 g/dl (32-36%)	Low – Hypochromic cell
Iron (Fe)	60-190 µg/dl	Low-iron deficiency anemia
Total iron binding capacity (TIBC)	250-420 µg/dl	Same as above
Serum haptoglobin	100-150 mg	Low-Hemolysis liver disease High-Inflammatory disease
Hemoglobin electrophoresis	Hgb A_1 95-98% Hgb A_2 2-3% Hgb F 0.8-2% Hgb S 0% Hgb C 0%	Variations indicate hemoglobinopathies, High Hgb F – thalassemia found in Central asians. Hgb S-sickle cell anemia and Hgb C mild hemolytic anemia found in American blacks
Direct Coombs' and Indirect Coombs	Negative	To detect antibodies against RBC in transplant rejection
Reticulocyte counts	0.5%-2% of total RBC	Low-inaquate RBC production

		High-Polycythemia vera
White Blood Cell (WBC) count	5000-10,000/cu mm	High-infection Low-Bone marrow failure
Platelet count	150,000-400,000/cu mm	Low-Bone marrow failure, hypersplenism, accelerated consumption High-Hemorrhage, polycythemia vera, malignancies
Coagulation Tests		
Prothrombin test (PT)	11-12.5 seconds (85-100%)	High-Deficiency of factors V and VII
Prothrombin time test (PTT)	30-40 seconds	High-Deficiency of factors II, V, VIII, IX, XI, XII
Platelet count	150,000-400,000/cu mm	Low-Bone marrow failure, hypersplenism, accelerated consumption High-Hemorrhage, polycythemia vera, malignancies
Bleeding time	1-9 minutes	High Thrombocytopenia, marrow infiltration, inadequate platelet function
Eublobin lysis time	90 minutes-6 hours	Low-Fibrinolysis
Fibrin degradation products (FDP) test	< 10µg/ml	High DIC, fibrinolysis
White Blood Cell (WBC) Differential		
White Blood Cell (WBC) count	5000-10,000/cu mm	High-infection Low-Bone marrow failure
Neutrophils	50-70	High-Inflammation, Invasive tumors
Eosinophils	2-4	High-Allergic states, Drug reactions, Parasitic Infections, Some skin disease and neoplasms
Basophils	0.5	High-Asthma, some Carcinogens, Inflammatory bowel disease, Chronic inflammation
Macrophages	5-7	High-Chronic infections, Liver disease, Neutropenia
Lymphocytes	20-35	High-some Carcinomas
Plasma Cells	?	Multiple myeloma

Source: Griffin '86: Table 1.1 pg. 5-6; Table 2-3 pg. 32

The iron level with Total Iron Binding Capacity (Fe and TIBC) test detect certain kinds of anemia, such as iron deficiency after blood loss. Serum Haptoglobin Test detect intravascular

destruction of RBCs associated with hemolytic anemia. Hemoglobin electrophoresis enable one to detect abnormal forms of Hgb (hemaglobinopathies). Direct and indirect Coombs tests detect the presence of antibodies to RBC found in tissue and fetal rejection. A reticulocyte count (Retic count) is a test for determing bone marrow function in which immature RBC as a percentage of total RBC production. The platelet count and plasma **clotting tests** (prothombin time, partial thromboplastin time, and thrombin time) may be used to evaluate bleeding and clotting disorders. To count the percentage of total white blood cell volume occupied by specific white blood cells a **CBC with Differential** is ordered. The white blood cell (WBC) differential is a measure of the total number of white blood cells and the percentages of the five types of WBC descriptive of infection, stress and bone marrow failure (Griffin '84: 3-16).

The **primary symptoms of pulmonary disease** are cough, expectoration, dyspnea, hemoptysis, wheezing, and chest pain. Key points in the patient's past medical history include smoking, allergies and occupational exposure to potential disease producing environments (Mitchell '89: 30). In the diagnosis of COPD the following tests are ordered (1) chest x-ray, (2) breathing tests, (3) arterial blood gas, (4) electrocardiogram and (5) exercise testing with oximetry to check oxygen level. The most useful test is **spirometry**, which is done by filling your lungs with air, then blowing out as hard and as fast as possible. Testing is repeated after 20 to 45 minutes to test the effectiveness of medication. The most important measurement made during the spirometry, and the one which most doctors mean when they say you have “60% of lung function” or “half lung function” is the amount of air which one can forcibly blow out in one second. This is called FEV_1. FEV_1 is the number which is best at predicting how a person with COPD will do. It helps your doctor decide how much risk there is for a surgical procedure and when to start watching for low oxygen level in your blood. It can also tell your doctor whether you are likely to die from your lung disease, or from something else. When the FEV_1 is less than normal but greater than 60% of the expected value for your age, race, sex, and size, you have mild disease. If the FEV_1 is between 40 and 60% of expected, disease is moderate. For an FEV_1 less than 40% of expected, disease is severe. FEV_1 should be measured before and after using a bronchodilator inhaler, in order to get a true picture of best value. Another measure of lung function is the fastest rate at which you can get air out, or peak flow rate. Although this test is helpful in asthma, it is not as useful in COPD. The total amount of air which you can get out is also less useful in assessing your illness than the FEV_1. Normal expected values for oxygen saturation very depending on altitude, but should be at least 90%. Values less than 90% indicate low oxygen in arterial blood. People desaturate (lose blood oxygen) during activity and it is appropriate to compensate by increasing oxygen flow. Arterial blood gas levels are important cues to the severity of and need for treatment of abnormality in the lungs. This test has to be done on arterial blood coming out of your heart before it circulates to tissues. This test can be painful as the artery is right beside a nerve in the wrist. A local anesthetic such as lidocaine is very helpful (Tucker et al '01: 57, 58, 59).

Exercise testing is used to determine whether exercise limitation is present if so to delineate the underlying mechanism of the reduced exercise tolerance. Exercise limitation may be caused by a ventilator defect, a cardiovascular defect, impaired physical fitness, or exercise-induced bronchospasm. Analysis of expired gas, heart rate and blood pressure simultaneously with arterial blood allows calculation of the cardiovascular response, the ventilator response (tidal volume and respiratory frequency), respiratory quotient (oxygen consumption and carbon dioxide production) the $P(A\text{-}a)O_2$ and the dead space tidal volume (VD/Vt) ratio. A change in the FEV_1 is used to assess whether exercise induced bronchospasm is present after an exercise load, which results in an increase in heart rate greater than 80% of the predicted maximum. Exercise

tolerance and the cardiopulmonary response to exercise can be assessed using either multistage testing or steady-state testing. Multistage testing is preferable in that it evaluates the patient's ability to adapt to exercise. Starting with a small workload the workload is increased by increments at 1-minutes, 5-minutes- 10 minutes, 30 minutes or longer. A rise in $PaCO_2$ and a fall in Pa_{O_2} during the exercise indicates that the patient is unable to increase alveolar ventilation sufficiently to cope with the increased metabolic production of CO_2 during the exercise load. Thus these findings indicate that the patient has exercise limitation because of mechanical impairment. In patients with restrictive disorders, ventilation increases predominately by increases in respiratory rate. A greater than expected heart rate and ventilation and an increase in respiratory quotient, as well as a fall in pH at a given workload, indicate oxygen delivery is inadequate to meet the energy demands of the exercising muscles. This occurs if the cardiovascular system is unable to cope with the increased tissue demands during exercise or if the individual is physically unfit (Cherniak '89: 54-58).

Dyspnea is the scientific term that describes the patient's sensation of shortness of breath, breathlessness, difficulty in breathing or being winded. Dyspnea literally means disordered breath. When a patient describes problems with respiration that produce a distressing sensation, the terms dyspnea or shortness of breath are interchangeable. The causes of dyspnea are numerous and can include virtually all pulmonary disorders and many cardiac disorders. Frequently, dyspnea is blamed on hypoxemia; however, the arterial oxygen tension is not severely low and supplemental oxygen does not entirely relieve the symptoms Major categories of the causes for Dyspnea are A Pulmonary (1) Parenchymal: obstruction to airflow, cancer, inflammatory diseases, infiltrative diseases, atelectasis, chronic bronchitis, emphysema, interstitial fibrosis and asthma, (2) Vascular: Left-sided heart failure, pulmonary edema, (3) Pleural: Fibrosis with trapped lung, pneumothorax, effusion, hemothorax, (4) Respiratory muscles: weakness or paralysis of intercostal muscles or diaphragm (neuromuscular diseases, potassium or phosphate deficiency, disuse), (5) Chest wall: trauma, obesity, kyphoscoliosis, ankylosing spondylitis. B Extrapulmonary. (1) Anemia: exertional, (2) sub-diaphragmatic: ascites, abscess, hepatomegaly, pregnancy, any process that can interfere with contraction and downward displacement of diaphragm, (3) Psychiatric: emotional interplay, (4) Metabolic: hyperthyroidism and fever (Martin '89: 22).

Assessment of **respiratory function** is an integral component of the clinical examination. Simple tests of function can be determined at the bedside or in the office. Evaluation of simple parameters allows valid interpretation. Repeated assessments allow the physician to follow the course of the disease and to evaluate the impact of therapeutic regimens. Respiratory symptoms usually arise as a result of alterations of the elastic or flow-resistive properties of the lungs or chest wall, or both. The maximum volume of air in the lungs is known as total lung capacity (TLC). The functional residual capacity (FRC) is about 40% of TLC. The residual volume is about 25%. The finding of a lower than expected TLC generally indicates either a restrictive disorder or respiratory muscle weakness. The principle behind calculation of lung volume in the **body plethysmograph** is simple: pressure in the airways is determined while the subject makes inspiratory and expiratory efforts at a rate of approximately 120 breaths/min against a closed shutter. During the panting maneuver the air int eh patient's chest is alternately compressed (airway pressure becomes positive) and decompressed (airway pressure becomes negative). (Cherni Determination of the flow-volume relationship during the forced expiratory maneuver and assessment of the maximal expiratory flow rate (V_{max}) at particular lung volumes. The finding of low flow rates may reflect patient effort rather than flow limitation as the FVC maneuver requires total patient effort. In restrictive pulmonary disease, lung volume is reduced,

and the V_{max}, or other tests such as FEV_1, $FEF_{25-75,}$ are lower than predicted values. In many laboratories, airway resistance (R_{aw}) is estimated in a body plethysmograph by determination of the relationship of airway pressure (P_{aw}) and airflow (V) during panting. As a corollary, if V_{max} is low R_{aw} is probably increased, in a patient with a restrictive disorder. In an obstructive disorder, assessment of the lung's pressure-volume characteristics helps the physician differentiate whether an elevated lung volume and low expiratory flow rates are associated with an increase in R_{aw} (as in asthma or bronchitis) or a loss of lung elastic recoil (as in emphysema). When an obstructive pattern of abnormality is demonstrated, the physician should repeat the FVC maneuver after the patient has inhaled an adequate dose of nebulized bronchodilator to determine the pattern's potential reversibility. In some patients increased bronchial reactivity may be difficult to ascertain. In these individuals a reduction in FEV_1 or V_{max} in response to inhaled methacholine or histamine is indicative of airway hyperactivity. Airway hyper-reactivity develops even in healthy individuals following an acute upper respiratory infection (Cherniak '89: 58, 43, 44- 49).

Measurement of airflow and lung volumes is abnormal during asthma attacks but may be normal between attacks. Airway obstruction during acute attacks decreases the forced expiratory volume in one second (FEV_1) and peak expiratory flow (PEF) and increases airway resistance. The FEV_1 and PEF reliably indicate the severity of airways obstruction and document whether obstruction improves with therapy. To diagnose asthma the effect of inhaled bronchodilators on airways obstruction is often determined. Arbitrarily, an increase in FEV_1 of 15% after inhalation of a bronchodilator is indicative of hyper-responsive airways. Arterial blood gases are usually abnormal during an acute asthma attack. Airway obstruction causes ventilation-perfusion mismatching and consequently cause hypoxemia. During acute asthma attacks, most patients are dyspneic and hyperventilate and therefore have hypocapnia and acute respiratory alkalosis. Normal or increase $PaCO_2$ during acute asthma indicates severe airway obstruction and patient fatigue. A patient with elevated $PaCO_2$ should be observed closely, since ventilator support may be needed. The sputum of patients who have asthma often contains numerous eosinophils (corticosteroid therapy suppresses these), Charcot-Leyden crystals (derived from eosinophil granules), and Curshmann spirals (mucous casts of the small airways). Patients may have eosinophilia of the circulating blood. Inhalation challenge tests are performed to diagnose asthma in cases where the diagnosis is in question. The patient inhales aerosols of solutions containing increasing concentrations of methacholine or histamine, and airflow is measured after each inhaled dose. Both methacholine and histamine cause bronchoconstriction in healthy persons but at lower concentrations cause bronchoconstriction in persons who have hyper-responsive airways (Bethel '89: 167-169).

The assessment of **arterial PaO_2, $PaCO_2$,** and acid-base balance, both at rest and during exercise, is frequently informative in subjects with chronic respiratory symptoms. Assessment of cardiopulmonary response to exercise is very important in the evaluation of the patient. If expired gas is collected simultaneously with arterial blood, the respiratory quotient (R), alveolar oxygen tension (PAO_2), alveolar-arterial oxygen tension gradient ($P(A\text{-}a)O_2$, and dead space-tidal volume ratio (V_D/V_T) can be determined. It is particularly important to follow $P(A\text{-}a)O_2$ at rest and during exercise. The $P(A\text{-}a)O_2$ can be determined by assuming that R was 0.8 if the patient was breathing room air and 1.0 if he or she was breathing oxygen; a simplified alveolar air equation is used to calculate the PAO_2. Even in healthy persons the P(A-a)O2 is about 10 to 15 mm Hg because of ventilation-perfusion mismatch (V/Q) and some mixing of venous blood with arterialized blood in the the bronchial veins. In all these conditions, as well as in alveolar hypoventilation, the PaO2 is less than normal. However in alveolar hypoventilation oxygen

equilibrates between the alveoli and the pulmonary capillary blood, making the $P(A\text{-}a)O_2$ within normal limits. An elevation of $PaCO_2$ occurs when the alveolar ventilation (V_A) is inadequate relative to carbon dioxide production (VCO_2). The amount of true venous admixture can be assessed qualitatively by sampling arterial blood while the patient is breathing 100% oxygen. Failure of the PaO_2 to rise above 500 mm Hg (at sea level) while the patient is breathing 100% oxygen indicates excessive shunting of blood, and a rise of the PaO_2 above 500 mm Hg while the patient is breathing 100% oxygen rules out excessive venous admixture. PaO_2 may also fail to rise above 500 mg Hg while the patient is breathing oxygen if non-ventilated lung lesions such as atelectasis or consolidation continue to be perfused (Cherniak '89: 50-54).

Assessment of **acid-base status** is an essential aspect of the investigation of patients with chronic respiratory insufficiency because the acid-base balance is affected by the $PaCO_2$. In patients who have a restrictive disorder or who have earlier stages of obstructive disorders, the PaO_2 and $PaCO_2$ are low and an alkalemia (pH over 7.45) is often present because of hypxemia-induced hyperventilation. If the patient has been hyperventilating for some time, the arterial pH is usually between 7.40 and 7.45 because of compensatory elimination of bicarbonate by the kidneys. In severe chronic airflow obstruction, particularly when the work of breathing becomes excessive, the alveolar ventilation may be unable to cope with carbon dioxide production; thus the $PaCO_2$ is elevated and the PaO_2 is low. When this occurs acutely, the patient will be academic (pH under 7.35) but if the alveolar hypoventilation has been present for some time, the pH will be between 7.35 and 7.40 because of compensatory retention of bicarbonate by the kidneys. Generally, if the patient's pH is within the normal range and the $PaCO_2$ is lower or greater than normal (that is, under 35 mm Hg or over 45 mm Hg at sea level), more than one disturbance is present. The level of the pH may also help: if the pH is below 7.40 an acidosis is likely the major disturbance; if it is above 7.40, it is likely an alkalosis (Cherniak '89: 54).

In the normal individual a delicate relationship exists between the metabolic production of carbon dioxide and its renewal by alveolar ventilation so that there is a near-normal level of PCO_2 – between 42 +/- 4 mm Hg at sea level (36 +/- 3 mm Hg, Denver altitude). This results in a narrow pH range of 7.35 to 7.45. Arterial puncture is simple and safe. Recent advances in arterial sampling syringes have reduced the pain, hematoma, and artifacts sometimes inherent in older techniques that used large-bore needles. Currently most blood-gas syringes employ lyophilized crystalline lithium heparin. The normal state is a PCO_2 of 40, a bicarbonate of 24 and a pH of 7.40. Acidosis can occur in diabetic ketoacidosis, lactic acidosis or in an uncompensated uremic state. Except in the case of severe respiratory muscle weakness, fatigue, or severe airflow obstruction, acid invasion responds to hyperventilation. Alkalemia is frequently the result of acute hyperventilation, from anxiety, pain or inappropriate mechanical ventilation. PO_2, PCO_2, and pH analysis is accomplished by electrode techniques, direct readout and printing of these values and a calculated arterial oxygenation saturation are offered and the relationship between oxygen tension and saturation and pH modifications is presented. Oxygen saturation can also be measured with a variety of oximeters that use reflected light at two wavelengths to reflect the reduced and oxygenated hemoglobin expressed as a percentage. Pulse oximetry is rapidly replacing arterial blood-gas analysis when only the state of oxygenation is in question. The continuous monitoring of oxygen consumption and CO_2 production is possible using a mass spectrometer (Petty '89: 121, 125, 134, 135).

Pulmonary hypertension is defined as the elevation of the mean pulmonary artery pressure above 15 mm Hg and systolic pulmonary artery pressure of above 30 mm Hg under resting conditions. Latent pulmonary hypertension exists when a significant rise in mean pulmonary

artery pressure (>5 mm Hg) occurs with mild exercise. The pulmonary circulation is a low pressure low resistance system. The resistance is 5 times less than in the systemic circulation. With an increase in cardiac output, as with exercise, a minimal rise in pulmonary artery pressure is followed by a fall in pulmonary vascular resistance (PVR = Pa – Pw/C.O.) because of capillary recruitment. The pulmonary circulation is unique because it is exposed to alveolar air, accepts the entire cardiac output, and empties into the left atrium. Each of these features can alter the behavior of the pulmonary vascular bed. Hypoxia cause pulmonary vasoconstriction and is a frequent cause of pulmonary hypertension. Agents that inhibit hypoxic vasoconstriction, such as bronchodilators, calcium antagonists, and nitro compounds, can worsen V/Q mathing. Localized hypoxic vasoconstriction is beneficial and generalized hypoxic vacoconstriction leads to pulmonary hypertension and cor pulmonale. In chronic lung diseases, chemical mediators (mainly products of inflammatory cells) can cause vasoconstriction. Generally, chronic hypoxia causes mild to moderate pulmonary hypertension (Voelkel '89: 276).

The diagnostic hallmark of **severe pulmonary hypertension** is the combination of high pulmonary artery pressure and low cardiac output. The cardiac output does not respond to exercise in severe pulmonary hypertension. The lower the cardiac output at the time of diagnosis the shorter the survival. The main symptom is dyspnea in patients with severe pulmonary hypertension. Fatigue, syncope, angina-like chest pain, nonproductive cough, and hoarseness also occur. A complete hemodynamic assessment is mandatory for patients with severe pulmonary hypertension. The determination of lung vascular reactivity to exercise, hypoxia, hyperoxia and the infusion of the potent pulmonary vasodilator rostacyclin provides a functional biopsy. A drastic acute reduction in pulmonary vascular resistance with oxygen administration or infusion of incremental prostacyclin doses signals the long-term therapeutic benefit of chronic oxygen or vasodilator drugs. Ideally, vasodilator treatment is initiated as an acute trial in the catheterization laboratory. The assessment of vasodilator efficacy is preceded by the assessment of the vasodilator response to prostacyclin that appears to be the "gold standard" test for pulmonary vascular reversibility. Hydralazine, Nitro-compounds, and ACE-inhibiors have produced favorable results in some patients. Because advanced, irreversible pulmonary hypertension occurs resulting from irreparable structural alterations some patients will be irresponsive to any vasodilator drugs. Few patients survive for long treated with either continuous intravenous prostacyclin or with other orally administered vasodilators. The value of anticoagulation has not been studied. A few patients with severe, unexplained pulmonary hypertension have undergone heart-lung transplantation, yet long-term follow-up data is not yet available. The overall prognosis in severe (primary) pulmonary hypertension is poor. After the disease has been diagnosed, survival is generally still a matter of months; a few cases have been documented to survive for several years in spite of very high pulmonary artery pressure. The severe reduction in cardiac output and the limitation to increased cardiac output with exercise, are known hemodynamic factors of poor survival. Patients die from progressive right ventricular failure, pulmonary hemorrhage, and syncope. Pulmonary angiography with rapid injection of a large load of contrast medium has resulted in death within 24 hours in a number of patients with "primary" pulmonary hypertension (Voelkel '89:278-283). The value of Hawthorne has yet to be investigated, the FDA writes, to conduct clinical trials to study the efficacy of Hawthorne in the treatment of heart disease, high blood pressure, arrhythmia, congestive heart failure, and other cardiovascular medical conditions.

One-fourth of all Americans who seek medical care do so because of an **infectious disease**. At least 150 million courses of antibiotics costing more than $16 billion are prescribed in the United States each year, largely to treat upper respiratory tract infections. Antibiotics are appropriate

only for bacterial infections. Viral infections that commonly involve the head and neck but do not benefit from antibioics include croup, bronchitis, influeznae, common cold, nonstreptococcal tonsillopharyngitis, and most ervical adenitis. Rhinorrhea accompanying a viral upper respiratory tract infecton may be clear, cloudy, green yellow or even purulent and that color alone does not imply bacterial origin. Not all presumed bacterial infections require antibiotics but withholding antibiotics is inappropriate for infections that are severe or complicated. Give the right drug for the right bug. Common causes of acute respiratory tract infection include *Streptococcus penumoniae*, *Haemophilus influenzae*, and *Morazella catarrhalis*, and group A beta-hemolytic streptococcus (*S. pyogenes*); chronic infections often include *Pseudomonas aeruginosa*, *Staphylococcus aureus* and anaerobic organisms. Certain commonly used antibiotics (e.g., azithromycin, clarithromycin, cefprozilad, trimethoprim-sulfamethoxazole) are relatively ineffective for several bacteria and have effects worse than placebo because they induce further resistance (Boruk & Rosenfeld '04: 427, 428). One does not become immune to pertussis without a DTaP (Diptheria and Pertussis) vaccine. Pertussis does not respond to antibiotics after it has descended to the lungs from the extremely runny nose of the first week. Unvaccinated persons who succumb to whooping cough can sterilize *Pertussis* against other opportunistic infections and reduce their contagiousness with a full course of antibiotics. Vaccination and antibiotics have been effective at controlling the incidence of pertussis for the past century. Between 1922-1925 the average annual number of reported cases of *Bordetella pertussis* was 147,271, by 2001 incidence of whooping cough had decreased 95 percent to 7,580 (Fisher ’06: 7).

Evidence of **hemolytic anemia** might suggest the presence of mycoplasma and lymphocytosis might suggest a viral rather than bacterial infection. **Cytomegalovirus** is the most common infectious agent to cause the combination of abnormal liver function tests and pulmonary disease. A rapid progressing alveolar infiltrate suggests a bacterial pneumonia. **Cavitary lesions** are more common in *Staphylococcus aureus* and gram-negative bacterial and fungal infections. A slowly developing interstitial infiltrate suggests a viral, a fungal or a mycobacterial infection rather than a bacterial infection. Pleural effusions are more common in bacterial than in fungal infections. Routine sputum Gram stains and cultures may be diagnostic in bacterial infections but are not helpful in fungal, viral or protozoal infections. Blood cultures may be positive in patients with bacteria, fungal or mycobacterial infections. Sputum can be sent for direct fluorescence antibody screen for *Legionella*, for acid-fast smear and culture for tuberculosis, and for either Fiemsa or methenamine silver stain for *Pneumocystis*, especially in patients with AIDS. **Serology** is available for the detection of fungal infection, *Legionella*, *Mycoplasma*, cytomegalovirus, *Chlamydia*, and toxoplasmosis. However, the diagnosis of these infectious agents often requires the evaluation of both and convalescent titers (obtained after 4 weeks) making them impractical for use in the acute setting. The patient may be treated empirically and observed for 24 to 48 hours. Empiric therapy for the majority of immune-compromised patients with a presumed pulmonary infection includes antibiotic coverage for both gram-positive and gram-negative organisms (usually a semi-synthetic penicillin or a cephalosporin plus an aminoglycoside. Patients who respond to empiric therapy are treated for up to 3 weeks (McClellan & Iseman '89: 74, 75).

Cough is the fifth most common reason why patients see a physician. The differential diagnosis of a cough can be divided into six categories: (1) extrathoracic causes: irritation of tympanic membrane or external auditory meatus (wax, foreign body, inflammation, hair), subdiaphragmatic (subphrenic or hepatic abscess), psychological (habitual cough) postnasal drip or gastroesophageal reflux; (2) pleura: effusion, emphysema or pneumothorax; (3) mediastinum:

aortic aneurysms, nodes (neoplastic, infectious), mediastinal tumors (thyroid, neurofibromata, dermoid cyst); (4) larynx and pharynx: laryngitis and pharyngitis (usually viral), neoplasia, tuberculosis, parasites or burns; (5) airways: tracheitis, bronchitis, irritant fumes and gases, burns, asthma, foreign bodies, bronchiectasis, cystic fibrosis and carcinoma and (6) lung parenchyma: pneumonia (bacterial, fungal, tuberculin, viral, parasitic), tuberculosis, carcinoma, congestive heart failure, noncardiac pulmonary edema, suppuration, cysts, alveolitis, sarcoides or insterstitial lung disease. For chronic persistent cough in the adult, the most useful diagnostic techniques are patient history and the physical examination, which yield 80% to 61% of the diagnoses, respectively. Methacholine inhalation challenge (a technique that identifies hyperreactive airways) is useful to diagnose asthma in about 25% of patients with chronic cough. Reflux accounts for about 8% of these patients. Reflux alone without aspiration can produce bronchoconstriction by vagal reflex mechanisms and produce coughing. An upper gastrointestinal radiographic series is useful; however, this x-ray technique is not the most sensitive in diagnosing reflux. A Bernstein test (dripping acid into the esophagus) can reproduce the symptoms of coughing. The chest and sinus radiographs identify the cause of coughing in 4% of cases. Although bronchoscopy is frequently of great value in the diagnostic approach to chronic cough, it defines the cause of disease in only 4% of the patients. However, bronchoscopy can rule out a serious endobronchial lesion. Only when the other noninvasive techniques have failed should bronchoscopy be performed unless some aspect of the history or physical examination reveals the need for bronchoscopy, such as hemoptysis. In about 2% of patients with cardiac disease, the disease is not detected by noninvasive techniques and a cardiac catheterization may be indicated. A cough can generate intrathoracic pressures as high as 300 mm Hg and can cause musculoskeletal complications ranging from asymptomatic elevation of serum creatinine phosphokinase level to rupture of the rectus abdomini muscle and rib fracture (Martin '89: 18, 19).

Hyperventilation can be caused by many factors. The common ones are A Central Nervous System: anxiety, neurosis (hyperventilation syndrome), drugs, disease, cerebrospinal fluid acidosis. B Peripheral action: arterial hypoxemia, hypotension, fever, sepsis. C Uncertain action: exercise and pulmonary parenchymal disease. It can be very severe and produce frank tetany during an anxiety attack. The central nervous system involvement in the hyperventilation syndrome may include dizziness, faintness, decreased mentation, insomnia and in rare situations loss of consciousness. The peripheral nervous system symptoms are numbness and tingling around the mouth and extremities. The musculoskeletal problems are weakness, fatigue, myalgias, carpopedal spasm, twitching and tetany. Cardiac-related problems include palpitations, tachycardia, ST-segment and T-wave changes, sharp twinges of chest pain, dyspnea and chest tightness. The gastrointestinal tract symptoms are dysphagia, dry mouth, bloating, belching and flatulence. Hyperventilation syndrome can be initiated by excitation of the central nervous system, cathecholamines, and awareness or preoccupation with one's breathing pattern. When the hyperventilation is established, a respiratory alkalosis occurs. This has effects on ionized calcium, phosphate, and magnesium levels that result in increased neuromuscular excitement and many of the symptoms which produce anxiety in a self-perpetuating cycle. The treatment of hyperventilation depends on the cause. Hyperventilation syndrome can be treated with emotional support, "brown paper bag", beta-blockers, calcium phosphate, or biofeedback-hypnosis. Emotional support is what the patient needs to break the hyperventilation cycle, but more intense psychological intervention may be needed. The "brown paper bag" placed over the mouth and nose forces the patient to rebreathe carbon dioxide and correct the respiratory alkalosis and secondary ion changes. Beta blockers attenuate the peripheral effects of anxiety and interrupts the cycle. With carpopedal spasms or tetany, intravenous calcium phosphate will

tend to terminate the problem. Biofeedback or hypnosis can alter the anxiety state and thus correct the symptoms (Martin '89: 27, 28).

A suspected **diagnosis of hypersensitivity pneumonitis** may be confirmed by three immunologic procedures (1) an inhalation challenge with suspected antigens, however, it is rarely necessary and should be performed only by personnel familiar with the disease and capable of treating the potentially severe pulmonary reactions that may ensue, (2) agar gel precipitation tests may be performed because more than 70% of patient sera contains precipitating antibodies. Generally, standard Ouchterlony double diffusion test is sufficient and (3) skin testing with the suspected antigen may elicit either a type III (Arthur) response or a dual response consisting of a type I response followed by the Arthus reaction in several hours. Delayed hypersensitivity skin reactions are not seen in these patients. In patients whose diagnosis remains uncertain an open lung biopsy is recommended. The only effective treatment hypersensitivity pneumonitis is complete avoidance of the offending antigen. Corticosteroids may dramatically abort the acute attack, with improvement seen as early as 1 or 2 hours following their administration. Treatment of the chronic forms of the disease is less successful and patients whose lungs have progressed to a state of centrilobular emphysema with interstitial fibrosis, even if further antigenic exposure is avoided, rarely improve even with corticosteroid therapy (Dreisin '89: 232-236).

Acute respiratory failure (ARF) occurs in many clinical situations and constitutes a medical emergency requiring prompt and exacting assessment, supportive management and therapy directed at the underlying insult to the respiratory system. ARF may be defined as the sudden inability of the respiratory system and the heart to maintain adequate arterial oxygenation and adequate carbon dioxide elimination. ARF occurs when tissue oxygen transport and carbon dioxide elimination are impaired. Arterial blood gas analysis is most commonly utilized to determine the presence and severity of ARF. Arbitrarily, ARF is defined as the sudden development of an arterial PO_2 of less than 55 mg Hg with or without CO_2 retention. An acute elevation of carbon dioxide tension to more than 50 mm Hg is sometimes called "acute ventilator failure". The differentiation of hypoxemia from hypercapnia or so-called ventilation failure has important therapeutic implications. The pathophysiology of ARF involves impaired lung mechanics, failure of the respiratory muscles (the most vital pump) and respiratory center unresponsiveness. Two common and important clinical states often resulting in ARF are chronic obstructive pulmonary disease (COPD) and primary pulmonary edema resulting in the adult respiratory distress syndrome (ARDS). Disease states leading to respiratory failure are A Impaired ventilation: (1) chronic airflow obstruction: emphysema, chronic bronchitis, chronic asthma and cystic fibrosis; (2) restrictive defects: (a) decreased lung expansion: interstitial fibrosis, pleural effusion, pneumothorax, and fibrothorax; (b) limited thorax expansion: kyphoscoliosis, multiple rib fractures, thoracic surgery and ankylosing spondylitis; (c) decreased diaphragmatic movement: abdominal surgery, ascites, peritonitis, severe obesity, and diaphragmatic paralysis; (3) neuromuscular defects: Guillain-Barre syndrome, myasthenia gravis, multiple sclerosis, muscular dystrophy, botulism, tetanus, brain or spinal injuries, drugs or toxic agents (e.g. curare, acetylcholinesterase inhibitors, aminoglycosides), antibiotics, polio, porphyria; (4) respiratory center damage or depression: narcotics, barbiturates, tranquilizers, anesthetics, cerebral infarction or trauma, uncontrolled high-flow oxygen therapy. B impaired diffusion and gas exchange: (1) pulmonary fibrosis: interstitial fibrosis, sarcoidosis,

Hemoptysis appears initially as recurrent nose bleeds, nasal trauma (most frequently by digital insertion), nausea and vomiting, and upper airway (laryngeal) symptoms, blood in the mouth.

The patient can usually locate the bleeding, even if it occurs in the lungs. The most common diseases associated with hemoptysis are chronic bronchitis, bronchiectasis and bronchogenic carcinoma. Occasionally tuberculosis, fungal infection, bacterial pneumonia, pulmonary abscesses, parasitic infections and pulmonary infarction can cause hemoptysis. Less common causes are bronchial adenoma, mitral stenosis, pulmonary arterial-venous fistulas, foreign bodies, connective tissue disorders (Goodpasture's syndrome or systemic lupus erythematosus) and broncholithiasis. Massive bleeding (200 to 600 ml/day) or moderate bleeding in a patient with poor pulmonary function produces an emergency situation. Death in this situation is from asphyxiation blood filling the alveoli and preventing gas exchange. Rarely is exsanguination the cause of death. If bleeding cannot be controlled, protection of the other lung is needed. A double-lumen endotracheal tube can isolate both lungs and allow lavage of the involved lung. Surgical resection is indicated for massive hemoptysis because the death rate can reach 75% in treated patients (Martin '89: 24-27).

In 1968 Ikeda described use of the **flexible bronchofiberscope** for the early diagnosis of peripherally located endobronchial neoplasms. A fiberoptic bundle consists of several thousand closely packed glass fibers, about 10 μm in diameter, allowing transmission of light and a clear image around curves. An excellent selection of fiberoptic bronchoscopes is available with a variety of flexing angles, diameters, and size of aspiration channels with or without fluoroscopic guidance, thus providing the most effective and widely applicable technique in diagnosing pulmonary disease. Flexible fiberoptic bronchoscopy (FFB) is performed with a variety of individually selected premedications, topical aneshtetics, and introduction techniques. Careful cardiac screening and monitoring can reduce the majority of serious complications. Oxygen may be administered during the procedure by a nasal or mouth cannula, by mask, or by way of the aspiration or oxygen channel of the bronchoscope. It special adaptors are used, patients who have endotracheal tubes or tracheostomies, with or without assisted mechanical ventilation, can safely undergo fiberoptic bronchoscopy. Over half the procedures are used in the diagnosis of bronchogenic carcinomas and the evaluation of hemoptysis. Bronchoscopy is used to obtain specimens to ascertain the bacteriology of the lower tract and to perform tracheobronchial toilet in carefully selected patients. The removal of foreign bodies, previously an absolute indication for conventional bronchoscopy is now possible by using a variety of grasping forceps and retrieval baskets. The indications for fiberoptic bronchoscopy in the intensive care unit are primarily therapeutic (radiographic atelectasis, retained secretions, and difficult tracheal intubations) and occasionally diagnostic. Bronchoscopy for atelectasis results in clinical and radiographic improvement in approximately 80% of patients when aggressive noninvasive techniques for retained secretions have failed (Ellis '89: 36, 37).

Transbronchial lung biopsy and bronchial brushing by way of the fiberoptic bronchoscope are adaptations. Transbronchial lung biopsy with the flexible fiberoptic bronchoscope and the standard biopsy forceps that accompany this instrument have been used with and without fluoroscopic guidance with good results and few complications – fewer complications, in fact, than percutaneous lung biopsy techniques or thoracotomy. Transbronchial lung biopsy with the flexible fiberoptic bronchoscope has been useful in the evaluation of opportunistic infections. Bronchial brushing is performed during the same procedure. Complications of FFB relate largely to excessive premedication or topical anesthesia and consist principally of laryngospasm, bronchospasm (especially in asthmatic patients, pneumothorax, hemorrhage, and hypoxemia. The complication rates remain very low, and deaths are rare. Percutaneous needle biopsy with or without fluoroscopic guidance has become an increasingly useful method in the diagnosis of diffuse or peripherally localized pulmonary lesions, thus obviating the need for thoracotomy in

many cases. Contraindications to these procedures are abnormal coagulation studies, emphysematous blebs of bullae in the biopsy area, evidence of pulmonary hypertension, central or obviously vascular lesions, pulmonary function impairment of a degree of indicating inability to tolerate significant pneumothorax, or inability to cooperate. Similar considerations are made before transbronchial lung biopsy. Three techniques are currently used: aspiration, cutting and drill biopsy. In one series, aspiration needle biopsy gave positive cytologic or bacteriologic results in over 70% of cases with a complication rate of 23% (consisting of 14% simple pneumothorax, 5% pneumothorax requiring treatment, 3% hemoptysis and 1% hemothorax) without fatality. However, rare fatalities have occurred, and the complications of cutting needle and drill biopsy techniques are much greater; consequently their use is diminishing. (Ellis '89: 37).

The type and the gauge of the needle are important to successful **transthoracic needle aspiration biopsy**. The three types of needles commonly used are the spinal needle, the aspirating needle, and the so-called fine needed. The only advantage of the spinal needles is low cost. Aspirating needles have a cutting edge and its lumen is wider than the needle. Fine needles refer to 22- gauge or 23-guage needles. The major disadvantage of fine needles are the relatively scant material obtained, limited diagnostic scope and difficulty in controlling the path of the needle within the lung parenchyma. A **C-arm fluoroscope** with good resolution or a biplane fluoroscopic setup is excellent for guiding transthoracic needle aspiration biopsies. Percutaneous needle biopsy of the lung has been performed successfully with computed tomography (CT) guidance. Biopsy performed with CT guidance is a longer and cumbersome procedure than fluoroscopy and may result in higher incidence of pneumothorax. In 1978 Wang used a needle designed for treating sclerosis of esophageal varices and described **transbronchial needle aspiration** for the diagnosis of paratracheal tumors. A sheathed needled was passed through the fiberoptic bronchoscope, advanced fro tis sheath when the distal tip is in view, and inserted into the area to be sampled. It was moved up and down within the sampling area while a syringe applied suction. The needle was withdrawn into its sheath, the apparatus was withdrawn and the aspirate was flushed from the needle into a fixative for cytologic examination. Eighteen of twenty patients with proven bronchogenic carcinoma yielded malignant cytologic specimens using this technique to ascertain metastatic spread. **Broncoalveolar Lavage** (BAL) has been performed with bronchoscopy for several years to r ecover respiratory cells for use in research studies. Recently BAL has shown promise in the diagnosis of interstitial lung disease and opportunistic infections. The procedure involves wedging the fiberoptic bronchoscope into a subsegmental bronchus and instilling 20 o 50 ml aliquots of normal saline. Gentle suction is applied after each instillation to recover bronchoalveolar material. BAL is particularly effective in diagnosing the opportunistic infections in acquired immune deficiency syndrome. BAL is also being used int eh evaluation of diffuse interstitial lung or alveolar disease (Ellis '89: 38, 39).

In the **differential diagnosis** of pleural effusion, it is helpful to classify the fluid as either a transudate or an exudate. If any one of the three following criteria is present the fluid is usually an exudate (1) a pleural fluid-to-serum total protein ratio of more than 0.5, (2) a pleural fluid LDH of more than two-thirds the normal upper limit of the serum, or (3) a pleural fluid-to-serum LDH ratio of more than 0.6. **Transnudate causes** of pleural effusion are congestive heart failure, cirrhosis of the liver, nephrotic syndrome, atelectasis, hypoalbuminemia, peritoneal dialysis, constrictive pericarditis, malignancy (under 10%) or urinothorax. **Exudate causes** of pleural effusion are bacterial pneumonia, pulmonary embolism, malignancy, viral disease, connective tissue disease, tuberculosis, fungal disease (blastomycosis), parasitic disease (amebiasis), rickettsial disease (Q fever), gastrointestinal disease (pancreatitis, subphrenic

abscess, esophageal rupture, drugs reaction (nitrofurantoin, methysergide), asbestos pleural effusion, Meigs' sundrome, post-cardiac injury syndrome, trapped lung, lymphatic abnormalities (yellow nail syndrome), uremic pleurisy, radiation therapy, chylothorax, and/or sarcoidosis. Transnudate fluids and some exudates are **clear and straw colored**. A white, milky color suggests chylothorax, a reddish tinge indicates blood, a brown color may suggest rupture of an amebic liver abscess into the pleural space, and a black discoloration suggests aspergillus infection. Elevated **white cell counts** and increased amounts of lipids make pleural fluid turbid. Pus aspirated fro the pleural space confirms the diagnosis of **empyema**. Anaerobic empyemas have a foul odor. A bloody, vicious fluid suggests a malignant mesothelioma.

If the fluid's leukocyte count is greater than 1000/µl, it is probably exudative. An **erythrocyte count** of 5000 to 10,000/µl is needed to make the pleural fluid hemorrhagic. If fluid is bloody without trauma a malignancy is likely. A low pleural fluid **glucose** (less than 60 mg/100 ml or pleural fluid/serum ratio (PF/S) of less than 0.5) narrows the differential diagnosis of the exudate to (1) rheumatoid pleurisy, (2) empyema, (3) carcinoma, (4) tuberculosis or (5) lupus pleuritis. A low pleural fluid **pH** (less than 7.30) has been found only in empyema, esophageal rupture, rheumatoid pleurisy, tuberculosis, malignancy and lupus pleuritis. If the pleural fluid pH in a para-pneumonic effusion is more than 7.30, the fluid will almost always resolve spontaneously with antibiotic therapy without sequelae. However, it the pleural fluid pH is less than 7.10, the patient will most likely have a complicated course requiring a surgical procedure to drained immediately from the pleural space with a chest tube. An elevated pleural fluid **amylase**, usually twice the serum amylase, suggests one of four possibilities, (1) acute pancreatitis, (2) pancreatic pseudocyst, (3) esophageal rupture, or (4) primary or metastatic carcinoma of the lung. Chylous effusions (caused by severing or obstructing the thoracic duct with drainage into pleural space) contain chylomicrons and a high triglyceride concentration (more than 110 mg/100 ml). On the other hand, chyliform effusions (long-standing, loculated effusions seen occasionally in tuberculosis, malignancy, trapped lung, or rheumatoid disease) contain a high cholesterol concentration and low levels of triglycerides (less than 50 mg/100 ml).

In cases of malignant disease of the pleura, cytologic tests are positive in 65% to 70% of patients. AFB, Gram, Wright stains, pleural biopsy and therapeutic thoracentesis, should be performed. Nasal oxygen should be given during and for several hours following therapeutic thoracentesis, since transient and sometimes substantial falls in Pa_{O_2} may occur despite relief of dyspnea. The incidence of pleural effusion associated with pneumonia depends on the cause of pneumonitis. *Streptococcus pneumoniae* causes parapneumonic effusion in 40% to 60% of patients and especially in patients with positive blood cultures and prolonged symptoms before antibiotic therapy. *Staphylococcus aureus* pneumonias are frequently complicated by effusion (70% in infants, 40% in adults). *Streptococcus pyogenes* pneumonias are not common but are frequently (55% to 95% of the time) associated with large pleural effusions. The gram-negative aerobic pneumonias (*Klebsiella*, *Escherichia coli*, and *Pseudomonas* species) are associated with a high incidence of parapneumonic effusion (Sahn '89: 288-291).

For accurate determination of the type and degree of **hearing loss**, an audiologic evaluation is performed with audiometer in a sound-treated room An audiometer is an electrical instrument that produces tones at various frequencies (measured in hertz) from 125 to 8,000 or 12,000 Hz and at intensities (measured in decibels) from 10 dB to 120 dB. Sensitivity to <20 dB is normal hearing, 20-40 dB mild hearing loss, 40-55 dB moderate hearing loss, 55-70 dB moderate-severe hearing loss, 70-90 dB severe hearing loss and > 90 dB profound hearing loss. Furthermore, speech testing is done to determine (1) speech awareness threshold, the lowest intensity sound

can be recognized as speech and (2) speech reception threshold to assess ability to repeat familiar two-syllable words that have equal stress on each syllable (e.g. hotdog, baseball) (Bhaya, Sperling & Madell '04: 65,66, 72-74, 78). Physical examination of the **tongue and oral cavity** requires bright illumination to assess areas of discoloration, edema and irregularity indicative of an infectious, hematologic or neoplastic abnormality. Complete examination or the oral cavity must include palpation of the tongue, floor of the mouth, buccal mucosa and retromolar trigone for masses, tenderness and induration (Schwartz, Lim & Har-el '04: 198-203).

A **cardiologist** is a doctor who specializes in the care of patients who have (or are suspected of having) heart disease. A general cardiologist specializes in a wide range of heart-related problems. In addition to medical school training, cardiologists have three years of internal medicine preparation and at least three years in cardiology. A **cardiac imaging cardiologist** specializes in noninvasive imaging studies that help diagnose structural and functional abnormalities of the heart. Studies include echocardiography, computer tomography angiography (CT angiography) with contrast dye, cardiac magnetic resonance imaging (cardiac MRI) and nuclear cardiology. An **interventional cardiologist** specializes in diagnosis and treatment of heart-related problems by inserting catheters into blood vessels and then injecting contrast due into the catheters to visualize abnormalities. One of the invasive procedures these specialists perform is a percutaneous coronary intervention (PCI) in which coronary artery blockages are opened via a balloon (angioplasty) and one or more stents (small metal mesh tubes) are placed to keep the vessels open. A **cardiac rehabilitation cardiologist** is a general cardiologist who helps patients recover from heart surgery and other heart interventions using a graduated and monitored exercise program. These doctors often educate patients and coach them on healthy diet, exercise, and lifestyle modifications. A **heart failure specialist** is a cardiologist who specializes in the treatment of congestive heart failure and helps patients maintain an optima diet and lifestyle. These specialists also prescribe and monitor patients' medications and strive to provide optimal medical therapy. A **cardiothoracic surgeon** performs open-heart surgery to bypass blocked arteries and to treat valvular heart disease. The cardiac surgeon may also perform procedures to treat heart rhythm abnormalities and has the advantage of directly visualizing the heart. Cardiothoracic surgery encompasses entirely different surgical training than is required in general cardiology and its subspecialties (Cohen '10: 9).

Blood pressure is usually measured by inflating a cuff that is connected to a column of mercury, or to a mechanical device that simulates a column of mercury. A **stethoscope** is placed over the brachial artery at the elbow; the cuff is wrapped around the upper-arm and inflated until the artery is compressed so firmly that blood can't get through, and then the cuff is deflated. Listening through the stethoscope over the artery reveals a tapping sound when the pressure of the blood in the artery is enough to push blood through, and the tapping sound goes away when the artery stays open between beats. Because the pressure wave is generated by the contraction of the heart (systole) the top pressure is called systolic pressure, when the artery stays open between beats, which corresponds to the relaxation phase of the heart (diastole), this is called diastolic pressure. Both readings are important. An ideal blood pressure would be below 120/80 (Spence '06: 78). The kidneys play an important role in blood pressure regulation by at least three mechanisms (1) renin-angiotensin system (2) sodium homeostasis and (3) renal vasodepressor substances, which should be confirmed by laboratory assay in cases of hypertension which are not immediately brought under control. Environmental factors implicated in the causation of hypertension include stress, obesity, smoking, inactivity, and heavy consumption of salt, found in bread and cheese and meat. Hypertension is associated with

two forms of small blood vessel disease: hyaline ateriolosclerosis and hyperplastic arteriolosclerosis (Schoen ’94: 485, 486, 488).

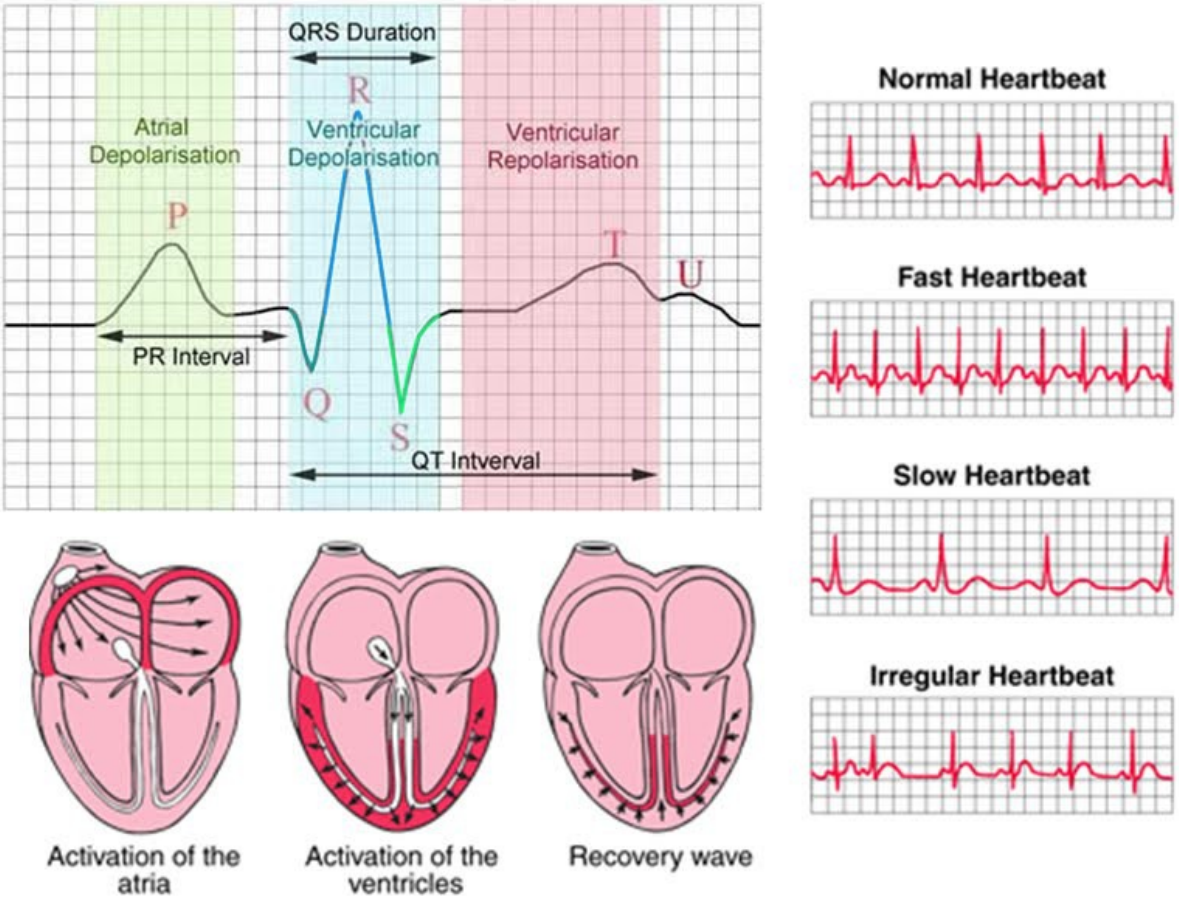
Categories for Blood Pressure Levels in Adults (in mmHg, millimeters of mercury)

Category	Systolic (top number)	Diastolic (bottom number)
Normal	Less than 120	Less than 80
Prehypertension	120–139	80–89
High blood pressure		
Stage 1	140–159	90–99
Stage 2	160 or higher	100

Credit: Schoen '94:

By counting the number of pulsations over a fifteen-second interval and multiplying that number by four, the heart rate can be calculated in beats per minute. A **normal heart rate** is between 60 and 100 beats per minute. A slower than normal rhythm in which the heart rate is below 60 beats per minute indicates sinus bradycardia. If the rhythm exceeds 100 beats per minute, a sinus tachycardia would be present. Heart rates slower than 60 beats per minute can be normal if you don’t have symptoms such as fatigue, shortness of breath, light-headedness or dizziness. Rapid heart rates (greater than 100 beats per minute) may be normal or abnormal, depending on circumstances. Conditions that weaken the heart muscle may cause rapid heart rhythms, called **tachycardias**, with rates greater than 100 beats per minute and possibly much faster. The faster the heart rate, the great the chance that delivery of oxygen and other nutrients to the brain and other organs will be impaired. With very fast beats (over 200 a minute) the person will likely become light-headed and dizzy and even pass out. The heart may also beat too slowly (called **bradycardia**) with heart rates below 60 beat per minute. Reversible causes of bradycardia are nonessential medicines such as beta blockers, calcium channel blockers, digitalis, antiarrhythmic drugs such as sotalol and amiodarone, Lyme disease, hypothyroidism, electrolyte abnormality and drug toxicity. **Sinus bradycardia** is commonly caused by second-degree heart block, Mobitz type I (block typically occurs in the AV node), second-degree heart block, Mobitz type II (block typically occurs in the His bundle or below), third-degree heart block or complete heart block, Asystole. An irregular heart rate might indicate early beats, called premature contractions (coming from either the atria or the ventricles) or may be an indicator of a rhythm problem called **atrial fibrillation**, in which the atria beats at rates greater than 400 beats per minute (Cohen ’10: 12, 61, 13, 22, 23, 14).

Electrocardiogram (ECG) Reading



Credit: IVLine May 2010

A single electrocardiogram (ECG) recording of a heartbeat shows the electrical sequence of the heart. The electrical signal may be broken into different waves. The P wave represents atrial electrical activity; the QRS complex represents ventricular electrical activity; and the QT interval (from the beginning of the Q wave to the end of the T wave) represents the ventricles returning to a resting state. Sometimes a test is performed through the esophagus (called a **transesophageal echocardiogram**) where it is particularly useful in looking for the presence of blood clots in the left atrium. Blood clots may form in the left atrial appendage (a site that is not well visualized by standard echocardiogram) (Cohen ’10: 60, 68). An electrocardiogram, or ECG, is an electrical recording from the limbs and the surface of the chest that shows the pattern of electrical activity in the heart. The ECG can detect rhythm disturbances such as atrial fibrillation, may detect the presence of an old myocardial infarction, and in some circumstances, particularly when repeated daily for several days, can detect a recent heart attack (myocardial infarction). The accuracy of this diagnosis by ECG is greatly aided by measuring enzymes or other markers from the heart released into the bloodstream when the heart muscle breaks down, such as CK (creatine phosphokinase) and troponin. An electrocardiogram requires sticking electrodes to the limbs and the chest, and then making a recording. It is completely safe and painless (except for the pulling of chest hair when the electrodes are removed) (Spence ’06: 43).

Cholesterol, triglycerides, saturated fats, trans-fatty acids, homocysteine and other harmful substances from food. Because fat is not soluble in water, and blood is mostly water, fat from food goes from the intestine to the liver in lymphatic fluid, and is then taken out of the blood by cells in the liver. It travels in the bloodstream in packages made up of an outer layer of protein,

with fat in the center. These proteins are called lipoproteins (proteins that transport lipids) (Spence ’06: 80). It is estimated that 65 million American adults with **high blood cholesterol** need to make the therapeutic lifestyle changes (TLC) needed to lower their cholesterol and, with it, their risk for heart disease. To understand high blood cholesterol, it is important to know more about cholesterol. **Cholesterol** is a waxy, fat-like substance that is found in all cells of the body. Your body needs some cholesterol to work the right way. Your body makes all the cholesterol it needs. Cholesterol is also found in some of the foods you eat. Your body uses cholesterol to make hormones, vitamin D, and substances that help you digest foods. Blood is watery, and cholesterol is fatty. Just like oil and water, the two do not mix. To travel in the bloodstream, cholesterol is carried in small packages called **lipoproteins**. The small packages are made of fat (lipid) on the inside and proteins on the outside. Two kinds of lipoproteins carry cholesterol throughout your body. It is important to have healthy levels of both: **Low-density lipoprotein** (LDL) cholesterol is sometimes called bad cholesterol. High LDL cholesterol leads to a buildup of cholesterol in arteries. The higher the LDL level in your blood, the greater chance you have of getting heart disease. **High-density lipoprotein** (HDL) cholesterol is sometimes called good cholesterol. HDL carries cholesterol from other parts of your body back to your liver. The liver removes the cholesterol from your body. The higher your HDL cholesterol level, the lower your chance of getting heart disease (Sanders ’08: 25).

Lipid Profile

LDL Cholesterol Level	**Category**
Less than 100 mg/dL	Optimal
100 to 129 mg/dL	Near or above optimal
130 to 159 mg/dL	Borderline high
160 to 189 mg/dL	High
190 mg/dL and above	Very high

Triglyceride Level	**Category**
Less than 150 mg/dL	Normal
150–199 mg/dL	Borderline high
200–499 mg/dL	High
500 mg/dL and above	Very high

Credit: American Heart Association

The American Heart Association endorses the National Cholesterol Education Program (NCEP) guidelines for detection of high cholesterol. The Third Report of the Expert panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III or ATP III) was released in 2001. It recommends that everyone age 20 and older have a fasting "lipoprotein profile" every five years. This test is done after a 9-12-hour fast without food, liquids or pills. If total cholesterol is 200 mg/dL or more, or HDL cholesterol is less than 40 mg/dL (for men) and less than 50 mg/dL (for women), a lipoprotein profile should be done to determine LDL cholesterol, triglyceride, homocysteine and C-reactive protein (CRP) levels (Sanders ’08: 26). **Triglyceride** is the most common type of fat in the body. Many people who have heart disease or diabetes have high triglyceride levels. Normal triglyceride levels vary by age and sex. A high triglyceride level seems to speed up atherosclerosis, the buildup of fatty deposits in artery walls and atherosclerosis increases the risk for heart attack and stroke. Other potentially cartiotoxic lipoproteins can be detected, but are not necessary to confirm a diagnosis

of hyperlipidemia. **C-reactive protein** (CRP) has been known for many years as a non-specific test for inflammation that led to the discovery in the 21st century of the use of CRP as a marker of arteriosclerosis risk. **Homocysteine** is major cause of arteriosclerosis and some process intimately involved in the methionine/homocysteine metabolic interplay but other factors are likely to be involved (Graveline '04: 72, 59). Folate is known to reduce homocysteine levels. Niacin reduces cholesterol. Statin drugs are effective at reducing cholesterol by 20-30% which reduces the death rate from ischemic heart disease and stroke by 30-50%, but the reasons for discontinuing the medicine unfortuneately does not include recovery, known to happen with **Hawthorne,** the supreme herb for the heart, and most necessarily a **vegan diet** until no longer overweight when a vegetarian diet, including aged cheese (does not contain lactose after two months) and probiotic yoghurt, will be needed daily to prevent vitamin B_{12} and phosphorus deficiencies in the absence animal products such as biologically metabolized triglycerides.

An **echocardiogram**, also called an echo or a cardiac ultrasound, uses sound waves to create images of the heart. This test can reveal your heart's ejection fraction (EF), the presence of leaky or tight (stenotic) valves, weak heart muscles (cardiomyopathies), thick heart muscles (hypertrophy), blood clots or masses in your heart, or fluid in the sac around the heart (the pericardium). The echocardiogram is also useful in showing the presence and location of a heart attack. An ultrasound examination called an echocardiogram –echo, for short, reveals the action of the heart valves, as well as the pattern of contraction of the heart muscle and areas that are not contracting, including aneurysms. Valves at the outlet of each chamber of the heart prevent the blood from going backward in the system. Sometimes problems with the valves can lead to stickiness on their surface, and to a buildup of clot or a clump of clotting protein and inflammatory cells, which may be infected. Sound beams are directed into the heart, and a computer analyzes the return echoes and converts them into images. The test is completely safe and harmless, it is essentially the same kind of imaging used to check out babies in the uterus. Occasionally the test may require putting a tube into the esophagus in a procedure called transeosophageal echocardiogram (TEE) (Spence '06: 43, 44).

Since 1990 it has been possible via ultrasound to see the plaque in the artery wall and in 1992 it became possible to use the software to measure the size of plaques which is useful over time to gauge the effectiveness of treatment. If all the plaques are measured, and the total area of plaque is added up, this gives information about both risk and response to therapy. Individuals with a lot of plaque have a higher risk of stroke, death and heart attack: those in the top quartile of plaque have a five-year risk that is 3.4 times higher than those in the bottom quartile, even after adjusting for all the traditional risk factors. Furthermore, those whose plaques increase in the first year despite treatment of the traditional risk factors have twice the risk of those with stable plaque or regression. For those individuals, physicians need to try harder. Tests can investigate newer risk factors such as homocysteine (an amino acid that increases clotting and irritates the lining of blood vessels), lipoprotein (a) borderline hypothyroidism, borderline B_{12} and so on. The latest development in the field of arterial plaque ultrasound is the ability to measure plaque volume in three dimensions (3-D) (Spence '06: 55).

A test called a **computer tomography** (CT) angiogram may be useful in demonstrating heart function and visualizing arteries in the heart. A CT angiogram is also helpful in diagnosing coronary artery disease because it is a direct method of looking at the coronary arteries. The cardiac **magnetic resonance imaging** (MRI) is used to take pictures of the heart to diagnose coronary artery disease, assess damage caused by a previous heart attack, and diagnose heart failure as well as valve problems. The cardiac MRI is particularly useful at looking for an

inherited condition called **arrhythmogenic right ventricular dysplasia** (in which fat deposits are seen within the wall of the right ventricle) who should be considered candidates for implantable cardioverter defibrillator (ICD) (Cohen '10: 71-72).

The definitive way to determine whether there is a problem with blockage of the coronary arteries is to do a radiological (X-ray) examination of the arteries, a procedure called **angiography**. This begins with putting a needle into the artery at the top of one leg. A thin plastic tube called a catheter is threaded through the needle and advanced up through the bloodstream until it reaches the top of the aorta, just where it leaves the heart. The catheter is maneuvered into the opening of each coronary artery, the first branches off the aorta, just above the aortic valve – and an injection of X-ray contrast material, or dye, is injected through the catheter to show up the artery and its branches. The feeling of heat that once accompanied each injection is much diminished with the development of newer dyes (nonionic contrast material) which are slightly safer than the older dyes and cost about ten times more. An angiogram does carry a small risk including a reaction to the X-ray dye as well as a serious complication from an injury to one of the arteries – about a 1: 1,000 risk of dying or needing an operation immediately to reopen a coronary artery blocked because the dye injection caused a peeling off or "dissection" of the artery lining (Spence '06: 46, 47).

In a **stress test**, one exercises on a treadmill while the ECG is monitored. Walking or running speed is progressively increased along with the grade (or slope) as the doctor continuously analyzes blood pressure as well as the ECG. **T-wave alternans** (TWA) is a test that can be performed in a doctors office. The patient is attached by electrodes to computerized equipment and undergo a stress test. An intravenous line is inserted and continuous ECG monitoring is performed. The computer analyzes the heart rhythm for a scientific phenomenon called microvolt T-wave alternans (TWA). TWA helps to determine the risk for ventricular tachycardia. It is not useful if the patient is in atrial fibrillation (Cohen '10: 77). The doctor may perform a **nuclear stress test** in which a nuclear agent (radioisotope) is injected into the vein and images of the heart are acquired to identify whether areas in the heart muscle are receiving enough blood. Stress tests are useful for sedentary patients before they begin an exercise regimen, to evaluate whether exercise is safe for them. For all stress tests and invasive procedures the patient must have nothing by mouth (NPO) for at least 6 hours prior to the procedure. In addition, the doctor may ask the patient to stop taking blood thinners, such as warfarin (Coumadin) and antiplatelet medications, such as acetylsalicylic acid (aspirin) and clopidogrel (Plavix), before a procedure (Cohen '10: 63, 64, 65).

A **nuclear medicine scan** assesses how well blood is flowing to the heart muscle (myocardium) and is most useful for diagnosing coronary artery disease individuals whose routine treadmill stress test is inconclusive. Many people with coronary artery disease have a history of chest pain brought on by exertion and relieved by rest; others may exhibit no symptoms, and about 40 percent of myocardial infarction are "silent" a heart attack without any chest pain or other symptoms. The nuclear medicine scan involves injecting a small dose of a radioactive tracer into a vein while the individual's heart is speeded up either by some kind of exercise such as rotating a pedal system with the arms, or by injection of a drug such as dipyridamole. An array of detectors similar to small Geiger counters detect the arrival and disappearance of the radioactive tracer in various regions of the heart muscle and thus image and measure the blood flow to the heart. If one of the coronary arteries is blocked or narrowed, the part of the myocardium that would normally get its blood supply from that artery fails to "light up" on the scan; in some cases this scan can also detect the abnormal movement of an aneurysm. Although radioactivity sounds

scary, one or even several scans pose no danger. The gamma radiation involved is the same kind we get every day from sunlight; the dose is about the equivalent of going to Denver for a week of skiing, or crossing the Atlantic once in an airliner (radiation levels are higher at higher altitudes) (Spence '06: 45, 46).

The procedure for **coronary angiography** involves inserting a needle into a large artery, usually in the leg; a thin plastic catheter is advanced through the bloodstream to where the brain arteries branch off the aorta and the catheter is advanced into the origin of the artery. Contrast material – dye – is injected into the artery, and a picture is made of the artery and its branches. With new computerized scanners, measurements can be taken from the screen, and the images are stored in a computer for analysis and prints some representative images, often on film that looks like X-ray film. The risks of coronary angiography include reactions to the dye and injury to the arteries by the needle or the catheter. The risk of dying form a bad reaction to the dye is approximately 1: 40,000. There is some risk of damage to the kidneys and of heart failure, which is lessened by the reduced dose of dye when digital imaging methods are used. Because the contrast material is denser than blood, it puts a strain on the heart similar to that caused by injecting a stronger than normal solution of salt. Kidney damage may be caused by the dye. The risk of angioplasty is warranted if the reason is to plan carotid surgery (endarterectomy), to look for inflammation of the arteries (vasculitis), or to look for and treat the cause of a hemorrhage, such as an aneurysm or arteriovenous malformation. There are essentially no serious medical risks from CT scanning, MRI or ultrasound (Spence '06: 56, 57, 58, 59).

An invasive procedure called a **cardiac catheterization** is performed in a specialized catheterization laboratory (cath lab) under x-ray visualization (cinefluoroscopy) by placing catheters (tubes) through sheaths into the blood vessels (artery and/or vein) and threading the catheters into the heart. Patients are generally given sedation before or during the procedure so they feel more comfortable. Contrast dye is administered to visualize structures, and pressures are recorded to determine heart and valve function. The doctor must be informed if the patient has a contrast dye allergy or a shellfish allergy (Cohen '10: 73). The **electrophysiology study** (EP study) is a crucial procedure for identifying heart rhythm problems. During the EP study catheters are guided through blood vessels into the heart using an x-ray technique called fluoroscopy imaging. The catheters are placed through the veins, arteries, or both up into the chambers of the heart. The doctor is able to pace (stimulate) the heart at a faster rate than normal and take readings of the signals. Electrical signals are recorded directly from the heart. This test can reveal if a pacemaker or a defibrillator is needed (Cohen '10: 78).

Most causes of heart failure result in dysfunction of the left ventricle (systolic and diastolic heart failure). The right ventricle also may be dysfunctional, especially in pulmonary disease (right ventricular failure). Left heart failure, commonly called congestive heart failure is categorized as heart failure with reduced ejection fraction (systolic heart failure) or heart failure with preserved ejection fraction (diastolic heart failure). These two types of heart failure can occur together or singly. Heart failure with reduced ejection (systolic heart failure) is defined as an ejection fraction of <40% and an inability of the heart to generate an adequate cardiac output to perfuse vital tissues. Some conditions cause inadequate perfusion despite normal or elevated cardiac output (high-output failure). Nearly 75% of heart failure cases have an antecedent in hypertension (McCance '14: 1175). Cardiac output is the volume of blood flowing through either the systemic or the pulmonary circuit and is expressed in liters per minute. Cardiac output is calculated by multiplying heart rate in bats per minute by stroke volume in liters per beat. Normal adult cardiac output at rest is about 5L/mi. The ventricles do not eject all of the blood

they contain with each heartbeat and the amount ejected is called the **ejection fraction**. The ejection fraction is calculated by dividing the stroke volume by the end-diastolic volume. The end-diastolic volume (EDV) of the normal ventricle is about 70 to 80 ml/m^2 and the normal ejection fraction of the resting heart is 55% or higher. According to the Frank-Starling law, the longer the initial resting length of the cardiac muscle fiber (optimal length is between 2.2 and 2.4 mm), the greater the strength of contraction. At 2.2 mm an optimal number of active cross-bridges exist between actin and myosin. However, if the fibers are stretched beyond 2.2 to 2.4 mm, the force of contraction decreases because actin and myosin become partially disengaged, disrupting may of the cross-bridges. Excessive stretching, to about 3.65 mm, causes actin and myosin to become completely disengaged so that tension (force of contraction) drops to zero. Laplace's law states that wall tension is related directly to the product of intraventricular pressure and internal radius and inversely related to the wall thickness as shown in the Laplace equation: $T = (p \times r)/\mu m$. Where T = wall tension, p = intravascular pressure, r = internal radius of the sphere, and μm = wall thickness. Essentially, the amount of tension generated in the ventricular wall (or any chamber or vessel) to produce a given intraventricular pressure depends on the size (radius and wall thickness) of the ventricle. Laplace's law is useful for understanding aneurysm formation distensibility in blood vessels and the effects of ventricular dilation on myocardial contraction (McCance et al '14: 1101-1102).

IV.4 Respiratory Medicine

All **lung diseases** put together are the third leading killer in the United States and is the cause of one in six deaths. Every year an estimated 400,000 people die from diseases of the lung; an age adjusted death rate of 135 per 100,000. More than 35 million people have chronic lung diseases. An estimated 12.1 million have COPD, also known as emphysema or chronic bronchitis. Lung disease may refer to the most frequent of cold viruses and many chronic conditions such as asthma, allergies, to deadly, but largely treatable diseases like chronic obstructive pulmonary disease, pneumonia and tuberculosis, to the two year prognosis of lung cancer. Health professionals should wear respirators when examining patient. In general, a wet cough is the flu, cured with Oseltamivir (Tamiflu), Zanamivir (Relenza) and Amantadine (Symmetrel). A dry cough is pneumonia, treated with ampicillin (Principen) or azithromycin (Z-pack). Corticosteroids are the most effective treatment for viral respiratory infections, including the coronavirus, that would be otherwise untreatable, and is highly curative for asthma, allergic rhinitis, and hypersensitivity, mostly caused by mold colonization. The mild but cloy respiratory anti-smoking virus warrants detection and hygiene. Hard lung nodules and coughing from aspergillosis are cured with a dab of hydrocortisone crème to chest. A runny nose indicates a viral cold, limited to one week, a very runny nose, the first week of pertussis while six weeks of whooping cough can be avoided by taking antibiotics, or if the runny or itchy nose lasts longer than a week it is allergic rhinitis, cured with a dab of hydrocortisone crème to the nose. Pertussis does not respond to antibiotics after it has descended to the lungs from the extremely runny nose of the first week. Persons who succumb after the first week of runny nose can prevent contagiousness with antibiotics, but the horrible whooping cough lasts six weeks. Vaccination and antibiotics have been effective at controlling the incidence of pertussis for the past century. Between 1922-1925 the average annual number of reported cases of *Bordetella pertussis* in the United States was 147,271, by 2001 incidence of whooping cough had decreased 95 percent to 7,580 (Fisher ’06: 7). Respiratory infections of bacterial and viral origin are highly contagious due to the spread of airborne water droplets by coughs and sneezes, that contaminate environment; mold infections don't distinguish between the environment and human host and are not considered contagious The cure is typically not complete until environmental exposure is

cleaned up, wherefore consumers must be exhorted to clean up. Body fat is needed to seal damaged lungs. Adequate nutrition must be emphasized for respiratory patients.

One-fourth of all Americans who seek medical care do so because of an infectious disease. At least 150 million courses of antibiotics costing more than $16 billion are prescribed in the United States each year, largely to treat upper respiratory tract infections. Antibiotics are appropriate only for bacterial infections. Viral infections that commonly involve the head and neck but do not benefit from antibiotics include croup, bronchitis, influenza, common cold, non-streptococcal tonsillopharyngitis, and most cervical adenitis. Rhinorrhea accompanying a viral upper respiratory tract infection may be clear, cloudy, green yellow or even purulent and that color alone does not imply bacterial origin. Not all presumed bacterial infections require antibiotics but withholding antibiotics is inappropriate for infections that are severe or complicated. Give the right drug for the right bug. Common causes of acute respiratory tract infection include *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Morazella catarrhalis*, and group A beta-hemolytic streptococcus (*S. pyogenes*); chronic infections often include *Pseudomonas aeruginosa*, *Staphylococcus aureus* and anaerobic organisms. Certain commonly used antibiotics (e.g., azithromycin, clarithromycin, cefprozilad, trimethoprim-sulfamethoxazole) are relatively ineffective for several bacteria and have effects worse than placebo because they induce further resistance (Boruk & Rosenfeld '04: 427, 428). In general, ampicillin (Principen) is the best antibiotic for upper respiratory infections, sinusitis, otitis media and meningitis, but some people are allergic. About 15% to 30% of pneumococcus is penicillin resistant. Although there are other causes of antibiotic resistant pneumonia, the most common cause is the combination of *Streptococcu*s spp. and *Staphylococcus aureus* causes toxic shock syndrome, for which the treatment is doxycycline or clindamycin (Cleocin) for pregnant women and children under age 8. Toxic shock syndrome manifests as an extremely painful rheumatic condition instigated by normal social loads of streptococcus, because the patient has staphylococcus lesion(s) on, or in, their body. Epsom salt baths, saline swimming pools and ocean water, may also be curative of Staph infections. Metronidazole (Flagyl ER) is indicated for lower respiratory, gastrointestinal and joint infections and to treat antibiotic associated colitis caused by a proliferation of *C. difficile* due to antibiotic consumption, also treated with probiotics.

Treatment for pneumonia depends upon its cause. Pneumococcus, *Haemophilus influenzae*, *Legionella pnemonphila*, *Mycoplasma* and viruses abound in the community and gram-negative bacteria and *Staphylococcus* species in hospitals. Cystic fibrosis patients are frequently infected with *Pseudomonas* and *Staphylococcus*. COPD patients are vulnerable to the typical community-acquired infections. The bacterium *Legionella pneumophila* causes both Legionnare's disease and Pontiac fever and is an occupational hazard contaminating air-conditioning units and water reservoirs (Berger '04:271). *Streptococcus pneumoniae* is the most common bacterial pathogen isolated in immunocompetent patients. The classic Gram stain demonstrates lancet-shaped, gram-positive diplococci. The pneumococcus resides in the nasopharynx of asymptomatic carriers and is dispersed and transmitted in all seasons, although the highest incidence of disease is recorded in colder weather. The virulence of the organism depends substantially on the capsular serotype (20% mortality with type III compared with 2% with type II). *Streptococcus pyogenes* (group A Strep) often super-infects a preceding viral pneumonia, especially influenza in adults. It generally causes Strep throat as an immune reaction to infected sputum or rheumatic heart disease in patients immunocompromised by unhealed heart attack scars. Thoracic complications of empyema, pneumothorax and bronchiectasis, as well as extrathoracic complications, including glomerulonephritis, anemia, thrombocytopenia, and bacteremia have occurred. Therapy with penicillin G or ampicillin is usually effective, if the

patient is allergic or has Strep throat, which can mimic the choking sensation of anaphylaxis, erythromycin or doxycycline should be substituted. *Streptobacillus agalactiae* (group B Strep) usually causes pneumonia and sepsis in newborns and infants, but has been detected with increasing frequency in adults (McClellan & Iseman '89: 64, 65) as a hyper-uremic gouty lower respiratory infection treated with hygiene and a seven to fourteen day course of metronidazole 400 mg for adults 200 mg for children, one twice a day. *Staphylococcus aureus* produce penicillinase, and penicillin, ampicillin and semisynthetic penicillin antibiotics (including methicillin, nafcillin, oxacilin and dicloxacillin) are inactivated by staphylococcal β-lactamase (McClellan & Iseman '89: 65, 66). It is necessary to treat staph infections with doxycycline or clindamycin (Cleocin) for pregnant women and children under age 8. Epsom salt baths may also be curative of Staph infections.

Diagnosis and Treatment of Respiratory Infections

Infectious Agent	Symptoms	Treatment
Common Cold		
Coronaviruses	Upper respiratory tract infection (URI) lasting for one week of nasal congestion, or in COVID-19 and SARS epidemics three weeks of severe lung infection.	Clean, corticosteroids and antibiotics for pneumonia. For SARS ventilate, medicate with antibiotic levofloxacin (Levaquin), and corticosteroids Methylprednisolone IV and then oral Prednisone
Rhinoviruses	URI, Swollen lymph nodes, upper respiratory tract infection, nasal infection, peak misery after two days, lasts a week	None, clean. Over-the-Counter: Diphenhydramine (Benylin, Benadryl), Chlorpheniramine (Telachlor, Chlo-Amine, Chlor-Trimeton, Aller-Chlor), Brompheniramine (Bromphen, Nasahist B, Dimetane Extentabs), Ipratropium intranasal (Atrovent)
Echovirus	URI, sore throat, skin rash, harpangia, croup, may inflame endocarditis, pneumonia, meningitis, prevalent in summer and fall in US	None, clean. Immune Globulin Intravenous (IGIV) for serious infections
Adenoviruses	URI and lower respiratory tract infection (LRI), may also cause conjunctivitis, bladder infection, inflamed pharynx, diarrhea and rheumatism of the lower extremities for a week, prevalent in late winter, spring and summer	None, clean. Vaccine re-authorized to Teva Pharm on contract with the U.S. Army. Get light exercise. Eat white rice for diarrhea. Clean. Avoid young children.
Flu Like Symptoms		

Influenza A & B	Body or muscle aches, chills, cough, fever over 101° F, 38°C, headaches, and sore throat, incubates for two days, lasts two days, prevalent in winter.	Bed rest for one to two days. Vaccine ineffective. OTC Theraflu, Allegra (Sanofi-Aventis) and Children's Allegra (fexofenadine) and Allegra-D (fexofenadine and pseudoephedrine); Prescription Oseltamivir (Tamiflu) and Zanamivir (Relenza). Antibiotics for pneumonia
Parainflueza Types 1-4	LRI in children, URI in adults, prevalent in fall and winter	No vaccine, clean. Treat secondary infections with Antibiotics
Respiratory Syncytial Infection	LRI and breathing passages. Most otherwise healthy people recover from RSV infection in 1 to 2 weeks	Ribavirin (Virazole), asthmas inhalers ie. corticosteroids: flunisolide (Aerobid), beclomethasone (QVAR), (Flovent); triamcinolone, (Azmacort), Antibiotics for pneumonia or ear infection
Bacterial Agent		
Whooping cough *Bordetella pertussis*	Sporadic epidemic respiratory infection begins with runny nose that lasts a week, before the infection descends to the lungs for six weeks of mild rheumatism and coughing	Antibiotics only cure if taken the first week before the infection descends into the lungs. Antibiotics taken later reduce contagiousness. Clean.
Strep Group A Rheumatic Heart Disease: *Streptococcus pyogenes*, acquired from young adults	Highly contagious URI, sore throat, lasting a week, rheumatic heart disease sets in after a week with a 25% chance of dying over 10 years, if untreated	Cured quickly with antibiotics and plenty of cardiovascular exercise. Eat vegan. No sugar. Clean. Stock up or get a refillable prescription for antibiotics.
Strep Group B Gout: *Steptobacillus agalactiae* acquired from nursing mothers	LRI infection, persistent endocarditis, hyper uremia and severe prolonged rheumatism of the lower extremities	Cured with a full course of antibiotics, long periods of light exercise, sunlight or Vitamin D for cripples. Eat vegan, no caffeine. Clean. Avoid nursing mothers and contaminated fabrics.
Pneumonia: *Streptococcus pneumoniae*, *Chlamydia pneumonia*e and *Staphylococcus aureus* acquired from hospitals, Strep + Staph = toxic shock syndrome	The term pneumonia is used to describe any severe respiratory infection, these strains are most highly contagious, also cause meningitis, ear and skin infection, endocarditis and mix and mutate with other resistant systemic bacterial	penicillin, ceftriaxone, cefotaxime and cardiovascular exercise. The corticosteroid Prednisone is also used, but is immune-suppressant. Ventilation in hospitals saves lives. Antitoxin for Step/Staph toxic shock syndrome. Eat vegan. Drink safely. Clean.

	and viral infections.	Avoid people for their sake.
Fungal Agent		
Histoplasma capsulatum	The Ohio and Mississippi River valleys are the most heavily contaminated regions in the United States, although distribution of the organism is worldwide. Infection results from the inhalation of spores from an environmental source and leads to several clinical states.	A total dose of 500 to 1000 mg of amphotericin B is used to treat severe primary infections, and 2 to 2.5 gm is used to treat all symptomatic disseminated infection. Ketoconazole 400 to 800 mg/day are used for non-meningeal infection and 800 to 1200 mg/day for disseminated infections with meningitis.
Aspergillus fumigatus, *A. flavus*, *A. niger* and others	Allergic aspergillosis, invasive or disseminated infection or fungus ball (or mycetoma), allergic bronchopulmonary or invasive disease, releases carcinogenic aflotoxin.	A total dose of 500 to 1000 mg of amphotericin B is used to treat severe primary infections. Oral sporanox (itraconazole) is reported to be effective. Topical hydrocortisone crème and oral corticosteroids work.

Source: HA

In recent years, *Branhamella catarrhalis* (formerly Neisseria), a gram-negative cocci, has been shown to be pathogenic, especially in patients with underlying lung disease. This organism also frequently elaborates β-lactamase, so simple penicillin or ampicillin therapy is inadequate. Isolates are usually susceptible to erythromycin, tetracycline, doxycycline. *Neisseria meningitides* is rarely the cause of adult pneumonia is treated with penicillin. Another commonly diagnosed community acquired pneumonia is *Haemophilus influenzae* which is aerobic, gram-negative rod frequently causing pneumonia in the elderly, alcoholics, patients with COPD, and those with preceding viral infections. The typical Gram stain finding (pleomorphic coccobacillus) direct therapy to Ampicillin (Principen) and Amantadine (Symmetrel). The majority of other gram-negative aerobes that cause significant morbidity and mortality include *Pseudomonas aeruginosa*, *Acinetobacter calcoaceticus*, and members of the Enterobacteriaceae family, including *Klebsiella penumoniae*, *Escherichia coli*, Enterobacteriaceae species, *Proteus* species and *Serratia marcescens*. If the epidemiology suggests the presence of Pseudomonas (patients with mechanical ventilation, burns, previous chemotherapy, or previous antibiotic therapy) an antipseudomonal penicillin such as azlocillin, piperacillin, mzlocillin, ticarcillin or carbenicillin could be used instead of the third-generation cephalosporin. Parenteral therapy should generally be continued for a minimum of 2 weeks. The mortality of these pneumonias ranges from 30% to 60% even when properly diagnosed and treated (McClellan & Iseman '89: 66, 67). Anaerobic bacterial pneumonia is usually polymicrobial. The most common organisms isolated include *Peptostreptococcus* species, *Fusobaterium* species, *Bacteroides malaninogenicus*, *Bacteroides fragilis*, and *Peptococcus* species. Drug reatment should consist of either high-dose penicillin or parenterally administered clindamycin. Metronidazole is also used in the treatment of anaerobic lung infection, but this medication has not been as effective as clindamycin (McClellan & Iseman '89: 67). *Legionella pneumophila* is a gram-negative organism responsible for sporadic cases of pneumonia, as well as outbreaks in the community. Typically this organism is transmitted via aerosol secretions. It frequently infects young adults and is uncommon after the age of 50. This organism is responsible for 10% to 50% of

pneumonia among college students and military recruits. The treatment of choice for "walking pneumonia" is erythromycin or tetracycline. The drug therapy consists of erythromycin for a minimum of two weeks. Rifampin can be added in refractory cases.

Many different viruses (influenza, parainfluenza, adenovirus rhinovirus, measles, coxsackievirus, varicella-zoster, herpes simplex, cytomegalovirus, and Epstein-Barr virus) are responsible for adult pneumonias. Most are community acquired. Amantadine (Symmetrel) is effective against influenza A both prophylactically and therapeutically. Response rates of other respiratory viruses to specific antiviral therapies are poor. *Actinomyces israelii* and *Nocardia* species are bacterial infections usually associated previous debilitating disease. Tularemia (*Francisella tularensis*), psittacosis (*Chlamydia psittaci*), and plague (*Yersinia pestis*) rarely cause pneumonia in humans. Mycobacterial disease, both tuberculosis and nontruberculosis mycobacterisis, fungal infections with *Aspergillus* species (e.g. *A. niger*), *Cryptococcus neoformans*, *Coccidioides immitis*, *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Candida* species and mucormycosis is capable of causing pneumonia best treated with Sporanox (itraconazole) if corticosteroids are not curative. Protozoan infections with *Pneumocystis carinii*, *Entamoeba histolytica*, nematodes, cestodes, trematodes, and rickettsiae such as *Coxiella burnettii* are treated with metronidazole (Flagyl ER). The etiologic agents responsible for pneumonia are diverse and the spectrum is constantly changing. Although improvement have been made in the diagnosis and therapy of pneumonia, little progress has been made in reducing morbidity and mortality (McClellan & Iseman '89: 68, 69). Successful treatment of pneumonia requires administration of antibiotics directed against the offending organism. A careful history, a physical examination, and a compilation of suitable laboratory information usually leads to a reasonable choice of antibiotics (McClellan & Iseman '89: 60, 61).

Respiratory syncytial virus (RSV) infections are usually mild and seem like a common cold. In most cases, RSV infections go away in about 10 to 14 days. Home treatment to ease symptoms and prevent complications is usually all that is needed. NSAIDS such as acetaminophen or ibuprofen may be taken to relieve suffering. Corticosteroids may be administered if the pneumonia worsens or does not go away on time. Antibiotics are not usually necessary but should be administered if an ear infection (otitis media) or pneumonia develop. Children who develop lower respiratory infections, especially bronchiolitis, may need medicines, such as bronchodilators, for the rest of their lives. When selecting an inhaler for the first time, or choosing a new one after triamicinolone (Azmacort) was removed by the producer for fluorocarbon concerns, avoid salmeterol, salmeterol has been known to be fatal. Flovent (Fluticasone Propionate) seems a safe corticosteroid inhaler. The control and treatment of allergic rhinitis falls into three major categories. The first is related to controlling contact with allergic material. Another prophylactic measure is hyposensitization of the patient with the affecting allergen, by injecting increasing amounts of the allergen to develop a high titer of blocking antibodies proper to normal exposure. Finally as an adjunct to hyposensitization, acute symptoms are also treated by the administration of antihistamines and vasoconstrictors such as ephedrine (*Ephedra sinica*) (Elvin-Lewis '77: 73-74, 77).

Hypersensitivity pneumonitis or extrinsic allergic alveolitis, is often associated with specific professions. In these instances, animal, vegetable or bacterial enzyme material may induce the disease. For example, inhalation of *Thermoactinomyces vulgaris* or fungal spores of *Microsporum faeni*, which can contaminate hay, moldy sugar cane, or mushroom compost, have been causally related to farmer's (thresher's) lung, bagassosis, and mushroomworker's lung. In a similar way, *Cryptostroma corticale* has been associated with maple bark disease of

woodworkers, *Penicillium caseii* to cheeseworker's disease, *Aspergillus clavatus* and *A. fumigatus* to brewer's lung disease. A regimen of environmental control and hyposensitization is normally prescribed for pollinosis. Currently, three basic drugs have preempted ephedrine for use in the control of asthmatic attacks: epinephrine (adrenalin) and its congeners administered by aerosol, the methylxanthines administered intravenously for acute attacks and orally for chronic asthma, and the steroids (cortisone), corticosteroids, for severe and intractable states, in combination with other drugs mentioned (Elvin-Lewis '77: 76, 77).

Allergic bronchopulmonary **aspergillosis** complicates asthma in some patients. It is caused by colonization of the airways with *Aspergillus* organisms and by the development of a hypersensitivity response to the organism. It usually occurs in patients with well-established underlying asthma. It is characterized by episodic bronchial obstruction, peripheral eosinophilia, immediate skin reactivity to *Aspergillus* antigen, precipitating antibody against *Aspergillus*, increased serum IgE concentration, a history of recurrent pulmonary infiltrates, and central bronchiectasis. Sometimes patients expectorate brown plugs or "fleks" and sometimes *Aspergillus* organisms are identified in the sputum. The disorder usually requires oral corticosteroid therapy, which is given in a tapering course over 6 months. Antifungal therapy and inhaled corticosteroids are of no benefit. Sporanox (itraconazole) is the only antifungal drug indicated for the treatment of *Aspergillus*. Close follow-up of the patient is needed to observe for recurrences, which require additional corticosteroid therapy. A rising serum IgE concentration is an early indicator of recurrence. Asthma frequently causes cough. Cough variant asthma is diagnosed by demonstrating hyperreactive airways with methacholine or histamine inhalation challenge test in a patient who has no other cause for cough (Bethel '89: 177, 178). Hydrocortisone crème and corticosteroids cure apergillus faster and with fewer side-effects.

The only **oral antifungal** drug indicated for the treatment of *Aspergillis* spp.is sporanox (**itraconazole**) but the price can be prohibitive and the adverse drug interactions with high blood pressure medicine and congestive heart failure are disconcerting. There is also the oral suspension posconazole, but this costs more than $600 a vial and is the preferred primary prophylaxis for leukemia and myeloma, before or after standard antineoplastic treatment, although itraconazole is also indicated. As alternatives or adjuncts to amphotericin B, two imidazole derivatives, ketoconazole and miconazole, have been approved for systemic fungal infection treatment. **Miconazole** is active against *Coccidioides immitis*, *Cryptococcus neoformans*, and *Candida* organisms. It must be administered intravenously and has side effects that include nausea and vomiting, phlebitis, hyponatremia and pruritis and should only be used in patients who fail to respond to amphotericin B. **Ketoconazole** is an oral preparation efficient against *Coccidiodes immitis*, *Cryptococcus neoformans*, *Candida* organisms, *Histoplasma capsulatum*, and *Blastomyces dermatitidis*. Absorption depends on an acid environment in the stomach, so it cannot be used in achlorhydria or in conjunction with bicarbonate, antacids, or H_2 blockers. Generally, doses of 400 to 800 mg/day are used for non-meningeal infection and 800 to 1200 mg/day for disseminated infections with meningitis. In 20% of patients, it causes significant nausea and vomiting and, in 1% to 2%, hepatic dysfunction (Bindschadler '89: 116, 117).

Amphotericin B IV, a polyene antibiotic in use since 1958, remains the IV treatment of choice for all serious infections caused by systemic fungi. Unfortunately, it is fungistatic, and not fungicidal, deriving its therapeutic as well as its toxic effects from its affinity for sterols in cell membranes. Its affinity for ergosterol in fungal membranes is 500 times greater than its affinity for the major human cell membrane sterol, cholesterol. Damage to the cell membrane induced

by this binding results in the leakage of necessary components and eventually cell death. As an amphoteric substance the antibiotic is highly insoluble and is available only as a colloidal suspension in buffer and deoxycholate. It is not absorbed from the gastrointestinal tract and must be given intravenously. It is prepared in sterile preservative-free water to a concentration of less than 0.1mg/ml, and then administered with a light protective wrapper around the bottle over a 4 to 6 hour period. The use of a butterfly needle for access and the administration of small amount sof added heparin (1,000 units) and hydrocortisone (25 mg) aid in the prevention of phlebitis. In the beginning a 1 mg test dose is given, followed by a daily increase of 5 to 10 mg, until a dose of 1 mg/kg/day is achieved, or toxicity occurs and alters the plan. An alternative is to increase the dose until 0.5/mg/kg/day is reach and then stick to that daily dose. Nephrotoxicity with the development of an active urinary sediment and progressive increase in blood urea nitrogen (BUN) and creatinine usually helps tailor the dose that can be given daily or every other day. It is often necessary to temporarily suspend treatment until the BUN is less than 50 µg/dl and the creatinine less than 3 µg/dl. For most systemic mycotic infections a total dose of 2 to 2.5 gm suffices. Irreversible nephrotoxicity almost always is noted with total doses in excess of 4 gm. Systemic reactions, hypokalemia and hematologic reactions make up the most common side effects besides renal dysfunction. Chills, fever, nausea, vomiting and hypotension occur frequently but can usually be managed orally by pretreatment with antipyretics, diphenhydramine, and occasionally by small doses of oral cortisone. Hypokalemia predictably develops with ongoing therapy and requires substantial replacement throughout most courses of amphotericin B (Bindschadler '89: 116, 117).

Corticosteroids are the most important class of drugs for the treatment of lung disease. Corticosteroid use is one of the most important and controversial subjects in rheumatology because corticosteroids cause osteoporosis and corticosteroids are therefore contraindicated for the treatment of bone pain. The discovery of the dramatic anti-inflammatory effects of cortisone in the setting of treating rheumatoid arthritis won a Nobel Prize in 1950 by Philip S. Hench and Edward C. Kendall. In 1955 American research scientists succeeded in dehydrating cortisone under the influence of micro-organisms. This resulted in the creation of cortisone derivatives which could be taken orally in tablet form as the corticosteroids prednisone, prednisolone and dexamethasome, considerably extended the range of application. The classic disease susceptible to cortisone treatment, chronic rheumatic endocarditis, has long stopped being the exclusive disease treated by the new preparations, they also act with considerable reliability on Addison's disease, gout, asthma, hay fever, and other conditions due to hypersensitivity, they are also used when extraordinary demands are placed on the body, such as the results of operations, graft versus host disease, accidents and the like, as well as in many other kinds of diseases (Venzmer '71: 343). Corticosteroids are not merely powerful anti-inflammatory drugs, but rather are essential hormones involved in maintaining homeostasis of numerous physiologic functions. Both corticosteroid deficiency and excess have pathophysiologic consequences (Klippel et al '01: 595). The undisclosed truth of the matter seems to be that corticosteroids are highly curative of molds and treat the symptoms of viruses other than influenza, the patient must only clean up and treat pneumonia with antibiotics. Corticosteroids are so effective at curing fungal infections, although uncorroborated in the literature, intravenous corticosteroid supplies have been maliciously contaminated with mold in the past. In general athlete's foot crème (clotrimazole) treats fungus of the foot and shin but unhealthily penetrates the blood-brain barrier when used higher up, and hydrocortisone crème is therefore needed to treat fungal and mold infections higher in the anatomy. Garlic helps to treat fungus and yeast in the digestive tract. With corticosteroids antifungals and antivirals, other than flu drugs, should not be needed, antibiotics are prescribed for pneumonia.

Hydrocortisone crème is highly curative of asthma, allergies, aspergillosis and allergic rhinitis when smeared on the chest or nose and can be purchased at the dollar store. Prescription (nebulized): Pulmicort Respules (budesonide). Prescription (systemic –inject and oral): Celstone (betamethasone), Decadron (dexamethasone), Medrol and Solu-Medrol (methylpresdnisolone), Prapred and Pediapred (prednisolone), Prednisone and Prelone Syrup (prednisone). Prescription (nasal): Flonase (fluticasone), Nasacort (triamcinolone), Nasalide (flunisolide), Nasonex (mometasone), Pulmicort and Rhinocort (budesonide), Qvar, Vancesnase DS, Vancenase pocket inhaler, Vanceril, and Vanceril DS (beclomethasone). Steroid Nasal Sprays. Common types of inhaled steroids include: beclomethasone (Qvar), budesonide (Pulmicort), budesonide/formoterol (Symbicort) – a combination of a steroid plus a long-acting bronchodilator drug, ciclesonide (Alvesco), fluticasone (Flovent HFA), fluticasone propionate (Flovent Diskus), fluticasone furoate (Arnuity Ellipta), fluticasone propionate/salmeterol (Advair) — a combination of a steroid plus a long-acting bronchodilator, fluticasone furoate/umeclidinium/vilanterol (Trelegy Ellipta) — a combination of a steroid, an anticholinergic, and a long-acting bronchodilator drug, mometasone furoate (Asmanex), and mometasone/formoterol (Dulera) — a combination of a steroid plus a long-acting bronchodilator drug.

Corticosteroids relieve most asthma attacks, both acute and chronic., that do not respond to bronchodilators. They suppress inflammation within airways, eliminate streptococcal infection and potentiate the effect of adrenergic drugs. Their frequent use can cause many adverse effects including hypertension, glucose intolerance, cataracts, myopathy, osteoporosis, dermal atrophy, immunosuppression and cushingoid habitus. Cushing's disease is entirely the result of corticosteroid abuse. Steroids are the most common cause of drug-induced bone loss. To prevent calcium loss, all patients on steroids need to take 1500 milligrams of calcium a day in their diet, with supplements, or both. Also to improve calcium absorption while on steroids, 800 IU per day of vitamin D is taken. Steroids lower the levels of gonadal hormones (estrogen in women and testosterone in men), which can also cause bone loss, therefore estrogen for women and testosterone for men, may need replacement. Steroids prevent osteoblasts from maturing and making new bone, resulting in bone loss. Steroids also prevent calcium absorption and increase calcium loss. At a dose of 7.5 milligrams a day for 6-12 months, prednisone results in a loss of 10 to 20 percent of spinal trabecular bone. After the initial rapid loss of trabecular bone, steroids cause slow but continual loss of both cortical and trabecular bone of 1 to 2 percent per year (Lane ’99: 149). Long term high dose consumers of corticosteroids must experiment with other analgesic and physical therapeutic pain management methods to minimize reliance upon corticosteroids. Calcitonin is an injectable drug used in the treatment of osteoporosis to increase bone density and mass that is also an effective analgesic for bone pain.

The effective action of corticosteroids begins several hours after administration. They are given through intravenously, oral or inhaled routes. The dose and length of therapy needs to be individualized for each patient. Some patients require only intermittent, tapering doses of steroids to treat acute attacks others require continuous inhaled steroids, some require oral administration of steroids every other day, and some require continuous daily oral administration. In general, minimum corticosteroid medication is given because of the significant adverse effects associated with its use. The most effective strategy is to use a rescue inhaler or other corticosteroid once to cure the disease. To treat acute asthma attacks, 30 to 60 mg of prednisone or its equivalent is often given orally during the attack, and the daily dose is tapered to extinction over 7 to 14 days. For severe exacerbations, intravenous corticosteroids are administered. A typical dose is 80 to 125 mg of methylprednisolone given intravenously every 6

hours. The dose is tapered rapidly and converted to oral therapy after the acute attack is relieved. Inhaled corticosteroids may decrease or eliminate the requirement or oral corticosteroids during chronic therapy. The three drugs available in metered-dose inhalers are beclomethasone, triamcinolone and flunisolide. The standard dose of these drugs varies from two puffs b.i.d. to two puffs q.i.d depending on the drug, but all can be given in higher doses. High-dose inhaled corticosteroids are especially effective in decreasing the requirement for oral steroids. The most frequent complications of inhaled steroid therapy are oral candidiasis and hoarseness. The frequency of these adverse effects can be decreased significantly if the patient inhales the drug through a spacer and gargles after use of the drug to clear the pharynx. Inhaled corticosteroids should be used to treat acute asthma attacks, since they may irritate the airways. Suppression of the pituitary-adrenal axis can occur with the use of high-dose inhaled steroids, every other day oral steroids or daily oral steroids. Many patients receiving these regiments require systemic corticosteroid supplementation to prevent adrenal crisis during periods of stress (Bethel '89: 170-172).

People with allergies are likely to be prescribed topical and nasal steroids, which are sniffed into the nose rather than inhale into the lungs. Several nasal steroids are also approved for nonallergic rhinitis, including fluticasone (Flonase) and budesonide (Rhinocort AQ). Steroid nasal sprays work by preventing mast cells and basophils from releasing chemicals that call in the cavalry ie. eosinophils and other inflammation-triggering cells, in response to the mast cell reaction. Corticosteroid therapy, which may be employed to terminate a single severe attack, is often effective, though not curative. Prolonged use of steroids may be dangerous. In prophylaxis, particularly where hyposensitization fails, cromolyn sodium is used, this new compound, obtained from the seeds of *ammi visnaga* (Apiaceae) is believed to affect the release of vasoactive substances and therefore, through a regimen of frequent inhalation, acts to prevent or modify the asthma. This plant, known as khella from its native Mediterranean region, has a long history of use as an anti-asthmatic among the Arab peoples, who also believe it is useful in the treatment of angina pectoris (Elvin-Lewis '77: 73-74, 77). Bronchodilators: Prescription (short-acting inhaled beta2-agonists) Alupent and Metprel (metaproterenol), Brethaire, Brethine, and Bricanyl (terbutaline), Isuprel, Norisodrine, and Medihaler (isoproterenol), Maxair Autohaler (pirbuterol), Proventil and Ventolin (albuterol), Tornalate (bitolterol mesylate), Xopenex (levalbuterol) Prescription (short-acting nebulized beta2-agonists): Bronkometer and Bronkosol (isoetharine) Prescription (long-acting inhaled beta2-agonists): Foradil (formoterol), Serevent and Serevent Diskus (salmeterol xinafolate) (Berger & Gordon '04: 109, 111 112, 113).

Bronchodilator medications open and keep open the large and small airways in the lungs. They come in two forms: short acting (rescue medications) and long—acting, used on a daily basis for prevention. The term **metered dos**e means the medication inside the pressurized canister is released in a single, measured, controlled dose every time you use the inhaler. You must shake the canister vigorously so the ingredients mix properly and you get the right amount of medication with each dose. Holding chamber and spacers are devices in which the inhaler mouthpiece or canister is inserted into the holding chamber, to help with the delivery of metered dose inhaled medication to the airways. **Dry-powder inhalers** come in different shapes and sizes and are set to deliver bronchodilators as well as anti-inflammatory medications. Unlike metered dose inhalers you are less likely to taste of eel the medication when using it. **Nebulizer therapy** is a special device used to deliver liquid medicines to the lungs. It's composed of an air compressor and a container for the medication. The force of the compressor helps you receive the medicine without having to take a deep breath, which is why they're particularly beneficial for infants and small children. **Spacers** are devices placed between a metered-dose inhaler or

nebulizer and the patient's mouth. Their purpose is to remove large drops form the aerosolized liquid, to allow the remaining drops to decrease in size by evaporation as they pass through the spacer, and to eliminate the need to coordinate activation of a metered-dose inhaler and inhalation. By decreasing the size of the droplets delivered to the mouth, a spacer allows more drug to be deposited in the airways and less in the pharynx. Spacers should be used with inhaled corticosteroids to decrease the incidence of pharyngeal candidiasis. A peak flow meter is an inexpensive, hand-held device with which a patient can measure peak expiratory flow and thus determine objectively the severity of airway obstruction (Bethel '89: 175). Current metered dose inhalers (MDIs) contain chlorofluorocarbon (CFC) propellants. A new propellant HFA134a, with no effect on ozone, may be a suitable alternative (Jenkins '10).

Allergy Medicines

Medication Class	Brand name (prescription)	Brand name (OTC)	Best way to use
Sneezing, Itchy nose and throat, runny nose, nasal congestion			
Topical corticosteroid nasal sprays	Beconase AQ, Flonase, Nasacort AQ, Nasalide, nasarel, Nasonex, Rhinocort AQ, Vancenase DS or Vancesnase pocket inhaler		Make sure your nose is clear enough for the spray to penetrate; you may need to use a decongestant first.
Antihistamines	Allegra, Aselin (nasal), Clarinex, Zyrtex	Alavert, Benadrylo, Chlor-Trimeton, Claritin, Dimetapp, Tavist-1	Take 2 to 5 hours before exposure to allergens. If you're constantly exposed, take daily.
Mast cell stabilizer	Nasalcrom		Start using 2 to 4 weeks before exposure to allergens
Leukotriene	Singulair		Daily as preventive
Runny nose			
Anticholinergic spray	Atrovent nasal		Works best preventively against runny nose
Nasal congestion			
Decongestants	Allegra-D, Claritin-D, Guaifed PD, Sinuvent, Zyrtex	Oral forms: Phenylephrine (found in numerous OTC products), pseudoephedrine (Sudafed) Sprays: Afrin, Allerest, Dristan	Be especially careful with nasal decongestants, don't take them longer or more often than the recommended dosage schedule or you may wind up with rebound

		Long Lasting, Neo-Synephrine, Otriving, Privine, Vicks Sinex, Vicks Sinex Long Lasting	congestion.
Antihistamine nasal spray	Astelin		Can be used preventively and to treat symptoms.
Allergic conjunctivitis			
Antihistamines	Emadine, Livostin	Clear Eyes, Visine	Use during peak pollen season in addition to regular medications
Combination antihistamine/decongestants	Naphcon-A, Ocuhist, Prefrin, VasoClear, Vasocon-A		Short acting relief of symptoms
Mast cell stabilizers	Alocril, Alomide, Crolom or Opticrom		Start using 2 to 4 weeks before exposure to allergens
Nonsteroidal anti-inflammatory	Acular		Symptomatic relief of symptoms
Combination antihistamine/mast cell stabilizer	Elastat, Optivar, Patanol, Zaditor		Can be used preventively and to treat symptoms
Asthma			
Corticosteroid inhalers		beclomethasone (Qvar), budesonide (Pulmicort), budesonide/formoterol (Symbicort), fluticasone (Flovent HFA), fluticasone propionate (Flovent Diskus), fluticasone furoate (Arnuity Ellipta), fluticasone propionate/salmeterol (Advair)	Used as rescue inhalers
Oral corticosteroids		Prapred and Pediapred (prednisolone), Prednisone and Prelone Syrup (prednisone)	Symptomatic relief of symptoms.
Intravenous corticosteroids		Celstone (betamethasone), Decadron (dexamethasone), Medrol and Solu-	Symptomatic relief of symptoms.

		Medrol (methylpresdnisolone)	

Source: Berger '04: 192-193

New asthma patients should not be denied corticosteroids. **Initial therapy** for acute asthma includes supplemental oxygen and inhaled beta-adrenergic drugs. Corticosteroids are indicated if the initial response is insufficient or if the patient has had several recent asthma attacks. The choice of oral or intravenous route for corticosteroids depends on the severity of the asthma attack. Intravenous aminophylline should be considered if the asthma attack is severe. Inhaled corticosteroids, cromolyn, acetylcysteine and ultrasonic mist may irritate airways and exacerbate an acute attack. Sedatives, beta-adrenergic blockers and drugs that contain aspirin should be avoided. Occasionally asthma attacks are so severe that the patient requires mechanical ventilation. Indications for mechanical ventilation are cardiopulmonary arrest, persistent or progressive carbon dioxide retention and respiratory acidosis and clinical deterioration indicated by fatigue and hypersomnolence. Patients who have intubation and mechanical ventilation should (1) use a large diameter endotracheal tube with a soft cuff, (2) use a volume ventilator, (3) ensure adequate humidification of air, (4) use the lowest possible ventilator cycling pressure, (5) keep the respiratory rate of the ventilator slow, (6) avoid hypocapnia, and (7) if necessary, suppress the patient's respiratory drive with a sedative or paralyze ventilation with neuromuscular blockade, although paralyzing a patient maintained on a ventilator should be avoided, in treating severe asthma it is sometimes necessary to obtain adequate ventilation (Bethel '89: 176, 177).

Cromolyn is a prophylactic drug used to prevent bronchoconstriction. It is administered by inhalation and is available as a powder that is inhaled through a device called a spinhaler, as a solution for nebulization and a metered-dose inhaler. Cromolyn decreases the requirement for corticosteroids and other asthma medications in many patients. It is costly but has few adverse effects. It is used four times a day to treat chronic asthma or is given before exercise to prevent exercise induced asthma (Bethel '89: 173, 174). Rather than treating the symptoms of allergic attack cromolyn sodium spray stops attacks before they start by preventing the release of chemicals such as histamine from mast cells, thus serving as an anti-inflammatory agent. Nasalcrom, available without a prescription, is not as effective as steroid nasal sprays, but it will help many people with mild allergies. It's also one of the preferred first-line therapies for pregnant women who have mild allergic rhinitis. Inhaled cromolyn should be the first line therapy for pregnant women with asthma. **Inhaled budesonide** (Pulmicort) can be used if cromolyn does not control symptoms. It is the only inhaled steroid that's approved as a category B drug, meaning it's generally safe for use during pregnancy. A Swedish study that evaluated 99 percent of the births in Sweden from 1995 to 1998 found that mothers who took budesonide had babies that were born on time and at normal weights and lengths, with no increase in stillbirths or multiple births. Serevent, leukotirne modifiers and newer inhaled corticosteroids may be continued during pregnancy with consideration of a doctor. Cromolyn sodium spray – Nonprescription and Prescription (nasal spray): Nasalcrom. Prescription (inhaled): Intal metered-dose inhaler or nebulized (Berger '04: 103, 104, 117-118).

Adrenergenic drugs cause bronchodilation ($beta_2$ receptors), vasoconstriction (alpha receptors), stimulation of the heart ($beta_1$ and to a lesser extent $beta_2$ receptors), tremor ($beta_2$ receptors, hyperglycemia ($beta_2$ receptors), and hypokalemia. Some adrenergenic drugs, such as albuterol and terbutaline, are selective agonists of $beta_2$-receptors and therefore cause bronchodilation with

less cardiac stimulation than nonselective agonists. Adrenergenic drugs can be inhaled or injected subcutaneously. In general, the inhaled route is preferred. Albuterol is a $beta_2$ selective agent that is available as metered-dose inhaler, solution for nebulization or subcutaneous injection, and in oral tablets. Terbutaline is a $beta_2$ selective agent that is available as a metered-dose inhaler, solution for nebulization of subcutaneous injection, and in oral tablets. Metoproterenol is a drug that is less beta1 selective than albuterol or terbutaline and therefore has greater cardiovascular effects. It is available as metered-dose inhaler, solution for nebulization and oral tablets. Fenoterol is a $beta_2$ elective agent that is used in many parts of the world but is not available in the United States. Isoproterenol is a nonselective adrenergic drug that has a short duration of action. It is available as a metered-dose inhaler and as a solution for nebulization. Isoetharine, a relatively $beta_2$ selective, short-acting drug, is available in a metered-dose inhaler, as a solution for nebulization and in oral tablets.

Epinephrine is available as a metered-dose inhaler, a solution for nebulization and solution for subcutaneous injection. It has a short duration of action. When injected subcutaneously, it is usually no more effective than inhaled $beta_2$ adrenergic drugs and has greater systemic effects. Bitolterol mesylate, available in a metered-dose inhaler, may have a longer duration of action than the other inhaled drugs. Some patients find the inhaled solution irritating and foul tasting. Ephedrin is an oral drug that has been used for many years to treat asthma. It is nonselective, causes central nervous system stimulation and probably should not be used. For many patients with mild asthma, one or two puffs of an adrenergic drug from a metered-dose inhaler, taken as needed, is the only treatment that is required. For patient who have more severe asthma, inhaled adrenergic drugs should be used regularly four to six times a day, but should be administered cautiously when tremulousness, tachycardia, palpitations, or excitation occurs (Bethel '89: 169-171). Epinephrine, often called adrenaline is administered via injection in the event of a severe allergy attack or anaphylaxis. Those severely allergic, particularly to insect stings and certain foods or penicillin, must carry epinephrine at all times as part of an emergency treatment kit. Emergency Medications Prescription (injected): Adrenalin chloride (epinephrine). Prescription (nebulized): Brethaire (terbutaline), Vaponefrin (epinephrine) (Berger & Gordon '04: 105).

Ipratropium bromide (Atrovent) belongs to the tongue-twisting class of drugs known as anticholinergic agents. They block the effects of acetylcholine, a neurotransmitter that stimulates mucus production, which makes them great for combating runny noses. Available only in a prescription spray, Atrovent is officially approved for the treatment of allergic rhinitis, but it does work quite well in some cases of asthma and chronic bronchitis because of its ability to dry up mucus secretions. It is particularly effective for older people with asthma who also have emphysema or chronic bronchitis or for those who don't respond completely to the common asthma medications known as beta2-agaonists. Anticholinergic spray: Prescription (Nasal spray): Atrovent nasal (ipratropium bromide). Prescription (inhaled): Atrovent 0.03% or 0.06%, nebulized or metered-dose inhaler (Berger '04: 103). **Ipratropium bromide** blocks muscarinic, cholinergic receptors on airway smooth muscle and causes bronchodilation. The parasympathetic nervous system continuously stiulates airway smooth muscle even in healthy persons and causes some smooth muscle tone. Ipratropium bromide interrupts this stimulation and causes bronchodilation. The drug is available in a metered-dose inhaler that delivers 20 µg/puff. The conventional dose is 40 to 80 µg, and optimal bronchodilation in stable asthma is obtained with dose. However in status asthmaticus the bronchodilator response increases through cumulative doses up to 500 µg. This dose is tolerated without adverse effect because the drug is poorly absorbed form the airway mucosa. Ipratropium is slower than other inhaled beta-adrenergic drugs. Peak effects occur only after 30 to 60 minutes, and bronchodilator effects last

at least 4 hours. In stable patients, dosages taken three or four times daily are usually sufficient. Adverse effects are rare except for dry mouth and bad taste. Ipratropium bromide dilates the airways in persons who have asthma; however, adrenergic drugs usually dilate them more effectively. In persons who have concomitant heart disease and poorly tolerate the tachycardia induced by adrenergic drugs and theophylline, ipratropium may be preferred. Similarly, for those who have tremor as a major complication of beta-adrenergenic drug therapy, ipratropium avoids this adverse effect. Patietns who have bonrchoconstriction precipitated by beta blockers often respond poorly to beta-adrenergic drugs and usually respond better to an anticholinergic drug. Anticholinergic drugs may be preferred to treat bronchoconstriction induced by anticholinesterase therapy. The bronchodilator effect of ipratropium is independent of and additive to that of adrenergic drugs and prolongs the bronchodilator response. Smaller doses may cause fewer adverse effects (Bethel '89: 173, 174).

In the summer of 2003 the FDA approved omalizumab (Xolair), the first in a new class of drugs for the treatment of allergic asthma. Eventually, this class of drugs, called **anti-IgE drugs** – is expected to revolutionize the treatment of allergies in a way no other has done. Xolair is a genetically engineers drug called a monoclonal antibody. It works by stopping an allergic reaction before it starts by blocking the IgE antibody that causes the reaction. Xolair came about as a result of the discovery in 1998 of the precise shape of the receptor molecule that triggers the allergic response in your immune system, high-affinity immunoglobulin-E (IgE) receptors. Currently Xolair is approved only for moderate to severe allergic asthma in people 12 and older whose asthma has not responded well to other treatments. It's given by subcutaneous injection once or twice a month. People taking Xolair are often able to live very normally for the first time, being able to visit a friend with a pet, or sleep with the windows open in the spring. Many people have been able to significantly reduce their use of other medications, if not discontinue them altogether. In studies of Xolair in adults and children, some of those taking the drug were able to cut back on or even stop using inhaled corticosteroids. Xolair is likely to be approved to treat allergic asthma in children soon. A year's supply of Xolair costs between $5,000 and $10,000 depending on the dose. It's so expensive because it requires a very sophisticated manufacturing. Olopatadine (Patanol) is the best-selling prescription eyedrops for allergic conjuncitivitis, and is being developed into a nonsteroidal nasal spray that's expected to be called Panase (Berger & Gordon '04: 120, 121). An antibody known as Dupilumab has scored high marks as possible treatment for asthma, according to researchers from the University of Pittsburgh. For the study, the researchers enlisted 108 volunteers around the country to receive a weekly dose of the drug for 12 weeks. They found that asthma incidents decreased by 86 percent for those taking the antibody as compared to those using a placebo. The drug targets the interleukin-4 (IL-4) receptor specifically, easing symptoms for those suffering from Th-2 type asthma. This study targeted those individuals who, on the basis of eosinophil levels in their blood, seemed to have evidence for Th2-type asthma. By using this drug that blocks this pathway, we observed a really robust response compared with placebo in patients with moderate to severe asthma.

Patients who have persistent airflow obstruction and frequent acute attacks of asthma require most therapeutic measures. Patients should avoid asthma attacks by pretreating themselves before exercise and by avoiding triggers of acute attacks. Most patients require inhaled beta-adrenergic drugs on a regular basis and many require inhaled corticosteroids and oral theophylline drugs. If these drugs are not effective inhaled cromolyn, and inhaled ipratropium bromide sometimes alleviate symptoms. Some patients require continuous oral corticosteroid therapy. The corticosteroid dose should be maintained as low as possible and should be

administered on alternate days, if possible. Maximizing the doses of other asthma medications and ensuring their regular administration allows minimization of the oral corticosteroid dose. Both elective and emergency surgery can usually performed in in patients who have stable asthma. Asthma medications should be continued up to the time of surgery and can be continued intraoperatively and postoperatively by parenteral administration and nebulation. Supplemental doses of corticosteroids may be necessary to cover the stress of surgery. In general, asthma is treated identicaly in pregnant and nonpregnant women. Some medical professionals favor treating pregnant women with drugs that have a known safety record (epinephrine, theophylline and corticosteroids) rather than with newer drug whose safety is uncertain (terbutaline, albuterol and metaproerenol), During the first trimester it is wise to administer only medications that are definitely indicated.

The goal in treating asthma is to use the smallest amount of medication necessary to achieve two goals: keeping the airways in the lungs open, both during attacks and over the long term, and reducing the ongoing inflammation that's the cornerstone of the disease. There are three types of anti-inflammatory drugs that doctors typically prescribe for asthma: inhaled corticosteroids, cromolyn and leukotriene modifiers. To keep airways open, they often prescribe short and long acting bronchodilators known as beta-2 agonists (Berger & Gordon '04: 107-108). Most doctors follow the National Heart, Lung and Blood Institute's step approach for treating asthma in adults and children:-Mild intermittent – prescribe only a short acting beta2 agonist for when attacks occur. Mild persistent – In addition, prescribe a daily low dosage of an inhaled corticosteroid, or cromolyn or nedocromil. Also consider a leukotriene modifier. Moderate persistent – Change the daily inhaled corticosteroid to a medium dosage. Also prescribe a daily inhaled long-acting beta2-agonist. Continue to consider a leukotriene modifier, and continue prescribing a short-acting beta2-agonist for when attacks occur. Severe persistent – change the daily inhaled corticosteroid to a high dosage, and prescribe oral steroids as needed for disease control.

Although *Nicotiana tabacum* (tobacco) is considered harmful to all lung conditions, *Cannabis sativa* (marijuana), *Datura stramonium* (Jimson weed), as well as *D. metel* and *D. fastuosa* can be smoked for the relief of asthma. *Verbascum thapsus* (mullein) can also be smoked for pulmonary ailments and is specifically indicated for bronchiolitis. Bronchodilators relax the smooth muscles of the bronchioles that lead to the air cells, thereby diminishing generalized peripheral airway obstruction. Bronchitis (inflammation of the bronchial tubes) and emphysema (enlarged air spaces in the lungs, making breathing difficult). There are two chief types of bronchodilator drugs: adrenergic agents and those derived from theophylline. The adrenergic drugs increase the volume and diameter of the bronchial smooth muscles by relaxing them, include norepinephrine, epinephrine (adrenaline), isoprenaline, and ephedrine. Ephedrine is now obtained synthetically, but may be extracted from its original sources*, Ephedra aquisetina* and *E. sinica* (Gymnosperms in the family Ephedraceae). The second type of bronchodilator includes the theophylline derivates (originally isolated from tea, *Camellia sinensis*) which act directly on the bronchial muscle to relieve obstructions, increase coronary blood flow and stimulate respiration centrally. **Tea**, green or black, *Camellia sinensis* - oral treatment of 100 patients for 20 days proved effective in 93% of cases, of which 58% could be described as excellent. During the course of treatment, sputum decreased in 91% of the cases, cough in 85% and asthmatic symptoms in 58.1%, Aerosol therapy was equally effective (Elvin-Lewis '77: 297, 298).

Theophylline relaxes airway smooth muscle, probably by inhibiting cytoplasmic phosphodiesterase and increasing cytoplasmic cAMP concentration. Theophylline has been used form many years to treat asthma and COPD, but recent studies indicate that it may contribute

little to treat asthma. Adrenergic drugs dilate airways more effectively. When theophylline is added to inhaled adrenergic drugs in the therapy of acute asthma, bronchodilation does not improve and the frequency of side-effects increases. However, theophylline decreases the frequency and severity of symptoms in chronic asthma and decreases the need for corticosteroids. Theophylline is available in oral tablets and solutions, in rectal suppositories and solutions and intravenously. Taken at bedtime theophylline may diminish nocturnal symptoms of asthma. Theophylline is given intravenously as aminophylline, which is a soluble ethylenediamine salt containing 85% theophylline. As theophylline takes time to build up in the blood stream to a therapeutic level, adjustment may be necessary, with blood testing to monitor your blood levels. Some people cannot tolerate theophylline. A major side effect is anxiety, which may lead to tremulousness and insomnia, even in therapeutic doses and with normal blood levels (Tucker et al '01: 75). Liver disease, congestive heart failure, chronic obstructive pulmonary disease, and sustained fever decrease clearance of theophylline, whereas smoking tobacco or marijuana and youth increases clearance. Erythromycin and cimetidine decrease theophylline clearance and phenobarbital increases it. The loading dose of aminophylline IV is usually 5 to 6 mg/kg given intravenously over 20 minutes if the patient has not been taking a theophylline-type drug. The maintenance dose should be about 0.6 mg/kg/hr. In patients who have liver disease, congestive heart failure, advanced age, or are being treated with erythromycin or cimetidine, the maintenance dose should be decreased to about 0.3 mg/kg/hr. The maintenance dose should be increased to about 0.9 mg/kg/hr if the patient smokes tobacco or is young. Serum theophylline concentration should be measured and the dose of aminophylline should be based on the concentration. The therapeutic concentration in serum is usually 10 to 20 µg/ml.. However, concentration less than 10 µg/ml cause significant adverse effects in some patients. Nausea, vomiting, diarrhea, headaches, nervousness, cardiac arrhythmia, insomnia, and seizures often occur when levels exceed 20 µg/ml (Bethel '89: 172, 173).

In Armenia in Eastern Europe people with asthma travel nearly 1/5 mile beneath the Earth's surface to reach **Republican Speleotherapeutical Hospital**, an underground medical clinic specifically designed for the treatment of asthma and other respiratory illnesses. Practitioners of speleotherapy believe that the salt environment, with its dry air and consistent temperature has a healing effect on the respiratory system. Similar clinics can be found in mines and caves throughout much of Eastern Europe. There's even some slight evidence that it may have some benefit. At least one scientifically designed study conducted in 1994 found a slight improvement in lung function after three weeks of speleotherapy. **Marijuana** was once touted as an asthma remedy. In the early nineteenth century, pharmaceutical manufacturer Grimault and sons actually marketed ready –made marijuana cigarettes for use as an asthma remedy, and doctors continued to prescribe it throughout much of the early twentieth century. It works as an excellent bronchodilator, opening up the large and small airways of the lungs. If you put the active ingredient in cannabis, tetrahydrocannabinol (THC) into a micro-aerosol form, for instance, it's up to 60 percent as effective as a pharmaceutical bronchodilator. One oft-cited study of 10 adult asthma patients found that after they smoked a 2 percent THC preparation for 2 hours, their airway resistance decreased 10 to 13 percent compared with when they used a placebo. In another study, researchers induced acute asthma attacks in eight healthy young men and then had them smoke 500 milligrams of marijuana. With the marijuana, the men's bronchial spasms immediately ceased. With a placebo or saline solution, it took about 30 minutes for their lungs to return to normal (Berger & Gordon '04: 164, 166).

70% of **sinusitis** patients will resolve without antibiotics but those patients who fail to improve within 48 to 72 hours should begin antibiotic therapy. For those who fail to resolve, or present

initially with severe or complicated infections, drugs of choice include amoxicillin, amoxicillin-clavulanic acid, or erythromycin plus sulfonamide for penicillin allergic patients unable to take ampicillin (Principen) the best antibiotic for sinusitis. Alternatives include second and third generation cephalosporins (e.g., ceftibuten, cefpodoxime or cefuroxime axetil). Fluoroquinolines are highly effective second-line agents for adult sinusitis. Ceftriaxone is effective for refractory or complicated acute otitis media or sinusitis. 50% to 70% of otitis media and acute sinusitis are comprised of *S. pneumoniae* and *H. influenza*. *M. catarrhalis*, a low-virulence pathogen, is also prevalent; over 80% of these cases resolve without treatment. B-lactamase resistance by *H. influenza* runs about 35% nationwide, and by *M. catarrhalis* more than 90%. About 15% to 30% of pneumococcus is penicillin resistant. Anaerobic organisms in acute sinusitis suggest dental disease as the source. **Chronic sinusitis** is a polymicrobial infection involving both aerobes (*S. aureus*, streptococci, *H. influenzae*, and *M. catarrhalis*); anaerobes (*Peptostreptococcus*, *Prevotella*, *Bacteroides*, and *Propionibacterium* organisms), and fungi (aspergillus). Chronic sinusitis affects as many as 75% of patients with HIV infection. Nosocomial sinusitis, which is associated with nasotracheal or nasogastric tubes or nasal packing is mostly cauased by gram-negative bacilli and is often polymicrobial (*P. aeruginosa*, *Klebsiella* pneumoniae, *Enterobacter* organisms, *Proteus mirabilis*, *Escherichia coli*). The mainstay of treatment is to remove indwelling devices and treat systemically with ticarcillin/clavulanate.

Chronic suppurative otitis media with tympanic membrane perforation, with or without cholesteatoma, results from mixed infections with both aerobic pathogens (*P. aeruginosa*, *S. aureus* and *S epidermidis*, *Proteus*, *Klebsiella*, and *Eschericia coli* organisms) and anaerobic pathogens (*Bacteroides fragilis*, Peptococcus organisms, and Eillonella organisms) that produce foul-smelling purulent discharge. Initial treatment includes ofloxacin otic drops; alternatives include neomycin-polymyxin, or gentamicin aphthalmic drops. Oral therapy alone is not very effective, however, adjunctive systemic therapy with oral ciprofloxacin, with or without clindamycin, or ticarcillin/clavulante IV is sometimes required. **Otomycosis** is usually caused by *Asperilllus niger* or *Candida albicans* (monilia). Treatment involves topical antifungal therapy (clotrimazole) athlete's foot crème. Otorrhea caused by external contaminants (e.g. swimming) more likely contains *P. aeruginosa*. Judicious use of ototopical antibiotics, especially fluoroquinolones, is essential to prevent fungal overgrowth (otomycosis). **Pseudomonas** is the predominant pathogen in cystic fibrosis and primarily ciliary immotility syndrome that are associated with nasal/sinus polyposis (Boruk & Rosenfeld '04: 428- 430). When *Pseudomonas* is clearly the causative organisms, gentamycin or tobramycin should be used (Mitchell '89: 102, 103). Doxycycline, the once a day antibiotic, is taken for *S. aureus*, *Propionibacterium*, and throat infections which resemble anaphylaxis, precluding the use of penicillin. Penicillin, ampicillin and amoxicillin are often the only effective treatment for resistant strains of *S. pneumoniae*. *H. influenza* is treated with ampicillin (Principen), levofloxacin (Levaquin) or Amantadine (Symmetrel).

A number of Over-the-Counter remedies are known to be effective with rhinoviruses ie. diphenhydramine (Benylin, Benadryl), chlorpheniramine (Telachlor, Chlo-Amine, Chlor-Trimeton, Aller-Chlor), brompheniramine (Bromphen, Nasahist B, Dimetane Extentabs) and Ipratropium intranasal (Atrovent). Normally there is no treatment for coronaviruses other than a caution to wash hand and keep clean. For Severe Acute Respiratory Syndrome (SARS), a coronavirus, the treatment with no fatalities was to ventilate the patient and medicate with the antibiotic levofloxacin (Levaquin), and corticosteroids methylprednisolone IV and then prednisone (Kit-Ying ’06). An effective vaccine against Adenovirus serotype 4 (Ad4) and serotype 7 (Ad7) was approved in 1971. The economy-driven cessation of vaccine production by

its sole producer in 1996 resulted in re-emergence of outbreaks, with Ad4 predominating in 98% of cases, 5 fatalities. On March 16, 2011, the FDA approved an adenovirus vaccine for manufacture by Teva Pharmaceuticals. Around 2010 the FDA removed some 600 different types of cold and flu remedies from the market. The most effective remedy has always been Over-the-counter Theraflu, most consumer are better the next day. The FDA has approved Allegra (Sanofi-Aventis) and Children's Allegra (fexofenadine) and Allegra-D (fexofenadine and pseudoephedrine) product lines to be marketed over-the-counter. The two prescription antivirals that are most commonly used these days are the neuraminidase inhibitors Oseltamivir (Tamiflu) and Zanamivir (Relenza). Systematic review of 51 studies found no evidence that the flu vaccine is any more effective than a placebo in children (Smith et al ’08). Studies published in 2008 found that influenza vaccination was not associated with a reduced risk of pneumonia in older people although it did contribute to a reduction in mortality (Jackson et al ’08)(Eurich et al ’08). Dangerous complications with influenza involve bacterial infections that cause pneumonia wherefore broad spectrum antibiotics that are effective against *Haemophilus influenziae* such as ampicillin (Principen) or levofloxacin (Levaquin) save lives, the antiviral antiparkinsons drug Amantadine (Symmetrel) is also effective.

Decongestants unclog the nose by restricting blood supply to the nose and sinuses, thus reducing swelling, excess secretions and congestion. They’re often combined with antihistamines, as in the oral nonsedating drugs Allegra-D and Claritin-D, and the less sedating acrivastine (Semprex-D) and Zyrtec-D). They also are frequently combined with guafenesin (an expectorant). Saltwater can relieve stuffiness and congestion. It can be bought over the counter in brands such as Ocean and Salinex or make your own by adding ½ teaspoon of salt and a pinch of baking soda to a cup of lukewarm water and using a bulb syringe like the ones used to clear an infant’s nose to spray the solution in your nose a few times, followed by a good, hard blow. Decongestants: Nonprescription: Actifed Allergy Daytime, Allerest, Drixoral Nondrowsy Formula, Edifc/24, Sudafed. Nonprescription Nasal Sprays: Afrin, Cheracol, Dristan, Neo-Synephrine, Nostril/Nostrilla, Otrivin, Privine, Vicks Sinex Long-Acting. Prescription: Dura-Vent (chlorpheniramine and phenylephrine), Entex LA, Guaifed PD, Respaire, and Sinuvent (guaifenesin and phenylephrine), Exgest LA (guafenesin and phenylpropanolamine)(Berger & Gordon '04: 102, 103).

The **first generation H_1 antihistamines** such as diphenhydramine, chlorpheniramine, brompheniramine and hydroxyzine are also referred to as the sedating antihistamines. These agents are effective at controlling the rhinorrhea, sneezing and pruritus associated with allergic rhinitis. Unfortunately these agents cross the blood-brain barrier thus producing undesirable side effects such as central nervous system depression, sedation leading to impaired performance at home, work and school and cardiotoxicity. There are no long-term safety studies on the first generation antihistamines. These agents have poor H_1 receptor selectivity and act on muscarinic receptors causing anticholinergic effects such as dry mouth, urinary retention, constipation and tachycardia. The **second-generation antihistamines** developed in the early 1980's, have improved H_1 receptor selectivity, absent or decreased sedation, faster onset and longer duration of action and fewer adverse effects. Their half-lives are longer (12-24 hours) compared to the first generation (4-12 hours). Of the second generation H_1-antagonists, fexofenadine has no sedating effects even at higher than recommended doses. Loratadine and desloratadine are non-sedating at recommended doses but may cause sedation at higher doses. Cetirizine, and its purified enantiomer levocetirizine, have more sedation potential that other second generation H_1-antagonists. All rhinitis symptoms, except for obstruction, can be alleviated by H_1-

antihistamines, and there does not seem to be a superiority of any one of the second generation H_1-antihistmines over another.

Topical H_1-antihistamines (azelastine, olopatadine) provide faster onset of action (less than 15 minutes) and similar to greater efficacy compared to oral preparations in regard to rhinitis and conjunctivitis. There has even been an association with improvement of congestion. However, their results are limited to the local organ effects, and require twice daily use to maintain a sustained response; whereas second generation oral H_1-antagonists can be taken on a daily basis. Some patients may complain of a bitter taste, and intranasal H_1-antagonists are less effective than intranasal steroids. In a direct comparison trial between azelastine nasal spray versus oral cetirizine, azelastine was found to have a significant improvement in nasal symptom scores for the specific symptoms of sneezing and nasal congestion over cetirizine. In addition to oral H_1-antihistamines, intranasal corticosteroids are a mainstay of treatment. They are the most effective medications for controlling all rhinitis symptoms. Their onset of action is from 3-12 hours. Their use on an as needed basis is not as effective as continual use but may not be required continually in all patients. They are generally safe, and there is little evidence to support suppression of the hypothalamic-pituitary-adrenal axis with prolonged use. Side effects are generally mild (crusting, dryness, and minor epistaxis). They can be minimized by proper nasal spray technique. Septal perforation has only been described anecdotally. For patients whose symptoms are not optimally controlled with intranasal steroids, adding an intranasal (but not oral) antihistamine may give some additional benefit. Systemic corticosteroids should be considered a last resort treatment option, but they may be necessary for severe or intractable symptoms. If they are used, then oral is preferred over parenteral because of the lower risk of systemic side effects and the ability to adjust doing. Steroids should never be injected into the turbinates. Recommendations on short courses oral steroids differ from 5-7 days to no more than 3 weeks.

Cough is a natural reflex to help clear the respiratory system of secretions and foreign materials. Do not cough on other people. Cover the mouth when coughing. Wash hands. Clean. Antitussive (anticough) agents are sometimes needed to suppress coughing to facilitate rest and sleep and to reduce irritation of the respiratory tract. Acting centrally by depressing the cough reflex of the central nervous system, codeine, and to some extent other opium alkaloids, are probably the most widely used compounds with nethol (peppermint oil) and eucalyptol. Many individuals who suffer from respiratory disease find it difficult to clear the chest of sputum. Expectorants and mucolytic agents are used to help them. Expectorants and mucolytics such as guafenesin (Humibid, Tussi-ortganidin) or the herb mullein help liquefy secretions and allow you to cough up mucus more easily (Tucker et al ’01: 75). One of the best expectorants is water. Drinking an adequate amount of water, about one quart per day, will make clearing phlegm easier, which may lead to improved breathing (Tucker et al ’01: 75). The treatment of cough is successful in over 95% of cases.

The common **antitussives** can be classified as central or peripheral acting. The central-acting agents depress the medullary integrative areas, or higher center whereas the peripheral agents increase the threshold of cough receptors. All narcotic antitussives are effective cough suppressants. Codeine phosphate is commonly used. In adults, 20 to 60 mg in a single dose of 45 to 160 mg daily has been shown to be beneficial in pathologic coughing. Codeine is preferred because of its low potential for abuse and uncommon adverse effects of constipation, histamine release, bronchial mucous secretion and bronchospasm. For significant coughing the nonnarcotic antitussives are not as beneficial. Dextromethorphan hydrobromide is the most commonly used in a single oral dose of 15 to 30 mg. However this agent has histamine-releasing

properties and should be used cautiously in patients with reactive airways. Peripheral antitussives either act on irritated receptors or block the vagal input. The irritated receptors can be anesthetized by inhalation of nebulized 1% to 4% lidocaine (Xylocaine). Intravenous lidocaines can be used to stop a severe, chronic cough. Atropine sulfate, 1 to 3 mg inhaled by nebulization, can interrupt the vagal component to the cough. This is most useful if the cough is secondary to asthma. There is no objective data demonstrating the usefulness of coughing agents such as cough drops, syrups, water, and other demulcents, but these may temporarily prevent the pharyngeal mucous membrane from drying out. If the cough is a "tic" type or from an irritable focus, a speech pathologists an frequently help control the problem with behavioral modifications. Persistent cough is a bothersome problem to the patient and may be the symptom of such diseases as lung cancer, infection and asthma (Martin '89: 20).

The National Tuberculosis Association, founded in 1904, was the first American charity to focus on a single disease. With the decline of TB in the mid-twentieth century, the organization changed its mission to include asthma, becoming the American Lung Association in 1973. Today, the association fights lung disease in all its form, with special emphasis on asthma, tobacco control and environmental health. A 2002 survey conducted by the American College of Allergy, Asthma, and Immunology found that 41 percent of those with allergies thought they had colds or viral infections when they first began having allergy symptoms. In a nationwide survey of 250 allergists, more than 80 percent said self-medicating for allergies was likely to mask more serious health problems and 60 percent said that seasonal allergies and allergic asthma are best treated with prescription medications (Berger & Gordon '04: 66, 82-83).

In 1989 ten drugs were used for the **treatment of tuberculosis** in the United States. The four most important drugs in contemporary chemotherapy are isoniazid (INH), rifampin, pyrazinamide, and ethambutol. Multiple studies confirm that 6 to 9 month short course of multiple drug chemotherapy may be regarded as adequate curative chemotherapy in virtually every patient with drug-susceptible tuberculosis. For nine months of chemotherapy, the combination of INH and rifampin will result in roughly 95% cure rates. Therapy with INH, rifampin and ethambutol is recommended to avoid the complication of drug resistance. The addition of pyrazinamide to INH and rifampin accelerates the rate of resolution of the disease, allowing reduction of therapy to 6 months' duration. However, side-effects and toxic reactions increase modestly with the addition of pyrazinamide. Side effects from antituberculosis medications are uncommon and usually minor. INH produces disturbances in the liver function of 10% to 20% of patients. Serious hepatitis requiring termination of INH occurs in 1% to 3% of patients. In patients with marginal nutritional status, caution may lead one to include 30 mg of pyridoxine (vitamin B_6) per day. Other uncommon reactions to INH include arthralgias, arthritis, a mild influenza like syndrome and the variable appearance of lupuslike syndrome associated with positive antinuclear antibody reactions. Such reactions are usually reverse on termination of the drug. Rifampin commonly produces a side-effect of red staining of the urine, tears, and other secretions. Hepatitis has been reported in 1% to 3% of patients receiving rifampin. When given erratically, rifampin can induce a pronounced flulike syndrome, thrombocytopenia and acute interstitial nephritis resulting in impaired renal function.

Ethambutol is the best tolerated of the tuberculosis medications. The only significant toxic effects of ethambutol is retrobulbar neuritis. When the drug is given at 15 mg/kg ocular disturbances occur rarely. The usual daily dose of pyrazinamide is 30 to 35 mg/kg in split dosages. A common complication of pyrazinamide is elevated levels of uric acid and up to 35% of these patients experience arthralgias and frank gouty arthritis. For the milder manifestations

of hyperuricemia low-dose aspirin may reverse this biochemical disturbance and alleviate the symptoms. Noncompliance can lead to the appearance of drug-resistant organisms if the patient takes the medication in suboptimal dosage or in an erratic fashion. Trials strongly support the use of 6 or 9 months' treatment in these patients. Only patients who are significantly immunosuppressed and have disseminated disease now need extended therapy. The only significant route of tuberculosis infection is person to person. One of the responsibilities caring for a patient with pulmonary tuberculosis is to ensure that a **contact investigation** has been performed to determine evidence of recent infection among the patient's home, work, or leisure contacts to administer INH preventive therapy by employing skin tests and other epidemiologic observations. **INH preventive therapy** is the keystone of tuberculosis control during contact investigation. The initial recommendation for IH preventive therapy required 12 months of INH, 300 mg orally per day. European studies however indicate the length of time may be reduced without loss of efficacy. In general if the source patient is being treated for 6 or 9 months for tuberculosis, it is also suitable to treat the patient's contacts with an equal duration of INH preventive therapy (Iseman '89: 97-100).

Various combinations of traditional "anti-TB" drugs are used against most of the Non-Tubercular Mycobacteria (NTM). For the usual case of pulmonary disease from *M. avium complex*, an initial regime of isoniazid (INH), rifampin (RIF), and ethambutol (EMB) supplemented by an initial two months of streptomycin (SM) is the standard regimen. If the disease is rapidly progressive or the patient does not respond to initial treatment, the regimen should be intensified according to drug sensitivity studies. Agents most likely to be active include ethionamide and cycloserine. Noteworthy is the lack of activity of pyrazinamide, a powerful agent against *M. tuberculosis*. The usual patient with pulmonary MAC disease receives treatment for 24 months. For the initial treatment of pulmonary disease, a regimen of INH, RIF and EM is given for 15 months. There is commonly partial drug resistance, usually to INH, this does not interfere with the response to this treatment, for which success rates are in the range of 95%. However, acquired resistance associated with ineffective or erratic pretreatment may predict failure to respond, of particular concern is resistance to RIF. Not treatment has proven effective against pulmonary disease caused by *M. fortuitum-chelonae*. Most isolates are susceptible in vitro to cefoxitin and amikacin (or kanamycin). These parenteral agents may result in substantial improvement when given for prolonged periods. The aminoglycoside antibiotic can rarely be used in full dosage beyond 3 to 4 months because of auditory, vestibular or renal toxicity, and most patients relapse. Most strains of *M. chelonae* are very resistant to the oral drugs that have been studied. However, many *M. fortuitum* isolates are susceptible to drugs such as doxycycline, minocycline, erythromycin, sulfamethoxazole, trimethoprim-sulfamethoxazole, or one of the fluoroquinolones such as ciprofloxacin. Hence, for a patient with symptomatic, progressive disease resulting from M. fortuitum, an initial intensive phase of parenteral medication followed by a long-term course of oral antimicrobials offers the best chance of effecting a cure or long-term remission. Agents should be chosen on the basis of *in vitro* studies. An empirical regimen of INH, RIF, EMB and SM may be employed for mycobacteria that are slow growing (Iseman '89: 90, 91).

Inpatient treatment of **lung abscess**, especially the putrid variety, should be 2 to 6 million U crystalline penicillin G intravenously daily; 600,000 U procaine penicillin G intramuscularly every 6 hours for 4 weeks may be sufficient in milder cases. In the presence of serious penicillin hypersensitivity, clindamycin 600 mg 4 times daily, lincomycin 600 mg intramuscularly every 6 hours, or erythromycin 2 gm/day may also be used. Some observers are in favor of adding streptomycin 1 gm intramuscularly daily for at least the first 7 to 10 days, or tetracycline 2 gm

daily to 3 to 5 days, then 1 gm daily. If *Staphylococcus aureus* is found and believed to be a causative agent, intravenous methicillin, or an equivalent drug such as nafcillin, 8 to 16 gm daily, if penicillin resistant. Vancomycin, 500 mg intravenously every 6 hours is an effective anti-staphylococcus drug but has significant toxicity, resistance and probably should seldom be used. Antimicrobial treatment should be continued for at least 2 to 3 months, sometimes even longer. Oral doxycycline 100 mg the once a day antibiotic, for the treatment of methicillin resistant *S. aureus* (MRSA), seems more ideal. If *Klebsiella* organisms are found and are the causative agent, the initial therapy should include kanamycin, 15 mg/kg/day intramuscularly in 2 or 3 divided doses, the total dose being decreased if renal insufficiency is present or appears. Antibiotics susceptibility studies may allow the use of a less toxic antibiotic than either kanamycin or trimethoprim-sulfamethoxazole. Metronidazole (Flagyl ER) is a safe alternative but clinical trials are needed for the FDA to indicate its effectiveness against *Klebsiella*. When *Pseudomonas* is clearly the causative organisms, gentamycin or tobramycin should be used. Penicillin is used for most *Bacteroides* infections that are causally related to lung abscesses, although penicillin-resistant *Bacteroides* have been identified in this setting and may require (Mitchell '89: 102, 103) Metronidazole (Flagyl ER).

Pulmonary hypertension is defined as the elevation of the mean pulmonary artery pressure above 15 mm Hg and systolic pulmonary artery pressure of above 30 mm Hg under resting conditions. Latent pulmonary hypertension exists when a significant rise in mean pulmonary artery pressure (>5 mm Hg) occurs with mild exercise. The pulmonary circulation is a low pressure low resistance system. The resistance is 5 times less than in the systemic circulation. Hypoxia causes pulmonary vasoconstriction and is a frequent cause of pulmonary hypertension. Agents that inhibit hypoxic vasoconstriction, such as bronchodilators, calcium antagonists, and nitro compounds, can worsen V/Q mathing. Generally, chronic hypoxia causes mild to moderate pulmonary hypertension (Voelkel '89: 276). Ideally, vasodilator treatment is initiated as an acute trial in the catheterization laboratory. The assessment of vasodilator efficacy is preceded by the assessment of the vasodilator response to prostacyclin that appears to be the "gold standard" test for pulmonary vascular reversibility. Hydralazine, Nitro-compounds, and ACE-inhibitors have produced favorable results in some patients. Because advanced, irreversible pulmonary hypertension occurs resulting from irreparable structural alterations some patients will be irresponsive to any vasodilator drugs. Few patients survive for long treated with either continuous intravenous prostacyclin or with other orally administered vasodilators. The value of anticoagulation has not been studied. A few patients with severe, unexplained pulmonary hypertension have undergone heart-lung transplantation, yet long-term follow-up data is not yet available. The overall prognosis in severe (primary) pulmonary hypertension is poor. After the disease has been diagnosed, survival is generally still a matter of months; a few cases have been documented to survive for several years in spite of very high pulmonary artery pressure. The severe reduction in cardiac output and the limitation to increased cardiac output with exercise, are known hemodynamic factors of poor survival. Patients die from progressive right ventricular failure, pulmonary hemorrhage, and syncope. Pulmonary angiography with rapid injection of a large load of contrast medium has resulted in death within 24 hours in a number of patients with "primary" pulmonary hypertension (Voelkel '89:278-283).

Chemotherapy can only rarely cure a patient with recurrent neoplastic disease. The most active single agents for recurrent disease are methotrexate and cisplatin. Each produces response rate of approximately 30% (mostly partial responses) of 4 to 6 months' duration. Cisplatin responses usually occur more promptly. **Methotrexate** is generally given at 40 mg/m^2 intravenously weekly, but is available in 2.5 mg once a week oral tablets, which are in too small of a dose to

cause most side-effects, such as alopecia and pulmonary infiltrates. There is no evidence that large doses are superior to standard doses. Because of renal excretion, the patiens should have naormal serum creatinine. Toxicities include mucositis, myelosuppression, hepatotoxicity, nephrotoxicity and severe fatigue. Elderly patients and those with poor nutritional status are more likely to have severe reactions. CBC and platelets should be monitored weekly, liver function tests and serum creatinine at least monthly. The cytotoxic effects of the drug can be reversed with a reduced folate, leucovorin. **Cisplatin** is an effective drug whose major route of excretion is renal, and its use should be limited to patents with a creatinine clearance that is more than 50 ml/minute. The standard dose is 100 mg/m^2 every 3 weeks. Because of nephrotoxicity, a 24-hour infusion or mannitol diuresis is recommended. Typical standing orders are 12 hours prior to administration of cisplatin, prehydrate with 2 liters dextrose, 5%, in 0.5 normal saline plus 20 meq of potassium chloride. Three hours prior to administration of cisplatin, increase to 300 ml/hour. Just prior to administration of cisplatin, manitol, 12.5 g by rapid intravenous injection, followed by cisplatin (100 mg/m_2) in saline to a concentration of 1 mg/ml is infused over 30 minuts. Follow this with a continuous infusion of mannitol 10g/hour for 6 hours, with concurrent dextrose, 5% in 0.5 normal saline plus 20 meq potassium chloride per liter at 200 ml/hour for 6 hours. Toxicities include nephrotoxicity, mild myelosuppression, moderately severe nausea and vomiting, hypomagnesemia, ototoxicity, and neurotoxicity. Response rates in excess of 15% for recurrent disease have been reported with several other drugs, including bleomycin, 5-fluorouracil (5-FU), Adriamycin, cyclophosphamide, and hydroxurea.

Multiple combinations have been reported for recurrent head and neck cancer with complete and overall response rates higher than those of single agents, however there is no evidence that combination chemotherapy prolongs survival compared with single agent chemotherapy. Single agent chemotherapeutic drugs for the head and neck are methotrexate, 5-Fluorouracil, Cisplatin, Bleomycin, Dozorubicin, Cyclophasphamide, Vincristine, Mitomycin-C, Paclitaxel (Taxol) and Carboplatin. Multiple agent combinations for the head and neck are Cisplatin and 5-Fluorouracil and Carboplatin and 5-Fluorouracil (Schwartz, Har-E; & DiPillo '04: 459-463). Two commonly used regimens are (1) Cisplatin, 50 mg/m^2 on day 6, methotrexate, 40 mg/m^2 on days 1 and 15; Bleomycin 10 mg on days 1, 8, 15; response rate is 61%. (2) Cisplatin, 100 mg/m^2 on day 1; 5-FU, 1000 mg/m^2 for 4 days, response rate is 70%. Chemotherapy has been used prior to surgery in attempts to reduce tumor size and to decrease local or distal recurrence. When using chemotherapy in this manner, the optimal response is obtained after two to three cycles of chemotherapy. Reported response rates vary from 70% to 90% overall with 20% to 50% complete responses. Cure for squamous cancers of the head and neck is measured in terms of 5-year survival, although most relapses occur in the first 3 years following therapy. Follow-up should include a thorough head and neck examination every 1 to 2 months for the first year, with progressively longer intervals up to five years. A chest film should be obtained early. Approximate cure rates are for (1) oral tongue, T1, T2 – 70%-85%, T3, T4- 30%-40%; (2) floor of mouth, T1, T2-70%, T3, T4-45%; (3) tonsil, T1, T2-60%-75%, T3, T4-20%-35%; (4) pyriform sinus, T3, T4-25%; (5) glottis larynx, T1, T2-80%-90%, T3, T4-75%; (6) supraglottic larynx, T1, T2,-70%-85%, T3, T4-25%-40%; (7) base or tongue, T1, T2-50%-60% , T3, T4-20%-30%, and (8) nasopharynx, T1, T2-70%-75%, T3-55%, T4-<10% (Jacobs '89: 219, 220).

Combination chemotherapy is the cornerstone of management of limited state Small Cell Lung Cancer. Overall response rates of 80% to 95%, complete response rates of 40% to 70%, median survival of 12 to 16 months, 2-year survival of 10% to 25% and 5 years survival (with probable cure of the original SCLC) of 6% to 12% can be expected when chemotherapy, with or without chest irradiation, is delivered. SCLC responds much more readily to chest irradiation, with

overall response rates of up to 90%. In most patients treated with radiotherapy alone, however, distant metastases ensue within a few months. In the 1970s studies demonstrated that chemotherapy plus chest irradiation improved survival compared with radiotherapy alone in limited stage SCLC. Randomized trials hae conclusively shown that combined therapy reduces the failure rate at the primary tumor site but is associated with more hematologic, pulmonary and esophageal toxicity, and combined modality programs have not shown better survival compared with chemotherapy given alone. Approximately 10% to 15% of limited stage patients present with surgically resectable disease using standard criteria employed for non small cell lung cancer. Particularly if a preoperative diagnosis of SCLC is unavailable, proceeding with tumor resection in patients without mediastinal node involvement at thoracotomy is perfectly appropriate. Postoperatively, a standard combination chemotherapy program with or without chest radiotherapy should be administered (Ihde '89: 197-199).

Chemotherapeutic drugs exert their effects by interfering with cell proliferation or the processes of DNA, RNA or protein synthesis. Most anticancer drugs indiscriminately attack rapidly dividing cells and damage both normal host tissues and cancer cells. Many chemotherapeutic drugs act at specific phases during the cell cycle and are termed cycle-specific agents. Agents that interfere with DNA synthesis are called S-phase specific, and those that interfere with microtubules to disrupt mitosis are called M-phase specific. DNA-alkylating drugs are considered cell-cycle nonspecific because they damage cells whether or not they are dividing, making these agents more effective against slow-growing and solid tumors. A chemotherapeutic agent will not affect tumor cells if the drug does not reach the cells, the cells are not in the proper phase of the cell cycle for the drug to work, or the cells are resistant to the effects of the drug. Cancer cells can gain resistance by reducing drug uptake, enhancing the repair of its DNA, producing altered drug-resistant enzymes, decreasing the amount of prodrug converted into active drug, and inactivating agents working within the cells. Also, multidrug resistance can develop and may be caused by a cellular pump that decreases drug levels. Antimetabolites are drugs that interfere with DNA or RNA synthesis such as methotrexate with or without leucovorin, 5-flurouracil, 6-mercaptopurine, cytarabine (Ara-C) and thioguanine. Mitotic inhibitors are drugs that bind to tubulin and depolymerize microtubules such as vincristine and vinblastine. Alkylating agents are drugs that cross link DNA and preventDNA replication and RNA transcription such as Cisplatin, busulfan, nitrogen mustards (cyclophosphamide, mechlorethamine). Antibiotics with inhibiting activity are drugs that affect synthesis of DNA such as bleomycin, mitomycin-C, actinomycin D, and doxorubicin. Nitrosoureas are drugs that are lipid soluble, penetrate the blood-brain barrier and inhibit DNA and RNA such as BCNU, CCNU and streptozotocin. Hormones are drugs that affects testosterone and estrogen-sensitive tumors, lymphoma and leukemia such as estrogen, progestins, androgens, leuprolide, flutamide, and adrenocorticotropic steroids (Schwartz, Har-E; & DiPillo '04: 459-463). Regimens used in the treatment of SCLC are the VAC Regimen, vincristine, doxorubicin (adriamycian), cyclophosphamide; the CMC regimen, cyclophosphamide, methotrexate, lomustine (CCNU); CAVp regimen, cyclophosphamide, doxorubicin (Adriamycin), etoposide (VP-16)' CMCV regimen, cyclophosphamide, methotrexate, lomustine (CCNU), vincristine' CAVVp regimen, cyclophosphamide, doxorubicin (Adriamycin), vincristine, etoposide (VP-16) and VP-16/Platinum Regimen, etoposide (VP-16) and Cisplatin (Ihde '89: 198). Methotrexate 2.5 mg, once a week, might be more effective with fewer side-effects, and at 70 cents a pill, lower cost.

Acute Respiratory Distress Syndrome (ARDS) is a group of disorders in which edema and atelectasis cause the lung to become stiff, interfere with oxygenation of the mixed venous blood

and result in progressively severe hypoxemia and circulatory deterioration. Experimental permeability edema produced with intravenous endotoxin on procoagulant and fibrinolytic activity tend to render the endothelial cell more thrombogenic and may contribute to the intravascular coagulation and fibrin deposition noted within days of onset of gram-negative sepsis. If the patient survives 2 to 3 weeks profound remodeling of the pulmonary vasculature may be encountered while pulmonary arterial pressure is often normal, these various structural changes form the basis of pulmonary hypertension reported late in the course of the syndrome. The development of ARDS is a late and often irreversible manifestation of endothelial injury. The use of corticosteroids is controversial and evidence improved survival is lacking. Supportive measures include osmotically active substances, either low molecular weight (urea and mannitol) or macromolecules such as albumin or dextran, are used to increased the return of lung water to the vascular compartment. Diuretics also may be used to promote renal elimination of the fluid load thus generated. Hypoxemia is dealt with by oxygen supplementation and assisted ventilation. While the response to such treatment can be gratifying, especially with early diagnosis and prompt admission to the intensive care unit, mortality remains quite substantial. Airway narrowing produced by chronic inflammation, loss of ciliary function and retained bronchial secretions markedly reduces alveolar ventilaton in a large portion of the lung (Enson '89: 1145, 1145).

Hypoxemia can be effectively corrected by using controlled oxygen enrichment of the inspired air. This can be accomplished either by double nasal cannula or by so-called Venturi masks that adjust the inspired fraction of oxygen. Both devices correct hypoxemia without the development of hyperoxia, and both may be used successfully without significant CO_2 retention. **Nasal cannula** are preferred for patient comfort, ability to eat and talk and for keeping the oxygen device in place over the Venturi mask. The nasopharynx effectively entrains the oxygen flow from the nasal prongs and the nasal prongs have an additional advantage in hypoventilation. Care must be exercised with the use of Venturi masks. The mask should bring the PO_2 to the desired level of 55 to 65 mm Hg and offers an oxygen saturation of 88% to 92%. Correction of hypoxemia is fundamental to patient care and results in improved oxygen availability to tissues and the consequences of hypoxemia on circulation, for example reactive pulmonary hypertension and impaired cardiac output. The mortality rate among the 150,000 adult respiratory distress syndrome (ARDS) cases seen yearly in the United States is still about 60% despite improvements in supportive respiratory therapy, 90% of deaths occur within 2 weeks of the onset of illness. ARDS and its many synonyms (including adult respiratory failure, shock lung, diffuse alveolar damage (DAD), acute alveolar injury, and traumatic wet lungs) are descriptive terms for a syndrome caused by diffuse alveolar capillary damage and characterized clinically by the rapid onset of severe life-threatening respiratory insufficiency, cyanosis, and severe arterial hypoxemia that is refractory to oxygen therapy, and that frequently progresses to the extra-pulmonary multi-system organ failure. In most patients there is evidence of severe pulmonary edema with chest radiographs showing a diffuse alveolar infiltration. The principles of ARDS management include: the establishment of a definitive airway (usually the endotracheal tube), the use of a volume ventilator employing large tidal volumes, approximately 10 to 12 ml/kg and the use of positive end-expiratory pressure (PEEP). Most patients improve with PEEP levels between 8 cm and 12 cm H_2O. Ventilator support must continue until the patient can achieve adequate ventilation and gas transfer without artificial means. In general this is when PEEP is no longer required and the inspired oxygen fraction is less than 40%. Generally patients can be weaned from mechanical ventilation when their resting minute ventilation is 10 liters or less, the respiratory rate is 20 or less, and the forced vital capacity measured by a simple hand spirometer

is 1 liter or more. The correction of anemia with packed red blood cells helps maximize oxygen carrying capacity and tissue oxygen delivery (Petty '89: 136-138, 257, 263, 265-267)

A screening test determines whether **hypoxemia** develops during the night. This test is performed by ear oximetry that continuously measures and records the oxygen saturation level. A 5% to 10% or more fall from baseline oxygen saturation develops, the cause of hypoxemia should be determined. If no oxygen desaturation is found, either the test is negative or the patient may have slept poorly and did not reach rapid-eye-movement (REM) sleep. The phase of sleep before REM is when the most severe abnormal breathing and hypoxemia occurs. **Protriptyline** is a tricyclic antidepressant that improves or terminates UAO and MA in about 20% of this population. The dosage is 5 to 30 mg orally at bedtime. Oxygen via nasal prongs at 2 to 3 liters/min helps about 40% of these patients, a drawback is the high cost, from $200 to $400 a month. Although the patient has appropriate weight loss, apneas may persist in some individuals. **Progesterone** acts as a respiratory stimulant and mainly helps those individual who have daytime hypercapnia and severe hypoxemia. Nasal CPAP is a new technique that provides a "pneumatic splint" to maintain patency of the oropharynx. This technique is the best medical intervention, with success in about 70% of patients. **Uvulopalatopharyngoplasty** is a surgical intervention with about 40% success. If previous therapies fail, tracheostomy is recommended. For CA and PAH patients respiratory stimulation is the initial therapeutic choice. A **carbonic anhydrase inhibitor** such as dicklorphenamide 50 mg p.o. b.i.d. or acetazolamide 250 mg p.o. qid is highly effective. Progesterone 20 to 40 mg orally t.i.d. can also be used. If needed, supplemental low-flow nasal oxygen can alleviate hypoxemia and occasionally apnea. Weight loss can be important. Nocturnal oxygen is the mainstay for COPD patients with hypopnea (Martin '89: 252-255).

Supplemental oxygen is prescribed for people with chronic bronchitis or emphysema, it may be prescribed for sleep, during exercise, or 24 hours a day. Present medical knowledge supports continuous use of supplemental oxygen for people with a low oxygen value at rest in their usual state of health. Oxygen flow rates may be adjusted for periods of increased activity and sleep. 85 Abnormal values have been arrived at by consensus among medical experts and are used for reimbursement by Medicare. The amount of oxygen in the blood is measured as the oxygen partial pressure. **Normal value** depends on the altitude, but at sea level in an older person the blood oxygen value is typically above 80 millimeters of mercury. In a person with COPD, an oxygen pressure below 55 is abnormal enough that extra oxygen is usually prescribed. The amount of oxygen which is bound to hemoglobin, the red pigment in the blood, is called the oxygen saturation or saturation. A normal level is above 96%. Saturation values at or below 87% are abnormal and enough extra oxygen is prescribed to get the saturation level above 90%. Arterial blood gas or **oximetry testing** is most commonly done during a daytime office visit. If the test demonstrates low oxygen level, supplemental oxygen will be started or increased, and your oxygen level will be rechecked to confirm your oxygen needs, or that adjustments are needed (Tucker et al '01: 86, 87).

The **warning label** on oxygen storage devices states: Stay at least eight (8) feet away from an open flame while using oxygen. Do not use oxygen while cooking with an open flame such as gas appliances, or gas or charcoal-fired barbecue. Never smoke while using oxygen nor around someone using oxygen. Put on a sign on the door of every room where oxygen is in use: Oxygen in use, No Smoking. Never use petroleum-based face creams or ointments, such as Vaseline. Use only water-based creams, lotions and cosmetics. Never use a hair dryer or electric razor when using supplemental oxygen. Store oxygen equipment at least five (5) feet from open

flames, space heater, large windows, or any heat source. Do not store a concentrator in a small enclosed space. Never allow the supply tube to be exposed to sharp edges, a heat source, or flame. There are two main categories of oxygen storage systems (1) stationary or base systems, and (2) portable systems. Stationary, or **base systems** provide oxygen in a fixed location and may be: (1) Liquid oxygen containers with gas condensed into liquid by extreme cold, (2) Concentrators with an electric motor to take nitrogen out of the air, concentrating oxygen to between 94% and 98% and (3) H.S, or M60 cylinders: large tanks containing oxygen under high pressure usually used as a backup and rarely as a base system for daily use. Oxygen concentrators are often used in the home and are probably the most economic source of supplemental oxygen. An oxygen concentrator passes room air through a powder to separate oxygen form nitrogen. The oxygen is concentrated and delivered while the nitrogen is periodically released back into the air. Concentrators are fairly small, weighing about 50-70 pounds, and need an electrical source. A backup oxygen supply system must be available during electrical failure. Some new oxygen concentrators, such as the CHAD Therapeutics, Oxylite™ can fill small cylinders at home, providing oxygen portability for more active people. The portable B/M6 unit weight about five pounds, holds 164 liters of oxygen, and can provide eight to ten hours of use with a conserving device, at two liters per minute. This conservation device administers oxygen during the first third of inspiration. Oxygen flow can be significantly reduced by using an oxygen-conserving device to reduce flow while maintaining the same level of oxygen delivery. Depending on the device, the flow of oxygen stops momentarily, while you exhale, during part of your inhalation, or both. Oxygen-conserving devices can lengthen use of a tank by up to eight times (Tucker et al '01: 88, 97).

The **nasal cannula** is the most common form of oxygen delivery. They are inexpensive, relatively comfortable, provide a great deal of flexibility, and allow you to pursue daily activities. You can talk, eat and cough while wearing them. A nasal cannula has two small prongs in the nose attached to a tube coming from an oxygen source. Two to six liters of oxygen per minute can be administered, but consistent use of more than three liters per minute may dry the lining of the nose and lead to sinusitis. Bubbling the oxygen through a humidifier before delivery at the nose moistens the gas. At low oxygen glow rates of one or two liters per minute, or with a conserving cannula, it may not be necessary to moisten the gas. A nasal cannula may produce some irritation around the ears. Face masks, called the Venti-mask, for oxygen delivery are not often used outside a hospital. **Transtracheal oxygen delivery** is efficient, cosmetically more acceptable for some people, promotes continuous use of oxygen, and reduces breathlessness during eating. For example, a person needing two liters per minute with a regular cannula may need only one liter per minute with a transtracheal catheter. This lengthens the amount of time for one E cylinder from five hours to ten. The system requires a surgical procedure. There are standard methods for inserting a catheter (small tube) through the skin at the front of the neck into the windpipe to enable the direct delivery of oxygen into the trachea. A needs is inserted through the cricothyroid membrane. Then a catheter is introduced through the needle and remains in place after the needle is withdrawn. The oxygen source is connected to the small tube. In order to prevent infection, the catheter needs attention and cleaning on a daily basis (Tucker et al '01: 96, 97, 100). Medicare in the US will only pay a standard rental to the supply company regardless of the type of system. US Medicare currently covers some of the cost of oxygen for those who need it continuously, but not only for use during exercise and not only for portable systems. Liquid oxygen systems need more service from home/health care providers, and are not fully reimbursed. With 25% cuts to reimbursement for oxygen implemented in January of 1998, many health care companies are attempting to remove liquid oxygen from some people. By law, however, the oxygen provider cannot change the method of

oxygen delivery prescribed by the doctor. Another 5% cut in US Medicare reimbursements took place in January, 1999, totaling 30% reduction in oxygen reimbursements and coverage by Medicare. Companies that provide oxygen equipment and service claim that they cannot withstand 25 and 30% cuts in their income. A person on Medicare may buy a system outright, but it is expensive and requires upkeep (Tucker et al '01: 101, 102).

Any change in **blood pH**, whether produced by respiratory or metabolic changes, alters O_2 affinity. Under pathologic conditions, blood pH can deviate markedly from pH 7.4 and have profound implications in oxygen delivery. Low pH may hamper oxygen uptake in the lung. Addition of CO_2 to blood causes pH to fall by 0.03 to 0.05 units. A low pleural fluid **pH** (less than 7.30) has been found only in empyema, esophageal rupture, rheumatoid pleurisy, tuberculosis, malignancy and lupus pleuritis. If the pleural fluid pH in a parapneumonic effusion is more than 7.30, the fluid will almost always resolve spontaneously with antibiotic therapy without sequelae. However, it the pleural fluid pH is less than 7.10, the patient will most likely have a complicated course requiring a surgical procedure to drained immediately from the pleural space with a chest tube (Sahn '89: 288-291). Sputum has a pH of 7.0 and must be removed through daily naso-bronchial hygiene. Ascent to high altitudes produces both hypoxemia and respiratory alkalosis. Alkalinity can be prevented by administration of acetazolamide (Klocke & Saltzman '89: 175). Acidosis is often corrected by hyperventilating through pursed lips and its cure is dependent on the excretion of acid by the kidneys. Although there is an immediate increase in hyperventilation due to peripheral chemoreceptor stimulation when metabolic acidosis is induced, up to 8 hours may be needed for the PCO_2 to fall to its expected value withing the 95 percent confidence band. If the academia is severe, bicarbonate therapy may be needed. **Bicarbonate therapy** is most effective when plasma bicarbonate is low and there is little be gained when the initial (HCO_3^-) is above 20 to 1 mEq/liter (Saltzman & Klocke '89: 205).

IV.5 Vaccines

Contracting and surviving an infectious disease is the most effective means of developing a lifelong immunity against a particular pathogen. However, some infections cause a great deal of morbidity and mortality. The purpose of vaccination is to induce active immunologic protection fore exposure to the risks of infection. For each vaccine an initial immunization protocol is developed to produce large numbers of memory cells and a sustained protective secondary immune response in the greatest number of individuals. In general, vaccine-induced protection does not persist as long as infection-induced immunity; thus, booster injections may be necessary to maintain protection throughout life. The Centers for Disease Control and Prevention maintain the most current immunization schedules for people of all ages. Mass vaccination programs have led to major changes in the health of the world's population. In the early 1950s an estimated 50 million cases of smallpox occurred each year, with about 15 million deaths. The World Health Organization (WHO) conducted a smallpox immunization campaign from 1967 to 1977 that resulted in the global eradication of smallpox by 1979. The 1988 immunization initiative against polio resulted in a 99% decrease in the disease. In 1960, 2,525 cases of paralytic polio were reported in the United States, but no cases of naturally acquired polio have been reported since 1979. In 1994, polio was declared officially eradicated in all the Americas. Similar trends occurred for each disease against which an effective vaccine has been developed. In 2003, groups in northern Nigeria claimed that the oral polio vaccine was unsafe, which led to suspension of polio immunization in two states and reduction of immunization in other states. The result was a 36% increase in cases of polio and thousands of cases of paralysis, including in

previously polio-free areas. The goal of the WHO is to eradicate polio worldwide by 2022 (McCance '14: 332, 333).

Generally it takes one year, from the outbreak of a novel virus, to develop a vaccine. Flu vaccines are notoriously ineffective at identifying all mutations. Development of a successful vaccine depends on many factors. These include characterizing the desired protective immune response (e.g. antibody, T cells), identifying the appropriate antigen to induce that response (i.e. immune response against some antigens on an infectious agent are ineffective or even increase the risk for infection), determining the most effective route of administration (e.g. injected, oral inhaled), optimizing the number and timing of vaccine doses to induce protective immunity in a large proportion of the at-risk population, and deciding the most effective, yet safe, form in which to administer the vaccine. For instance, most vaccines against infections (e.g measles, mumps, rubella, varicella [chickenpox], rotavirus) contain live viruses that are weakened (attenuated) to continue expressing the appropriate antigens but are unable to establish more than a limited and easily controlled infection. Two exceptions are the vaccines against hepatitis B, which uses a recombinant viral protein, and hepatitis A, which is an inactivated (killed) virus (McCabce '14: 332).

Even attenuated viruses can, however, establish life-threatening infections in vaccine recipients whole immune system is congenitally deficient or suppressed. Two different vaccines were developed against polo. The Sabin vaccine is an attenuated virus that is administered orally (oral polio vaccine [OPV]). It provides systemic protection and induces a secretory immune response to prevent growth of the poliovirus in the intestinal tract. The live attenuated vaccine causes polio in some children who have unsuspected immune deficiencies (about 1 case in 2.4 million doses). The Salk vaccine is a completely inactivated virus administered by injection (inactivated polio vaccine [IPV]) It induces protective systemic immunity but does not provide adequate secretory immunity. Therefore, even if the individual is protected from systemic infections the "wild-type" poliovirus can transiently infect the intestinal mucosa, be shed and spread to others. When polio was epidemic, the live oral vaccine was preferred; however, about eight cases of paralytic polio per year in the United States resulted from the vaccine strain proliferating in individuals with inadequate immune systems. As a result, the CDC currently recommends vaccination with the killed virus (McCance '14: 332, 333).

Some common bacterial vaccines are killed microorganisms or extracts of bacterial antigens. The vaccine against pneumococcal pneumonia consists of a mixture of capsular polysaccharides from 10 strains of *S. pneumoniae*. Of the more than 90 known strains of this microorganisms, only these 10 cause the most severe illness. However, the capsular vaccine is not very immunogenic in young children. A "conjugated" vaccine is available that contains capsular polysaccharides from seven strains that are conjugated to carrier proteins in order to increase immunogenicity. A similar vaccine is available for *Haemophilus influenzae* type (Hib). Some bacterial diseases are caused by potent toxins that act locally or systemically. These include diphtheria, cholera and tetanus. Vaccination against the toxins is achieved using toxoids – purified toxins that have been chemically detoxified, without loss of immunogenicity. Pertussis (whooping cough) vaccine was changed from a killed whole cell vaccine to an acellular vaccine that contained the pertussis toxin and additional bacterial antigens. With so many available vaccines there has been an effort to mix vaccines in order to minimize the umber of required injections. One of the first licensed vaccine mixtures was DPT, which now usually contains diphtheria (D) and tetanus (T) toxoids and acellular pertussis vaccine (aP). More recent mixtures include DTaP with inactivated poliovirus, either with Hib conjugate to tetanus toxoid or with

hepatitis B vaccine (McCance '14: 333). An effective vaccine against Adenovirus serotype 4 (Ad4) and serotype 7 (Ad7) was approved in 1971. The economy-driven cessation of vaccine production by its sole producer in 1996 resulted in re-emergence of outbreaks, with Ad4 predominating in 98% of cases, 5 fatalities. On March 16, 2011, the FDA approved an adenovirus vaccine for manufacture by Teva Pharmaceuticals (Sanders '11).

The refusal to vaccinate has generally been based on potential **vaccine dangers**. As with any medicine, complications can arise. In the case of vaccines, these include pain and redness at the injection site, fever, allergic reactions to vaccine ingredients, infection associated with attenuated viruses I immunodeficient individuals, and others. For instance, rotavirus is the most common cause of diarrheal disease in children globally and more than 500,000 children die each year from severe acute diarrhea. A rotavirus vaccine approved more than a decade ago was found to increase the risk for a life-threatening bowel obstruction resulting from twisting of the intestines, and the vaccine was recalled. New rotavirus vaccines are available that are safe from adverse events. A commonly discussed fear is related to the presence of the preservative thimerosal in vaccines. Thimerosal is a mercury-containing compound that has been used as a preservative since the 1930s. Although no cases of mercury toxicity have been reported secondary to vaccination, thimerosal was removed from all vaccines in 2001, with the exception of inactivated influenza vaccines (McCance '14: 333).

Vaccines are the greatest achievement of modern preventive medicine. Polio and smallpox have been eradicated and one more generation of vaccines will eliminate whooping cough, measles and mumps as threats to our children. In 1905 the Supreme Court ruled that an individual could not refuse the smallpox vaccine on constitutional grounds of infringement on personal liberty. The court found that an individual's personal liberty must give way to the state's protection of other citizen's health (*Jacobson v. Massachusetts*, 197 US 111, 25; 1905). Since that time, various state courts have ruled that compulsory immunization statutes cannot be stricken down on constitutional grounds. Every state has a compulsory vaccination law, though the specific requirements for individual vaccines vary from state to state. The federal Public Health Service Act 42 USC§262 requires that participating governments have a "plan to assure that children begin and complete immunizations on schedule…and…a plan to systematically immunize susceptible children at school entry through vigorous enforcement of school immunization laws. 42CFR§51b.204. **Legal exemptions** may be granted on medical, religious or philosophical grounds depending on the state. Arizona, California, Colorado, Idaho, Indiana, Louisiana, Maine, Michigan, Minnesota, Nebraska, New Mexico, North Dakota, Ohio, Oklahoma, Rhode Island, Utah, Vermont, Washington and Wisconsin provide for a philosophical exemption from vaccination. Idaho, Maine, Missouri, New York, Oregon, Pennsylvania, Texas and Washington do not require a Pertussis vaccination for Grades K-12 (Neustaedter '96: 69, 79, 86, 92, 93).

Recommended Vaccination Schedule for Children up to 7 years Old

Vaccine	Birth	1-2 mos	2 mos	4 mos	6 mos	6-18 mos	12-15 mos	15 mos	4-6 yrs
Diphtheria-tetanus pertussis			DTP	DTP	DTP			DTP/ DTaP	DTP/ DTaP
Polio, live oral (option)			OPV IPV	OPV IPV	OPV			OPV	OPV OPV
Measles-							MMR		MMR

mumps-rubella									12-13 yrs
Haemophilus influenza b conjugate			Hib	Hib	Hib		Hib		
Hepatitis B (optional schedule)	HepB	HepB HepB		HepB	HepB	HepB			
Varicella-zoster virus (chickenpox)							VZV		VZV

Source: Neustaedter '96: 199

Pediatric well child visits center around the vaccination schedule. The CDC recommended immunization schedule. First Hepatitis B (Hep B) is given at birth. 2nd Hep B, and 1st Diptheria and Tetanus [Diphteria, Tetanus and Pertusis (DPT or DtaP acellular Pertussis], Hib, Inactivated Poliovirus (IPV), rotavirus and Pneumococcal are at 2 mo, DPT or DTaP, Hib, IPV at 4 mo., Hep B, DT [DPT or DtaP], Hib, IPV at 6 mo. Hep B, DT [DPT or DTaP], VZV at 12 mo., MMR at 15 mo., DT [DPT] at 18 mo., DPT or DTaP, IPV, MMR at 4-6 years. Hep B, MMR, VZV at 11-12 years. The second dose of MMR is recommended at 4-6 years and should be received no later than 11-12 y. Susceptible children can receive the varicella vaccine at any visit after the first birthday, and children should be immunized by age 11-12 y. Susceptible children 13 y or older should receive two doses, at least 1 mo apart. Rv (rotavirus vaccine) was removed from the market in 1999, it had been administered at ages 2, 4 and 6 mo. Pneumococcal vaccine recently has been recommended to be administered at 2, 4 and 6 mo with a booster dose as 12-15 mo. Between 18 months and 18 children are also subjected to an annual influenza vaccination, Hep B at 18 mo., DTaP at 18 mo and 4-6 years, IPV 18 mo and 4-6 years, MMR 4-6 years, VAR 4-6 years, Hep A 18 mo and 19-23 mo, Meningococcal HibMenCY at 11-12 and at 16 years, Tdap 11-12 years. 2vHPV females, 4vHPV for males. Polio and smallpox have been eradicated and measles and mumps are been greatly reduced as threats to children. Flu vaccines are ineffective and must be advertised with one dose of Amantadine (Symmetrel) as cure for influenza type A coughs. The rubella vaccine is active, infectious and dangerous to unvaccinated pregnant mothers. A transient morbilliform rash is an adverse effect associated with the MMR vaccine. The pertussis vaccine is thought to cause death, neurological and developmental hip disorder in some babies and small infants and is not administered to children under age 2 in Europe. The United States now provides a DT (Diphtheria and Tetanus) vaccine to replace the DTP (with pertussis) and DTaP (activated Pertussis).

In 1975, Japanese parents refused to give their children the pertussis vaccine after widespread publication of two deaths following vaccination. The Japanese government changed its policy in response to this protest, and delayed the recommended age for vaccination until two years. Delay of DTP vaccination until two years of age in Japan resulted in a dramatic decrease in adverse vaccine effects. During the period 1970 through 1974 when DTP was begun at 3 to 5 months of age, the Japanese national compensation system paid claims for 57 permanent severe vaccine reactions and 37 deaths. During the following six-year period, 1975 to 1980, when DTP vaccine was begun at 24 months of age, severe reactions were reduced 85 to 90 percent, to a total of eight with three deaths. Only two diseases that have corresponding vaccines cause any significant problems within the first year o fife in countries with modern sanitation systems. These two are whooping cough (pertussis) and *Haemophilus meningitis*. The pertussis vaccine

has caused so many dangerous reactions that Western European countries consider its use unjustifiable and have eliminated it from the roster of routinely administered vaccines. In 1990, JAMA published a study finding no risk of seizures and other neurologic events following the DTP (**Diptheria-Tetanus-Pertussis**) vaccine. The medical profession results in constant denial of claims for compensation for vaccine reactions, and absolute refusal to report adverse reactions (Neustaedter '96: 34, 16, 34, 28, 29, 33).

The **vaccine controversy** reaches its zenith with reports of pertussis vaccine reactions. Children in countries throughout Europe and the United Kingdom no longer receive the pertussis vaccine in the DT vaccine. Japan has postponed pertussis vaccination until children are two years old. The United States congress passed the National Childhood Vaccine Injury Act to provide compensation t parents of children injured by vaccines, all in response to this public scrutiny of vaccine reactions. Reaction to the vaccine have included fever, persistent crying, encephalitis, epilepsy, retardation and death. Other neurologic diseases have been associated with the vaccine as well (Neustadter '96: 123-125). The dramatic rise in ear infections, allergies and asthma in children can attributed (at least in part to the damaging effects of vaccines, environmental pollutants such as organophosphate pesticides and the toxic effects of asthma medicine. The incidence of asthma, the most serious and life-threatening of these conditions, has steadily increased in the modern era since the introduction of vaccines. Just during the period 1980 to 1980 the prevalence rate of self-reported asthma in the United States increased 38 percent, and the death rate for asthma increased 46 percent. Just in the five years from 1985 to 1990, projected estimates for asthma's medical costs increased 53 percent. The total estimated cost of asthma rose from $4.5 billion to $6.2 billion or 1 percent of all U.S. health-care costs. The ability of pertussis and DTP vaccines to stimulate the onset of paralytic polio provides further evidence that vaccines can promote serious disease processes and immune system dysfunction. Paralytic polio has occurred frequently following vaccination. This phenomenon was first reported in 1909. Scattered cases were reported over the next 40 years. Then, during the polio epidemics of the 1950s, series of cases of polio following pertussis-vaccine injections were reported around the world. During a recent polio epidemic in Oman the problem of paralytic polio infection's onset soon after DTP vaccination occurred crippling 70 children aged 5 to 24 months between 1988 and 1989, presumably due to the immune suppressant effects of the vaccines (Neustaedter '96: 40, 41, 42).

Pertussis is an infectious disease associated with a specific bacteria. The illness usually begins as a mild cold, which lasts for a week. Then the characteristic cough starts, which makes this disease recognizable. The cough comes in paroxysms and is often preceded by a feeling of apprehension or anxiety and tightness in the chest. The cough itself consists of short explosive expirations in rapid succession followed by a long crowing inspiration. A number of such paroxysms are sometimes followed by spitting up a mucus plug and vomiting. The disease usually lasts for 6 weeks regardless of treatment. Complications of pertussis may include cerebral hemorrhage, convulsions and brain damage, pneumonia, emphysema, or a collapsed lung. Deaths are usually due to complicating respiratory infections. Pneumonia is the most frequent cause of death in children under three years of age, but fatalities in children over 12 months are rare. Standard treatment with antibiotics may help reduce the period of contagion to others and prevent complications but does not change the course of symptoms. The incidence of pertussis has declined from at least 100 reported cases per 100,000 population during the period 1930-1945 to an average of 1.5 per 100,000 population during 1984-`993. Several thousand cases occur per year, most during childhood. During the 10 year period 1982-1991 an average of 5 reported deaths per year were associated with pertussis. Immunity derived from the vaccine

wanes after 5 to 10 years and the pertussis vaccine cannot be administered past 7 years of age because of severe reactions. Pertussis occurs regularly in older children and adults who have been fully vaccinated (Neustadter '96: 123-125).

When European countries began suspecting that the pertussis vaccine was dangerous, they eliminated the recommended schedule of childhood vaccinations When parents in the United States have refused to administer this vaccine to their children, however their children have been taken into the protective custody by the state. When vaccine companies began losing million-dollar lawsuits to parents with vaccine-damaged children, the United States government intervened and removed all vaccine manufacturer liability, assuming and limiting damage claims, and removing the possibility of any other compensation. This was the origin of the **National Childhood Vaccine Injury Act of 1986** and the Vaccine Compensation Amendments of 1987. The Institute of Medicine Vaccine Safety Committee established thereunder published two reports, titled, Adverse Effects of Pertussis and Rubella Vaccines in 1991 and Adverse Events Associated with Childhood Vaccine: Evidence Bearing on Causality in 1994. The only conditions for which a causal relationship was established were (1) anaphylaxis (a sudden, potentially life-threatening systemic allergic response) caused by several vaccines; (2) polio and death caused by the polio vaccine; (3) thrombocytopenia (a decrease in the number of platelets, the cells involved in blood clotting) caused by the measles vaccine; (4) death caused by the measles vaccine and (5) acute arthritis caused by the rubella vaccine. Evidence favoring a causal relationship were (1) acute encephalopathy after DTP; (2) shock and unusual shock-like states after DTP; (3) chronic arthritis after rubella vaccine; and (4) Guillain-Barre syndrome after DT and polio vaccines. The vaccine injury table contained within Public Law 99-660, upon which compensation awards are based, allows only a 3 day window for development of encephalopathy (impairment of brain function) or residual seizure disorder following the DTP vaccine (Neustaedter '98: 34-37).

The dramatic rise in ear infections, allergies and asthma in children can attributed (at least in part to the damaging effects of vaccines, environmental pollutants such as organophosphate pesticides and the toxic effects of asthma medicine. The incidence of asthma, the most serious and life-threatening of these conditions, has steadily increased in the modern era since the introduction of vaccines. Just during the period 1980 to 1980 the prevalence rate of self-reported asthma in the United States increased 38 percent, and the death rate for asthma increased 46 percent. Just in the five years from 1985 to 1990, projected estimates for asthma's medical costs increased 53 percent. The total estimated cost of asthma rose from $4.5 billion to $6.2 billion or 1 percent of all U.S. health-care costs. The ability of pertussis and DTP vaccines to stimulate the onset of paralytic polio provides further evidence that vaccines can promote serious disease processes and immune system dysfunction. Paralytic polio has occurred frequently following vaccination. This phenomenon was first reported in 1909. Scattered cases were reported over the next 40 years. Then, during the polio epidemics of the 1950s, series of cases of polio following pertussis-vaccine injections were reported around the world. During a recent polio epidemic in Oman the problem of paralytic polio infection's onset soon after DTP vaccination occurred crippling 70 children aged 5 to 24 months between 1988 and 1989, presumably due to the immune suppressant effects of the vaccines (Neustaedter '96: 40, 41, 42).

Studies of vaccine efficacy involving vaccinated children living in a house with someone who has contracted the disease, demonstrated vaccine efficacy of 63 to 91 percent, or 80 percent 3 years after the last dose, 50 percent between 4 and 7 years, and none after 12 years. 95 percent of children in the United States are vaccinated. In a UCLA study children who received the DTP

vaccine were compared to those who received the DT vaccine, found that within 48 hours, 50 percent of vaccines developed fever, 34 percent irritability, 35 percent had crying episodes and 40 percent had localized inflammation. 3 percent had persistent inconsolable crying and screaming and 31 percent with excessive sleepiness (compared to 14 percent in the DT controls). 1 in 1,750 doses of DTP caused seizures, or 1 in 333 children suffered seizures within 48 hours of vaccination. An early report in 1948 described 15 cases of encephalopathy following pertussis vaccination at Children's Hospital in Boston. These cases consisted of fever, irritability, convulsion, and coma occurring within 12 hours of pertussis vaccination. Six of these children suffered from permanent cerebral palsy, 6 had seizures and mental retardation and 2 died of pneumonia. Controversy surrounds the issue of permanent neurologic damage (injury to the brain and retardation) caused by pertussis vaccine reactions. The typical case involves n initial seizure after the vaccine's administration, followed by recurrent seizures after a few days or weeks. Then mental or motor retardation become apparent over the ensuing months. The estimated risk of persistent neurologic damage 1 year later is estimated at 1:310,000. Given the controversies surrounding the association of permanent neurologic damage to pertussis vaccine the Institute of Medicine Committee found insufficient evidence to establish a causal relation between these permanent symptoms and the vaccine in 1991. 125-130 **Anaphylaxis**, sudden onset of a life-threatening allergic reaction and systemic collapse, has been recognized as a consequence of many vaccines including pertussis. Hemolytic anemia, the destruction of red blood cells that could be caused by toxic agents or antibody responses to vaccines has been associated with the DTP vaccine. The pertussis vaccine is ill-advised. The disease itself has these same risks, though the incidence of pertussis is now low in the United States (Neustadter '96: 132, 133).

In 1981, the Japanese switched from a whole-cell pertussis vaccine to a more complex acellular vaccine, primarily because of public pressure. The first acellular pertussis vaccine was licensed in the United States in 1991 for use as the fourth and fifth doses of the recommended DTP schedule for children ages 16 months through 6 years. Japanese studies had shown that the acellular vaccine was 79 to 97 percent effective, in children older than 2 years. Acellular vaccine was adopted for use as a booster in older children, in an attempt to reduce severe reactions to the pertussis component of DTP. Sweden withdrew an application for licensure of the vaccine on the basis of tests observing efficacy of 64 percent for one strain and 54 percent for another strain of acellular vaccine. This vaccine seems to cause fewer of the mild-type reactions than the older whole-cell vaccine. In Japan, the replacement of whole-cell with acellular vaccine resulted in a 60 percent reduction of "mild' reactions, particularly febrile seizures. But the rate of severe reactions did not differ significantly between the acellular and whole-cell vaccine. The pertussis vaccine is dangerous in all forms developed thus far. The Japanese experience with the use of acellular vaccine beginning at 2 years of age shows that reactions are significantly reduced if vaccination is delayed, whether whole-cell vaccine or acellular vaccine is used. Infants will continue to be severely damage by these pertussis vaccines, and the true extent of undetected, long-term disease may never be discovered (Neustadtr '96: 134-138).

Vaccination for **Measles, Mumps and Rubella** is usually given as a single shot of combine live viruses (the MMR vaccine) at 12 months of age or older. Mass vaccination of children for mumps, measles and rubella has resulted in this disease becoming a a disease of adolescents and young adults. The vaccines seem to have caused atypical forms of the diseases to appear. Measles was a common disease of childhood prior to the widespread use of measles vaccine. The disease is transmitted by a virus that is highly contagious. The symptoms of measles are cold symptoms, cough, irritated eyes, and high fever, with the appearance of a rash on the fourth

day of illness. The symptoms, including the rash, reach a climax on about the sixth day and then subside in a few days. Occasionally measles leads to ear infections, pneumonia, infection of the lymph nodes and encephalitis. In the past, deaths from measles were not uncommon during epidemics. Now the disease is milder and deaths are rare. Measles is usually a self-limited disease. Encephalitis is reported to occur in one out of 1,000 cases, of these 25 to 30 percent show manifestations of brain damage. Measles was contracted by most children prior to vaccine licensure in 1963. Following the vaccine the incidence of measles decline to an average of 3,000 cases per year in the 1980s. However, in 1989 a resurgence of measles occurred in the United States, constituting an epidemic that brought levels back up to the 1970s rate of 27,000 reported cases per year. In 1990 the epidemic was traced to measles antibodies in young mothers. Epidemics occasionally break-out in vaccinated schools. The measles vaccine is known to cause many problems such as encephalitis, meningitis, subacute sclerosing panencephalitis, seizure disorder, sensorineural deafness, optic neuritis, transverse myelitis, Guillain-Barre syndrome. However, the only conditions attributed to the MMR vaccine by the Institute of Medicine are thrombocytopenia, a decrease in blood platelets responsible for blood clotting with accompanying spontaneous bleeding, and anaphylaxis, that is often due to egg proteins contained in the measles and mumps vaccine due to a hypersensitivity to eggs, however, other antibiotics contained in these preparations have been implicated in triggering severe allergic reactions. One of the most dangerous reactions cause by measles vaccine is an inflammatory response in the brain known as subacute sclerosing panencephalitis (SSPE) that causes demyelination of nerve sheaths and slow, progressive deteriorating condition resulting in death, often within 1 to 2 years, since 1968 there have been 575 cases, but incidence has declined since the 1970s accompanying a decline in natural measles, the proportion of cases with an antecedent history of measles vaccination has increased. A disturbing but rare syndrome of atypical measles has occurred in children previously vaccinated consisting of an illness with exaggerated rash, muscle weakness, peripheral edema and severe abdominal pain with persistent vomiting. Recent research has shown an association between measles vaccine and inflammatory bowel disease. In one study individuals who had received measles vaccine in the 1960s were more likely to suffer from chronic intestinal disease including Crohn's disease (characterized by deep ulcers, holes and thickening of the intestinal lining) and ulcerative colitis thirty years later compared to controls. This is not surprising because persistent measles virus infection has been located in intestinal tissue. Mass vaccination has resulted in a dramatic decline in measles incidence, but outbreaks now occur in older populations and in infants born to women whose immunity from vaccination has deteriorated. Periodic epidemics continue to occur (Neustadter '96: 145-150).

Mumps was a common and very mild disease of childhood that was not even noticed in an estimated 30 percent of cases prior to widespread vaccine use. The illness begins with fever, headache and fatigue, and within 24 hours the child complains of earache near the lobe of the ear. The next day the salivary gland in front of the ear becomes swollen. Within one to six days, the illness has run its course. Infection of the testicles, ovaries, and other organs are not unusual, but occur much more commonly in adults. Infection of the testicle occurs in 20 to 30 percent of mumps cases in adolescent or adult males. Sterility following such an illness is extremely rare. Encephalitis and meningitis complications during epidemic outbreaks occur at a rate of 2 to 4 cases for every 1,000 reported cases of mumps. However only an estimated 70 percent of mumps cases rare reported. A live mumps virus vaccine was licensed in 1967 and recommended for routine use in 1977. The number of mumps case decreased during the early 1980s to 3,000 to 5,000 cases per year, a dramatic decline from 100,000 cases per year of the early 1970s. However during 1986, 7,800 cases occurred and during 1987 there were nearly 13,000 reported mumps cases. During the early 1990s the number of reported cases declined again to around

4,000 cases per year. Before the introduction of the vaccine 1967-1971 the annual average of cases in persons 15 years of age or older was 8.3 percent, this age group accounted for 38.3 percent of cases in 1987, an eightfold increase, and remained there, 34 percent in 1993. Mumps in young children is a mild, benign disease. In adolescents and adults, it is a disease associated with more complications. The response of public health authorities is to revaccinate during the adolescent years. The efficacy of mumps vaccine has ranged from 75 to 95 percent in various studies. The vaccine is associated with adverse effects similar to the measles vaccine. The rate of virologically confirmed mumps-vaccine associated aseptic (nonbacterial) meningitis was 1 case in 3,800 doses. Two conditions are associated with the mumps virus and not with measles. These are meningitis and diabetes and other pancreatic disease. Researchers calculated an incidence rate of 1 in 2,000 people who receive the MMR. Many studies have proven that natural mumps infection causes pancreatitis (infection of the pancreas) and stimulates the onset of diabetes. Mumps vaccination has similarly stimulated the onset of diabetes. The Vaccine Safety Committee declined to accept diabetes as a consequence of mumps vaccine (Neustadter '96: 151-154).

Haemophilus influenza bacterial infections occur frequently in childhood, accounting or a large percentage of common sinus, throat and ear infections. The bacteria has no relationship to influenza. It was named influenziae because early researchers found the bacteria in people with flu, but did not recognize until later than Haemophilus is a normal resident of mucus membranes. They usually resolve on their own without treatment. However, one strain of Haemophilus, the type b encapsulated strain, is capable of causing invasion of infections to deeper levels in the body, particularly the spinal fluid, lungs, heart and blood. Vaccines have been developed because Haemophilus can cause meningitis, pneumonia, epiglottitis, and other complications. Between 20 and 30 percent of children with bacterial meningitis have seizures. Arthritis, pericarditis and pneumonia are common complications. Disease of sudden onset with rapid progression is usually associated with a different bacteria, *Neisseria meningitides*, which has a much higher risk of death. Mortality from Hib meningitis is 3 to 8 percent. Appropriate treatment of Hib meningitis includes the use of antibiotics, particularly penicillin or erythromycin, for resistant strains. The estimated incidence of Hib meningitis is 8,000 to 15,000 cases per year. Native American and Eskimo children are particularly susceptible to Hib meningitis. Incidence has increased over the past three decades, possibly due to the administration of other vaccines. Approximately 1 in 350 children younger than 5 years of age develops Hib meningitis. Children under 6 months are protected by maternal antibodies and breastfeeding reduces incidence rates. The peak incidence of meningitis is is at 6 to 7 months. The attack rate decreases rapidly with increasing age. Fifty percent of cases occur in infants under 1 year, only 25 to 30 percent of cases occur in children over 18 months. The congregation of infants in day are setting creates a significantly higher risk of infection (Neustater '96: 161-163).

Several different *Haemophilus influenza* type b (Hib) vaccines are manufactured. Efficacy studies for the newer vaccines have only been published since 1987 and conclusions are tentative. In 1985 the first Hib vaccine, a purified form of the polysaccharide capsule (called PRP, from the chemical name of the capsular substance) was licensed The PRP vaccine was not effective in children under 24 months old, and these children represented 80 percent of Hib meningitis cases. JAMA found that 41 percent of Hib cases occurred in vaccinated children. The vaccine's protective efficacy was minus 58 percent. Children were more likely to get the disease if they received the vaccine. In other studies efficacy ranged from 41 to 88 percent. Vaccine researchers found that when the PRP form of the vaccine was joined to a protein carrier,

then the vaccine was more effective and developed antibody responses in younger children. These conjugated forms are now used beginning in infancy. In 1990 the first conjugate vaccines were licensed for used beginning at 2 months of age. The effectiveness of various conjugate vaccines has varied in studies, the PRP-T study was terminated because in favor of the PRP-D conjugate vaccine showed an efficacy of 74 to 96 percent in various studies, but in Alaskan Natives the efficacy was only 35 percent. In another study 90 percent of children vaccinated with the PRP-D conjugate vaccine responded with antibody levels considered to be protective, but only 60 percent produced levels of antibody indicating long-term protection. Nonetheless, millions of children are vaccinated with PRP-D. Other conjugate vaccines (PRP-OMP [93%] and HbOC [97-100%]) have shown high levels of efficacy. Hib infection has declined (Neusadter '96; 163-166).

Evaluating reactions to the Hib conjugate vaccines presents problems because Hib vaccines are given together with the DTP vaccines, sometimes in the same shot. The withdrawn PRP vaccine caused significant adverse effects including seizures, anaphylactoid allergic reactions, serum sickness-like reactions (joint pain, rashes and edema) and one death within 4 hours of vaccination. The most common and potentially significant Hib vaccine reaction has been the increased incidence of Hib disease following vaccination. The older PRP vaccine caused Hib disease within the first 7 days following vaccination in children over 18 months. The new conjugate vaccines also cause a decline in antibody levels immediately following vaccination with conjugate vaccines were reported through VAERS between 1990 and 1992. All case occurred within 5 days of vaccination. The conjugate vaccines have been associated with the onset of Guillain-Barre syndrome (GBS). Cases of transverse myelitis, a paralyzing disease of the spinal cord, following Hib vaccine have been reported. In a study on the safety of Hib conjugate vaccine (PRP-T) compared to hepatitis B vaccine, in which the infants were also given DTP, five infants developed seizures within 48 hours, three more between 3 and 14 days. Thrombocytopenia, has been reported following Hib conjugate vaccination. Haemophilus meningitis is not uncommon. If a child stays home with a parent in the first 12 to 18 months of life, when Hib disease occurs most often, the n the likelihood of exposure decreases dramatically compared to a child who attends a large day care center. Although new conjugate vaccines are highly effective serious reactions have been reported (Neustadter '96: 166-169).

Almost all elderly people and people with chronic disease are highly encouraged to get yearly influenza vaccine or **flu shots**. Most years these shots are effective, but effectiveness depends on the vaccine development process. Most viruses which produce epidemics in North America and Europe have previously done so in Asia (Beijing Flu, Taiwan Flu). The Centers for Disease Control in Atlanta develops vaccine for the United States to protect from whatever viruses were in Asia six months earlier. But sometimes new viruses occur in the U.S. without first showing up in Asia, and sometimes the viruses change. Therefore, there is no guarantee, even with vaccination, that the flu can be avoided. However, one will probably have a milder case if you've had the shot. The pneumonia vaccine, **Pneumovax**, was developed to prevent pneumonias caused by the pneumococcus bacteria, which can cause severe, even fatal pneumonia. After receiving Pneumovax, the body is able to make antibodies against the pneumococcus bacteria. These antibodies, in people with COPD, appear to remain at high levels for five to ten years or longer, so injections at about ten-year intervals are usually recommended. This vaccine can cause increased soreness and swelling at the injection site if given too soon after the last injection, because of the high antibody levels still present in the body (Tucker et al '01: 77).

Streptococcus pneumonia (pneumococcus) is a bacterium associated with many cases of pneumonia, meningitis, bacteremia (systemic infection in the bloodstream) and ear infections. At least 10 to 25 percent of all pneumonia cultures *S. pneumonia* and approximately one-third of all ear infections in children are associated with *S. pneumonia* growth. In addition the estimated incidence of pneumococcal meningitis is 1 or 2 per 100,000 persons, and pneumococcal bacteremia (infection in the bloodstream) may occur as often as 160 per 100,000 children under two years of age. In 1977 a pneumococcal vaccine was licensed which contained 14 types of S. pneumonia. This was replaced by a vaccine of 23 types in 1983. These early polysaccharide vaccine have met with limited success, and new vaccine technology is under investigation in which the polysaccharide is bonded to a protein barrier to produce a conjugate vaccine that researchers hope will be more successful. The estimated effectiveness of the pneumococcal vaccine is 60 to 70 percent. However, three studies hound little or no effect from the vaccine. The currently licensed polysaccharide vaccine is ineffective in children under 2 years of age. Research has shown that vaccinated children had significantly fewer episodes of ear infections associated with the types of *S. pneumonia* present in the vaccine. But children in the vaccine and control group had the same number of ear infections. The vaccine did not prevent ear infections; it only altered the types of microbes present in the ear. The vaccine is not currently recommended for prevention of ear infections. The only children now routinely receive the pneumococcal vaccine are those at increased risk of serious pneumococcal infections. The vaccine has been associated with few adverse effects. Approximately 50 percent of vaccines (30 to 40 percent in children) develop swelling and pain at the injection site. Fever, muscle pain and severe swelling occur in less than one percent of those vaccinated (Neustadter '96: 187-189).

Systematic review of 51 studies found no evidence that the flu vaccine is any more effective than a placebo in children (Smith et al ’08). Studies published in 2008 found that influenza vaccination was not associated with a reduced risk of pneumonia in older people although it did contribute to a reduction in mortality (Jackson et al ’08)(Eurich et al ’08). In the winter flu season of 2012-2013 the flu vaccine was only 8% effective. The viruses that cause flu are prone to antigenic drift, making vaccine manufacture difficult. Type A Influenza viruses are subdivided into groups based on two surface proteins, HA and NA, Influenza B or Influenza C based on protein composition. Type A viruses are found in many kinds of animals, including ducks, chickens, pigs, and whales, and also humans. The type B virus widely circulates in humans. Type C has been found in humans, pigs, and dogs and causes mild respiratory infections, but does not spark epidemics. Flu viruses last for hours in dried mucus. The antigenic shift is a sporadic and unpredictable event in which one entire gene, the hemagglutinin gene or the hemagglutinin gene and the neuraminidase gene are entirely replaced resulting in a new sub-type. The population doesn’t have any immunity and this can result in a pandemic. When they surveyed more than 6,000 available HA genetic sequences of the 16 HA subtypes, they found the pockets to be very similar within each Group but to be significantly different between the two Groups. One of the most remarkable findings of the work is that it identified a highly conserved region in the neck of the influenza hemagglutinin protein to which humans rarely make antibodies because the head of the hemagglutinin protein acts as a decoy by constantly undergoing mutation and thereby attracting the immune system to produce antibodies against it rather than against the pocket in the neck of the protein (Fiore "09).

Current influenza vaccines target the constantly mutating head of the HA protein and do not readily generate antibodies against the conserved region in the neck. An important goal is to redirect the immune response of vaccines to this invariable region of the hemagglutinin to try to obtain durable lifelong immunity. These are fully human monoclonal antibodies that are ready

for advanced preclinical testing. Researchers are currently is arranging to use NIAID research resources to take the next steps: first, testing the antibodies in ferrets, the gold standard animal model for influenza, and then developing a clinical grade version of one antibody that could enter human clinical trials as soon as 18 months from when the development program begins. Should the antibodies prove safe and effective in humans, it could take several years to develop a licensed product (J. Sui '09). Using standard methods of production, initial doses of a new influenza vaccine to fight pandemic influenza would be expected to take four to six months to produce. It is highly important that the vaccine industry be highly regulated and that the regulation be cross-examined by independent government agencies because vaccine researchers are have access to the actual viruses and have both the means and motive to deliver them to the public in order to create demand for their products.

Passive immunotherapy is a form of countermeasure against pathogens in which preformed antibodies are given to the individual. This form of therapy has been used for decades. Horse serum-containing antibodies were given to treat diphtheria, pneumococcal pneumonia, tetanus, and other diseases in the early twentieth century. However, because of foreign proteins in the serum, many individuals developed an immune reaction against the horse proteins and an immune complex-mediated serum sickness. Passive immunotherapy with human immunoglobulin has been approved for several infections, including hepatitis B and hepatitis A. treatment of potential rabies infection after a bite combines passive and active immunization. The rabies virus proliferates very slowly. Individuals who have been bitten receive a onetime injection with human rabies immunoglobulin, or more recently with monoclonal antibody to against respiratory syncytial virus has been approved for therapy (McCance '14: 333).

Subcutaneous immunotherapy (SCIT) has been shown to be effective in treating allergic rhinitis in patients with identifiable IgE mediated symptom triggers. It has some advantages over the above mention treatments. Effects can be sustained for years, and it may prevent the development of new allergen sensitivities or even asthma. It is effective for not only control of allergic rhinitis but also of allergic conjunctivitis and allergen induced asthma. However, immunotherapy is underutilized with only 2 to 3 million US individuals on SCIT of the estimated 55 million people with allergic diseases. In regard to specific inhaled allergens, evidence supports immunotherapy for pollens, animal dander, and dust mite. Large local reactions at the injection site are the most common adverse reaction. The risk of severe systemic reactions during subcutaneous immunotherapy is rare but present in less than 1% of those receiving standard immunotherapy. Near fatal events occurred at a rate of 5.4 per million injections. High ambient pollen levels and dosing errors were the two main risk factors for such a reaction. It is advised that patients receive immunotherapy injections in a setting with staff and equipment that can handle anaphylaxis, and that patient be observed for 30 minutes after each injection. Other disadvantages include injection discomfort, the frequency of shot visits, and the total cost. However, immunotherapy is the only treatment that can modify the disease. When the direct costs of symptomatically managed allergic rhinitis are compared to the cost of immunotherapy, the values are virtually the same. When indirect costs are factored, immunotherapy may be much more economical. Subcutaneously is the most common way to deliver immunotherapy, but sublingual immunotherapy (SLIT) is also used. SLIT has been reported to cause oral itching and gastrointestinal side effects, but in most studies, these rates seem to be the same as those observed in the placebo arm. There is a lack of standardization in SLIT with timothy grass pollen extracts being the only commercially available therapy (Grazax by ALK-Abelló Hørsholm. Denmark), and there are no SLIT therapies approved for the US by Food and Drug Administration. Advantages of SLIT include an extremely low risk of

anaphylaxis and the ability to begin therapy at the maintenance dose without a build-up phase. SLIT for dust mite allergy has been specifically studied in the Korean population and found to be effective in reducing symptom scores. Although anaphylaxis has not been noticed in studies on SLIT, there are case reports of anaphylaxis occurring during treatment, even with the first dose. SLIT is not as well established as SCIT, and further investigation is required to determine the optimal dose and patient selection (Tran, Vickery & Blaiss '11).

Immunotherapy for asthma is the repeated injection of increasing doses of extracts of substances to which asthmatic patients have immediate skin responses. In theory the injected antigens induce "blocking antibodies" that inhibit subsequent allergic responses to the antigen. Whether immunotherapy is an effective treatment for asthma is controversial. Problems with immunotherapy are: the lack of quality extracts of molds and animal danders to test or treat patients, the lack of objective studies to determine whether immunotherapy is effective and the lack of diagnostic criteria to establish the relevance of positive skin-test reactions to allergens such as house dust mite and animal danders that are perennially present in the environment (Bethel '89: 175). Immunotherapy involves getting a shot once or twice a week for six months or more but often leads to remission from allergy attacks for years after treatment has ended. Allergy shots have been around since 1911. It's the only treatment for allergies that reduces symptoms over the long term rather than just treating them for a few hours. Each successive injection contains a tiny bit more of the substance to which you're allergic. Eventually, your body becomes desensitized to the allergen, decreasing the IgE reaction to it by blocking IgE antibodies. Experts analyzing 24 studies involving more than 900 people with asthma who also had documented allergies found that allergy shots effectively treated allergic asthma in 71 percent, resulting in fewer symptoms, less lung inflammation, and a reduced need for medications. Overall, other studies found that immunotherapy can reduce the sneezing and wheezing of allergic rhinitis by 80 percent and the need for allergy medications by 88 percent.

The biggest drawback to immunotherapy is the needle and treatment may require well over 100 shots. That's why a growing number of physicians in Europe have turned to **sublingual-swallow immunotherapy** (SLIT). Of 18 double blind, placebo-controlled clinical trials in the past 15 years, 16 confirmed the effectiveness of SLIT in reducing allergy symptoms triggered by grass pollen, house dust mites, or birch pollen. Other studies found that drops were as effective as shots, that patients liked them better and that they were safer than shots. In November 2003, the World Health Organization supported the use of SLIT for certain patients, particularly those who don't take their meds, refuse injections and/or have systemic reaction to injection immunotherapy. SLIT is under investigation in the United States and may be available in the near future. A report from the Mayo Clinic on 79,593 immunotherapy injections over a 10-year period showed the incidence of adverse reactions was less than 2/10 of 1 percent. Most were mild and responded to immediate medical treatment. There no fatalities during the study. Between 1985 and 1993 when an estimated 52.3 million immunotherapy shots were given, 35 deaths occurred, making the incidence of fatality less than 1 per million (Berger & Gordon '04: 105-107).

IV.6 Heart Medicine

Above all else, guard your heart, for it is the wellspring of life (Proverbs 4:23). Heart attack is a leading killer of both men and women in the United States. Of the estimated 50 million, 166 out of 1,000, with unhealthy levels of lipoprotein in their blood, 7 million Americans feel angina (23 in 1,000), 1.5 million will suffer an acute myocardial infarction (heart attack) for which 550,000

will be hospitalized (1.8 out of 1,000) and of the 2.4 million people who died in 2004, 666,000 died from heart disease (2.2 out of 1,000) and 150,000 from stroke. Only severe ischemia, with blood flow of 10% or less of normal, lasting at least 20 to 40 minutes or longer leads to irreversible damage (necrosis) of some cardiac myocytes. After the onset of an acute ischemic event, sudden cardiac death (SCD) may occur within 1 to 2 hours in 20% of patients (Schoen '94: 528, 537 539). The AMA Code of Medical Ethics states "The right of self-decision can be effectively exercised only if the patient possesses enough information to enable an intelligent choice" (Graveline '04: vi). To treat heart disease, fresh air, fabric, vegan diet and athletic level of cardiorespiratory exercise are essential, antibiotics cure endocarditis, statins reduce cholesterol and hawthorn is the supreme herb for the heart. 90 percent of heart disease involves the deposition of fat in coronary artery disease, as the result of excessive lipid consumption, insufficient exercise, carbon monoxide and/or cardiotoxin. Besides trans-fats, an invisible dye can contaminate the laundry making therapeutic cardiovascular exercise counterproductive to lethal, because it is activated by water, ie. Sweat, and the heart is stressed by the exertion. Carbon monoxide also causes angina. Treatment of heart disease involves, fresh air, fabric and vegan diet, no trans-fats; antibiotics cure endocarditis, statins reduce cholesterol, Hawthorn is the supreme herb for the heart, sage help digest fats. Patients must run the minimum three miles of the Marine Corp Physical Fitness Test (PFT) daily rather than 1 ½ mile run perpetuating the struggle with the Army Weight for Height Chart. Endocarditis is most frequently caused by *Streptococcus pyogenes* and can be caused by *Bactroides fragilis* treated with metronidazole, and most dangerously by *Staphylococcus aureus* with a 50% mortality on hospital admission better treated with doxycycline or clindamycin for pregnant women and children under age 8. Do not let the blood be contaminated by fatty foods, fat should normally be less than 30% of caloric intake, whereas unlike other macronutrients, carbohydrates and protein, that are detoxified by the liver, fats go directly to the heart via the little-understood lymphatic system (Enders '15: 50-54). To prevent chest pain it is important to limit fat consumption according to the guidelines provided by the American Heart Association. During chest pain from heart disease it is essential to completely eliminate all fat from the diet. Though the strong eat whatever they want, the weak eat only vegetables (Romans 14:2). Test your servants for 10 days. Give us nothing but vegetables to eat and water to drink (Daniel 1:12).

Bacterial endocarditis results from actual colonization of the endocardium by infectious agents through the interstitial capillary bed beneath the endothelium and the blood within the endocardial lumen. *Chronic angina pectoris* that doesn't fully go away after a day or two, week, month or year, usually happens when dead heart muscle from a myocardial infarction (heart attack) becomes infected with pyogenic organisms usually *Streptococcus pyogenes*, in about 50% of cases of endocarditis. *S. pyogenes* causes strep throat and rheumatic fever in children and **rheumatic heart disease** in adults with necrotic heart attack damaged cardiac muscle that doesn't go away like most infections, attacks the valves, creates huge septic vegetations over the myocardium and burdens the vegetarian patient with a 25 percent chance of dying over 10 years, if untreated by antibiotics. Untreated or drug resistant infection is the main reason that the body doesn't heal and acute injury progresses to chronic disease in six months, generally. Some streptococcal illnesses of the heart may last up to 6 weeks without antibiotics and can be severe. Organisms most commonly recovered from such infections are *Streptococcus sanguis*, *S. faecalis*, and in heroin addicts, also *Candida parapsilosis*. It has been reported that 90% of plaques contain *Chlamydia pneumoniae*. Antibiotics may be necessary to treat bacterial endocarditis, usually caused by β-hemolytic strains of pneumococcal bacteria. Penicillin is generally the most effective treatment for *Streptococcus* spp. but some people have a life threatening allergy to penicillin, and any antibiotic will work. Most of the bacterial species that

infect the heart are easily treated with a five day course of any twice a day broad-spectrum antibiotic. Doxycycline, the once a day antibiotic, that permanently yellows the teeth of children under 8 and metronidazole (Flagyl ER) are essential to solving the problem of **antibiotic resistance.** When pyogenic organisms such as *Staphylococcus aureus* and *Bactroides fragiles* are involved, acute bacterial endocarditis may result that does not respond to most antibiotic drugs. *Staphylococcus aureus* is an extremely dangerous heart infection with 50% mortality when admitted to the hospital, it is best treated with doxycycline or clindamycine (Cleocin) for pregnant women and children under age 8. *Bactroides fragilis*, from as far away as the large intestine, can be involved, and there is a connection between diet and the heart involving rotten food, rather than just hyperlipidemia. The fecal coliform *Bactroides fragiles and Peptostreptococcus,* which may infect the heart, resist any antibiotic but metronidazole (Flagyl ER). Viruses and fungi are rare in the heart and many bacterial diseases are kind to the heart although they devastate other parts of the anatomy (Elvin-Lewis ’77: 178, 28).

Angina pectoris pain occurs when myocardial oxygen consumption exceeds the capacity of the coronary system to deliver oxygen. Papaverine, from *Papaver somniferum* and aminophylline from *Camellia sinensis* (**black and green tea**) relax smooth muscles and used in the treatment of *angina pectoris* (Elvin-Lewis ’77: 178). It is probably a good idea to drink tea (*Camellia sinensi)* instead of coffee. Coronary vasodilators act directly but non-selectively on smooth muscles to produce relaxation without paralyzing the muscle. **Nitrates and nitrites** are somewhat effective but have not been shown to improve life expectancy. Although they have been shown to improve exercise tolerance and the quality of life of patients with coronary artery disease enabling a full recovery in many cases, there is no evidence that nitrates improve mortality as a result of ischemic heart disease. The usual maintenance dose of isosorbide dinitrate is 30 mg for the immediate-release preparation and 40 mg for the extended-release preparation. All nitrates cause rapid development of tolerance, but a dosing interval at 7 am, noon, 5 pm and a drug free overnight interval can reverse the tolerance that develops during the day. Transdermal nitroglycerin preparations, are being replaced with extended-release oral preparations. Unfortunately, although some patients are able to exercise and make a recovery nitrates and nitrites do not show the statistical improvement in longevity and resistance to heart attacks exhibited by statins and anti-platelet drugs such as Aspirin (Heger et al '04: 278).

Five main kinds of **drug treatments** exist for adverse lipid profiles: (1) bile-acid sequestrant resins such as cholestyramine and colestipol, which work by binding bile salts, which are made from cholesterol, in the bowel, so they are eliminated); (2) exetimibe, which reduces absorption of cholesterol; (3) niacin (a B vitamin); (4) fibrate drugs such as gemfibrozil, bezafibrate, and fenofibrate; and the (5) statin drugs, which inhibit cholesterol synthesis in the liver by inhibiting an enzyme, HMG CoA reductase – often called HMG CoA Reductase Inhibitors, called statins such as: Lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, and rosuvastatin. The easiest and cheapest cholesterol lowering treatment is **Niacin** B vitamin 100 mg, or half a 5000 mg tablet three times a day after meals, and then increase it about every third day until you are up to 500 mg three times a day. Some people take a gram (1,000 mg) or more three times a day, but 500 mg three times a day will achieve most of the benefit with less risk of gout and diabetes. For many individuals with osteoarthritis, best treated with ibuprofen, or painful backs and necks, acetylsalicylic acid (ASA, Aspirin) or acetaminophen (Tylenol) may be more effective than other NSAIDs. People with gout may find allopurinol a useful preventive and colchicine, a useful treatment, rather than relying on NSAIDs for prevention. Colchicine, which can be used even in kidney failure and heart failure, is an old remedy (Spence '05: 113, 115, 123, 124).

Statin drugs, which reduce blood cholesterol levels by inhibiting a key enzyme involved in the biosynthesis of cholesterol, reduce heart attacks by 40 percent in six years, or better. They also reduce stroke in individuals with coronary disease by about 30 percent. The risk of a significant adverse reaction from a cholesterol-lowering drug is about 1:1,000 and that risk can be virtually eliminated by having a blood test to measure the blood levels of enzymes from the muscles and liver; if a problem shows up and you stop the drug, the problem will almost always clear up, unless the blood test was done too late A risk of 1: 1,000 is 0.1 percent; subtract that from 40 percent and you still have a net benefit of 39.99 percent – in other words, the benefit outweigh the risk by about 400 to 1. The risk of a serious adverse effect from the drug is about one in a thousand, so the balance is strongly in favor of staying on the medication unless there is strong evidence that the medication is causing the symptoms. Most people tolerate statins very well; only about 1 in 15,000 will have significant liver problems which go away after stopping the drug. About 1-3 percent of people will have an increase in blood levels of liver enzymes, reflecting not liver damage, but a change in enzyme kinetics. Occasionally, diarrhea is a problem. In addition to large studies that show a decrease in coronary events with use of statins, a number of smaller studies show that these drugs result in improvement of the coronary arteries in some individuals and slow down the rate at which they get worse in virtually all individuals. Ultrasound studies of the carotid arteries also show regression of atherosclerosis with effective LD cholesterol reduction and increases in HDL. Lowering cholesterol makes plaques less likely to rupture and improves the function of the endothelium (the lining of the artery) (Spence '05: 112, 117).

Cholesterol, discovered as a major constituent of gallstones, was identified in 1775 as the first known steroid. After decades of concentrating on cholesterol as the supposed culprit in arteriosclerosis the development of statin drugs was almost inevitable. Statin drugs Lipitor, Mevacor, Zocor, Pravachol, or the ill-fated Baycol, all use HMG-CoA reductase enzyme inhibitors to halt the cholesterol synthetic pathway. HMG-CoA reductase step is a natural control point for cholesterol synthesis since the reaction was not reversible and it was the slowest step of the entire cholesterol pathway. The Baycol trial held in Corpus Christi, Texas, studied the side effects of statin drugs ending in an injunction against the drug. *Monascus purpureus*, red yeast rice, is a natural HMG-CoA inhibitor that has been used to ferment rice into wine and as both a spice and preservative (Graveline ’04: 39, 40, 43, 41). A 1994 study called the Scandinavian Simvastatin Survival Study (also called 4S) found that lowering cholesterol can prevent heart attacks and reduce death in men and women who already have heart disease and high cholesterol. For over 5 years, more than 4,400 patients with heart disease and total cholesterol levels of 213 mg/dL to 310 mg/dL were given either a cholesterol-lowering drug or a placebo (a dummy pill that looks exactly like the medication). The drug they were given is known as a statin, and it reduced total cholesterol levels by 25 percent and LDL-cholesterol levels by 35 percent. The study found that in those receiving statin, deaths from heart disease were reduced by 42 percent, the chance of having a nonfatal heart attack was reduced by 37 percent, and the need for bypass surgery or angioplasty was reduced by 37 percent. A very important finding is that deaths from causes other than cardiovascular disease were not increased, and so the 42 percent reduction in heart disease deaths resulted in a 30 percent drop in overall deaths from all causes (Sanders ’08: 28).

In 1996 the results of the Cholesterol and Recurrent Events (CARE) Study also showed the benefits of cholesterol lowering in heart disease patients. This study reported that even in patients with seemingly normal cholesterol levels (average of 209 mg/dL), cholesterol lowering with a statin drug lowered the risk of having another heart attack or dying by 24 percent. A study

published in 1998, the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) study, examined the effects of cholesterol lowering in people with CHD (those who had already experienced a heart attack or had been hospitalized for angina) and who had relatively average cholesterol levels. The LIPID study used a statin drug to lower cholesterol levels in the treatment group. All study participants were counseled about following a cholesterol-lowering diet. The LIPID results showed that a drop of 18 percent in total cholesterol and 25 percent in LDL-cholesterol produced a 24 percent decrease in deaths from CHD among the treatment group compared with the control group (Sanders '08: 28, 29). A recent study of statin drugs in British patients with established, severe arterial damage and were considered at high risk of heart disease. Although a third of these patients had cholesterol levels that were below the level recommended for statin treatment by US guidelines, they like others in the study, lowered their risk for heart attack and stroke by a third if they took Zocor, the statin used in the study. Present knowledge, however, suggests caution against the tendency for broader use of statin drugs (Graveline '04: 72, i)

The Scandinavian simvastatin survival study, CARE (Cholesterol and Recurrent Events trial) ECEL, the WOSCOPS (West of Scotland Coronary Prevention trial) and the AFCAPS/TEXCAPS (Air Force/Texas Coronary Atherosclerosis Prevention study) have failed to show significant statin benefit. Every report of stroke or heart attack risk reduction is effectively neutralized by corresponding increases in all cause mortality or cancer death risk. Recent large-scale prospective trials of statin therapy to lower plasma cholesterol have shown no benefit to all-cause mortality, and several studies show that statin therapy slightly increases the incidence of cancer mortality, offsetting the slight improvement in mortality from vascular disease. Defenders of Lipitor, Zocor, Pravachol, Mevacor and Lescol point out that statins reduce the risks of heart attacks, strokes and cardiovascular deaths. This is true, but helping people also means reducing the risks of serious side effects like chronic muscle pain, muscle injury, liver injury, kidney injury, psychological changes, cognitive impairments, global amnesia and cancer. After years of using statins without difficulty, 1 in 2,000 people develop nerve injuries that can be severe and permanent. With twenty million Americans taking statins, that's 10,000 people per year (Graveline '04: i, v). Statins should probably be discontinued in cases of cancer, dementia, and muscle which is the most common reason given for discontinuing statins. Although recovery is not given as a reason for discontinuing statin use, the $2 per pill price surely limits its use to acute hyperlipidemia following exposure to a cardiac glycoside or fatty meal.

Statins are drugs that inhibit cholesterol synthesis in the liver by inhibiting the enzyme, HMG-CoA reductase. There most common side effect is aching and cramps in the muscles, caused by depletion of ubiquinone, also called co-enzyme Q_{10} (CoQ_{10}). This happens because inhibiting the liver enzyme HMG-CoA reductase lowers not only the cholesterol levels but also the levels of all the metabolites along the pathway, including one that is used to make CoQ_{10}. Biosynthesized in the mitochondria, the tiny powerhouse of the cell that is responsible for cellular respiration and energy – ubiquinone – functions as a vital and necessary electron carrier to our ultimate respiratory enzyme, cytochrome oxidase. Because of the extremely high energy demands of the heart, this organ is usually the first to feel statin associated CoQ_{10} depletion as cardiomyopathy and congestive heart failure. CoQ_{10} supplementation is highly recommended for all patients on statin drugs, as well as limiting doses or stopping statins (Graveline '04: 42).
The mitochondria (the metabolic engines of the cells) in the muscles need CoQ_{10} to work properly, so its depletion can cause muscle cramps and aching. People who develop muscle problems with statins have a genetic predisposition because of metabolic abnormalities that

affect the function of the mitochondria. Supplements of CoQ10 reduce muscle pain from statins taken about 60-120 mg twice daily. Another approach is to reduce the dose of statin and add ezetimibe, a drug that lowers cholesterol by blocking its absorption in the lining of the intestine. Ezetimibe doesn't affect the muscles, but it helps the statin work eight times better, so a much lower dose of statin will be effective (Spence '05: 153, 154).

Homocysteine is an amino acid (protein building block) produced in the body that may increase blood clotting and irritate blood vessels, leading to blockages in the arteries. High levels homocystine (two homocysteine molecules attached) in the blood and excreted in the urine (homocystinuria) have been identified in seizures, premature strokes, abnormalities of the lens of the eye and development problems. Homocystinuria is due to an inherited deficiency in the enzyme that converts homocyteine to another amino acid, cystathionine. To do its work, that enzyme needs vitamin B_6 also called pyridoxine, as a cofactor. High blood levels of total homocystein (tHcy, which mens the total of three variants of homocysteine in the blood) affect about 20 percent of North Americans, and about half of individuals who have artery problems. Homocysteine creates problems by producing free radicals such as hydrogen peroxide and by damagaing the inner lining of the artery (the endothelium). Free radicals are chemically active compounds that, among other negative reactions, oxidize LDL cholesterol; homocysteine also consumes nitric oxide, the protective substance produced by the artery wall. High blood levels of homocysteine therefore increase the activatin of platelets and blood clotting, cause constriction of the arteries, and cause proliferation of smooth muscle cells in the artery wall called atherosclerosis, blockage in the arteries. **Folic acid** 2.5 mg daily will normalize blood levels of homocysteine in about half the cases; a combination of folic acid 1 mg, vitamin B_6 10 mg, and vitamin B_{12} 1 mg (1000 mcg) will normalize levels in more than 95 percent of cases. A high dose of B_{12} is needed. Blood levels of B_{12} should be above 300 pmol/L. In some cases it is necessary to add a fourth supplement called betaine, and vitamins are not as effective for individuals with kidney failure. Overnight daily dialysis is more effective at lowering homocysteine than routine dialysis three times a week, and sulfur containing compounds called thiols may be useful (Spence '05: 157, 158).

Besides, vegan diet, exercise and hygiene, statin cholesterol reducing drugs are the best and least controversial option for people struggling with hyperlipidemia and chest pain from atherosclerosis, 90% of heart disease. There are three fundamental problems with the usual medical treatment of arrhythmias and congestive heart failure, whereby cardiac drugs are reported the second leading cause of fatal drug overdose by the National Poison Control Center. First, Digitalis at 70% of toxic dose, and not Hawthorn the supreme herb for the heart, has been incorporated into the hospital treatment of congestive heart failure. Second, high blood pressure medicine should not be used to treat certain arrhythmias and other rhythm disorders because they are misinterpreting the dangerous cardiac side-effects of hypertensive drugs. Third, Hawthorn is contraindicated for use with digitalis or hypertensive medicines because it impairs the blood pressure moderating effects of the heart. Right treatment with Hawthorn therefore requires exclusion of the vast majority of the drugs used for the cardiac complications of heart failure. Congestive heart failure is best treated by naturopaths, who offer cures in six months to a year, where the prognosis is otherwise five years. The FDA required warning for Digitalis and related cardiotonic drugs for human use in oral dosage forms, states "Digitalis alone or with other drugs has been used in the treatment of obesity. This use of digoxin or other digitalis glycosides is unwarranted. Moreover, since they may cause potentially fatal arrhythmias or other adverse effects, the use of these drugs in the treatment of obesity is dangerous" to which could be appended, "Hawthorne is the supreme herb for the heart" under 21CFR§201.317.

Hawthorne (*Crataegus laevigata*) is considered the herb supreme for the heart (Elvin-Lewis ’77: 194)(Gladstar '12). The berries are tasty and often enjoyed in syrups, jams and jellies. They also make good medicine, as do the flower and leaf. The berries, leaves and flowers are rich in bioflavonoids, vitamin C, antioxidants, choline, acetylcholine, quercitin, triterpenoids, cretegin, rutin and procanidins, which feed and tone the heart. Hawthorne works in part by dilating the arteries and veins, enabling blood to flow more freely and releasing cardiovascular constrictions and blockages. It strengthens the heart muscle while helping to normalize and regulate blood pressure. It also helps maintain healthy cholesterol levels. Hawthorne is outstanding both to prevent heart problems and to treat high or low blood pressure, heart disease, edema, angina and heart arrhythmia. Hawthorn doesn’t store in the body and isn’t accumulative in action, it’s important to take on a regular basis if using as a heart tonic. Hawthorne also helps to stabilize collagen and support the health and repair of ligaments, tendons and muscles. Hawthorne strengthens capillaries, useful for bruises. Combine with lemon balm, the milky tops of oats and St. John’s wort for a wonderful tea that helps alleviate grief. Powder dried Hawthorne berries with cinnamon, ginger and cardamom powder and sprinkle on boiled or steamed vegetables to boost flavor and treat heartache. The trees are hardy and can live 200 years. Some species are short and scraggly, some grow as thick hedgerows in the Irish, English and Italian countryside, all have thorns. Hawthorne does well in full-sun or partial shade at the edge of a forest or wooded area. It prefers rich, alkaline soil. Several varieties can be found at nurseries but hawthorne self-sows readily, and it’s easy to dig up the young saplings usually found in abundance beneath the mother tree to transplant to a new location (Gladstar '12).

Digitalis purpurea, or **foxglove** had been used by illiterate farmers and housewives in England and on the Continent for centuries to treat congestive heart failure and arrhythmia. *Digitalis* slows the wildly beating ventricles to a normal level by blocking or delaying the conduction of the electric impulse through the atrioventricular node. By increasing the heart stoke, *Digitalis* increases the amount of blood being oxygenated by the lungs, as well as the blood in general circulation, by as much as 30% with each beat. Because of this improved action of the heart and circulation, the drug tends to improve renal secretion to relieve edema, and to aid the cardiac muscle to compensate for mechanical defects or structural lesions. More than 3 million heart patients in the United States routinely use the glycoside digoxin from *D. lanata*, and this is but one of six glycosides from *Digitalis* prescribed today. *Digitalis* whole leaf, digitoxin, digoxin, lanatoside C, acetyldigitoxin and deslanoside. Digitoxin and digoxin are not only listed toxic cardiac glycosides but are sold under those names. Since the effective dose may be as high as 70% of the toxic dose, administration must be done carefully on an individual basis. Various Digitalis glycosides, all taken orally, include *D. purpurea* whole powdered leaf, containing a large number of glycosides of which about 30 are identified besides the medicinally important digitoxin, gitaloxin, and gitoxin. The average concentration of these three glycosides in a leaf is 0.16%. Recently it has been recommended the use of whole leaf preparations over isolated glycosides. Cardiac glycosides bring only temporary relief and must be administered orally during the whole course of the disease. Adverse reactions are found in about 20% of hospitalized patients receiving *Digitalis* preparations. Without foxglove, or other plants producing cardiotonic compounds, congestive heart failure and death would occur inevitably, and perhaps quickly. More than 3 million Americans take an extract of foxglove daily (Elvin-Lewis '77: 184, 186, 193, 194). Prescription cardiac drugs, other than statins which reduce the risk of dying from heart attack by 30% and stroke by 50%, but including digitalis and antihypertensive drugs which are rattled off as heart medicine by every nursing school graduate, the ACE inhibitor, Angiotensin Receptor Blocker (ARB), **A**lpha, **B**eta and **C**alcium channel

blockers, are consistently the second leading cause of fatal drug overdose reported by the annual report of the National Association of Poison Control Centers (Bronstein '10-11).

Cardiovascular and Hypertensive Drugs

Drug Class	Generic (Trade) Name
Vasodilators	
Nitrates and Nitrites	Nitroglycerin, Isosorbide dinitrate, and Isosorbide mononitrate
Digitalis drugs	Digitoxin (Crystodigin), Digoxin (Lanoxin)
Peripheral vasodilator	Hydralazine (Apresoline), Terazosin (Hytrin)
Antiplatelet agents	
Cyclo-oxygenase inhibitor	Acetylsalicylic acid (ASA; Aspirin)
Thienopyridines	Clopidogrel (Plavix), Prasugrel (Effient), Ticlopidine (Ticlid),
Phosphodiesterase inhibitor	Dipyridamole (Persantine)
Combination	Dipyridamole/ASA (Aggrenox)
Anticoagulant	Warfarin (Coumadin), Heparin (Heparin)
Low-molecular weight heparin	Enoxaparin (Lovenox), Dalteparin (Fragmin), Nadroparin (Fraxiparine), Danaparoid (Orgaran), Tinzaparin (Innohep), Fondaparinux (Arixtra)
Lipid lowering	
Statins (cholesterol lowering)	Atorvastatin (Lipitor), Fluvastatin (Lescol), Lovastatin (Mevacor), Rosuvastatin (Crestor), Pravastatin (Pravachol), Simvastatin (Zocor)
Cholesterol absorption inhibitor	Ezetimibe (Ezetrol, Ezetia)
Fibrates	Gemfibrozil (Lopid), Bezafibrate (Bezalip), Fenofibrate (Lipidil)
Bile-acid sequestrant	Cholestyrmaine (Questran), Colestipol (Colestid), Psyllium mucilloid (Metamucil)
Niacin, slow-release	Niacin SR (Ezetrol, Ezetia)
Folate vitamin B_9 (homocysteine lowering)	
Antihypertensives (to reduce blood pressure)	
Rauwolfia alkaloids	Rauwolfia serpentine, Rauwolfemms, Reserpidine Oral (Serpasil, Serpalan, Harmonyl, Novoreserpine, Raudixin, Rauval, Rauverid, Reserfia, Serpalan, Serpasil, Wolfina), Deserpidine and Hydrochlorothiazide or Methyclothiazide (Demi-Regroton, Diupres, Diurigen with Reserpine, Diutensen-R, Dureticyl, Enduronyl, Enduronyl Forte, Hydropres, Oreticyl, Oreticyl Forte, Rauzide, Regroton)
Diuretic (to reduce water retention)	Hydrochlorothiazide (HCTZ) (Hydrodiuril, etc.), Amiloride (Midamor), Chlorothalidone (Hygroton), Furosemide (Lasix), Indapamide (Lozide), Spironolactone (Aldactone)
Angiotensin receptor blocker (ARB)	Candesartan (Atacand), Eposartan (Teveten), Irbesartan (Avapro), Telmisartan (Micardis), Valsartan (Diovan), Losartan (Cozar)

ARB plus diuretic	Candesartan/HCTZ (Atacand Plus), Eposartan/HCTZ (Tevetan Plus), Irbesartan/HCTZ (Avalide), Telmisartan/HCTZ (Micardis Plus), Valsartan/HCTZ (Diovan Plus)
Diuretic combination	Amiloride/HCTZ (Moduret), Atenolol/chlorothalidone (Tenoretic), Ethacrynic acid (Edecrine), Spironolactone/HCTZ (Aldactazide), Triamterene/HCTZ (Dyazide)
ACE inhibitor	Captopril (Capoten), Cilazapril (Inhibace), Enalapril (Vasotec), Fosinopril (Monopril), Lisinopril (Zestril), Quinapril (Accupril), Ramipril (Altace), Trandolapril (Mavik)
ACE inhibitor plus diuretic	Enalapril/HCTZ (Vasoretic), Lisinpril/HCTZ (Zestoretic), Perindopril/indapamide (Coversyl Plus), Quinapril/HCTZ (Accuretic)
Alpha blocker (to block adrenaline receptors that constrict the arteries, called alpha receptors)	Doxazosin (Cardura), Prazosin (Minipress)
Beta blocker	Acebutolol (Monitan), Atenolol (Tenormin), Metoprolol (Lopressor), Nadolol (Corgard), Pindolol (Visken), Propranolol (Inderal), Timolol (Blocadren)
Beta blocker plus diuretic	Atenolol-chlorthalidone (Tenoretic), Pindolol/HCTZ (viskazide)
Calcium channel blockers (to reduce blood pressure, heart pain and arrhythmias)	Amlodipine (Norvasc), Felodipine (Plendil), Nifedipine (Adalat), Nicardipine (Cardene), Verapamil (Isoptin, Chronovera)
Anti-arrhythmic	Quinidine Glutonate, Allocryptopine
Wegener's granulomatosis and Polyarteritis nodosa (PAN)	Corticosteroids (prednisone) and cyclophosphamide IV
Kawasawki Disease	Gamma globulin IV administered with aspirin

Source: Spence '05: xvii – xix

Drugs called **anticoagulants**, such as warfarin (Coumadin, and other names), which reduce the production of clotting proteins, will reduce stroke risk by about half over one year in patients with atrial fibrillation (rapid, irregular heart contractions), and in other cases where clots are forming in the heart or veins and embolizing to the brain. Other drugs that reduce clotting by interfering with blood platelets, anti-platelet agents such as Aspirin, (acetylsalicylic acid (ASA), Plavix (clopidogrel) or combination of ASA/dipyridamole (marketed as Aggrenox) – will reduce ischemic stroke risk by about 25-30 percent in three to four years, but these will prevent only strokes due to embolization of platelet aggregates, and would very likely be fatal in a hemmorhagic stroke usually caused by high blood pressure. When administered within three hours of a stroke tissue plasminogen activator (tPA) reduces the chances of permanent disability by 30% (Spence '05: X). Heparin, a natural anticoagulant in blood, is commercially available from animal sources, especially beef lung. Hemorrhage due to overdose of anticoagulants may be controlled quickly by the administration of vitamin K, found in green leafy vegetables (Elvin-Lewis ’77: 192).

At any given time, the blood of an average adult carries over a trillion **platelets** throughout his or her body, each one surviving for about a week before being replenished by new platelets arising in the marrow. Platelets are like microscopic circulating band-aids, constantly looking for leaks in the vascular system and then instantaneously plugging these bleeding sites by sticking to the wound (a process called adhesion), becoming activated locally, and then attracting other circulating platelets to build an impermeable clump (a process called aggregation) at the exact point of damage. This protective mechanism, which is a desirable function of platelets, is called hemostasis. But under some conditions platelets can become harmful, causing plugs to form where there is no bleeding and they are not needed. This typically happens in arteries that have become diseased with atherosclerosis, a condition in which deposits of fat or plaque collect and harden in the arteries, blocking the normal flow of blood. Platelets can stick to atherosclerotic plaques in the coronary and brain arteries and obstruct, or occlude, these vessels causing heart attacks and strokes. This undesirable, pathological process is called thrombosis (Schafer '08).

There are two classes of **antithrombotic drugs**: anticoagulants and antiplatelet drugs. Anticoagulants slow down clotting, thereby reducing fibrin formation and preventing clots from forming and growing. Antiplatelet agents prevent platelets from clumping and also prevent clots from forming and growing. The first antiplatelet drug was aspirin, which has been used to relieve pain for more than 100 years. In the mid-1960s, scientists showed that aspirin prevented platelets from clumping, and subsequent clinical trials showed that it reduces the risk of stroke and heart attack. In 1980, researchers showed that aspirin in very low doses (much lower than that required to relieve a headache) blocked the production of a chemical in platelets that is required for platelet clumping. Antithrombotic therapy has had an enormous impact in several significant ways. Heparin has made bypass surgery and dialysis possible by blocking clotting in external tubing. Antithrombotic therapy has reduced the risk of blood clots in leg veins (also known as deep-vein thrombosis or DVT), a condition that can lead to death from pulmonary embolism (a clot that blocks an artery to the lungs) by more than 70 percent. And most importantly, it has markedly reduced death from heart attacks, the risk of stroke in people with heart irregularities (atrial fibrillation), and the risk of major stroke in patients with mini-strokes (Hirsh '08).

It was first noted more than 50 years ago by a private practitioner that **aspirin**, which had been used in its native form since antiquity to treat fever and pain, was remarkably able to protect individuals from heart attacks. The ability of aspirin to prevent cardiovascular disease was subsequently found by hematologists to be due to its effects on platelets. Beginning in the mid-1960s, several investigators conducted basic hematology research to clearly identify the precise mechanism by which aspirin inhibits platelet activation and aggregation. Aspirin thus became the first effective antiplatelet drug. It is still in wide use today to prevent cardiovascular complications that are caused by pathological platelet occlusion of atherosclerotic arteries.
the next clinically effective antiplatelet agent, a monoclonal antibody against the platelet membrane protein that initiates aggregation (the glycoprotein (GP) IIb/IIIa complex). This drug (abciximab) was approved by the FDA in 1994 to reduce the thrombotic complications of coronary angioplasty. Other GP IIb/IIIa receptor antagonists soon followed, and this class of drugs is now in wide use to also treat acute coronary syndromes. Yet another class of antiplatelet drugs called ADP receptor antagonists (ticlopidine, clopidogrel) were first found in 1998 to greatly reduce the occlusion of coronary stents (devices placed inside an atherosclerotic artery to hold it open and prevent further narrowing), a particularly thrombosis-provoking intervention. These new antiplatelet drugs may have wider application in the prevention of vascular disease by improving on or adding to the beneficial actions of aspirin. Excessive interference with platelet

function with any of these antiplatelet agents carries with it the risk of causing the opposite of thrombosis, namely bleeding complications (Schafer '08).

The **anticoagulants** heparin and dicumarol were discovered by chance, long before we understood how they worked. Heparin was first discovered in 1916 by a medical student at The Johns Hopkins University who was investigating a clotting product from extracts of dog liver and heart. In 1939, dicumarol (the precursor to warfarin) was extracted by a biochemist at the University of Wisconsin from moldy clover brought to him by a farmer whose prize bull had bled to death after eating the clover. Both of these anticoagulants have been used effectively to prevent clots since 1940. These drugs produce a highly variable anticoagulant effect in patients, requiring their effect to be measured by special blood tests and their dose adjusted according to the results. Heparin acts immediately and is given intravenously (through the veins). Warfarin is swallowed in tablet form, but its anticoagulant effect is delayed for days. Therefore, until recently, patients requiring anticoagulants who were admitted to a hospital were started on a heparin infusion and were then discharged from the hospital after five to seven days on warfarin (Hirsh '08).

In the 1970s, three different groups of researchers in Stockholm, London, and Hamilton, Ontario, began work on **low-molecular-weight heparin** (LMWH). LMWH is produced by chemically splitting heparin into one-third of its original size. It has fewer side effects than heparin and produces a more predictable anticoagulant response. Because LMWH is injected subcutaneously (under the skin) in a fixed dose without the need for anticoagulant monitoring, patients can now be treated at home instead of at the hospital. The first successful synthetic anticoagulants were fondaparinux and bivalirudin. Bivalirudin, a synthetic molecule based on the structure of hirudin (the anti-clotting substance found in leeches), is an effective treatment for patients with heart attacks. Fondaparinux is a small molecule whose structure is based on the active component of the much larger LMWH and heparin molecules. It has advantages over LMWH and heparin and has recently been approved by the FDA. Newer designer drugs that target single clotting factors and that can be taken by mouth are undergoing clinical testing. If successful, we will have safer and more convenient replacements for warfarin, the only oral anticoagulant available for more than 60 years (Hirsh '08).

The **Sickle Cell Anemia** Control Act of 1972, allotted government health funds for screening, research, and treatment programs. As scientific progress and technology improved, new treatment regimens evolved for sickle cell disease patients. The Prophylactic Penicillin Study (PROPS) found that giving penicillin, an antibiotic, when patients were not sick could prevent death related to serious infections in sickle cell disease. Later, the Multicenter Bone Marrow Transplant Study demonstrated that 84 percent of children with sickle cell disease who received a bone marrow transplant from a matched relative could be cured. Finally, in the mid-1990s, the U.S. Food and Drug Administration approved a new therapy called hydroxyurea as a treatment to decrease complications of the disease. Hydroxyurea works in part by stimulating the body to resume production of fetal hemoglobin (hemoglobin F), a normal hemoglobin in the fetus that prevents sickling. In the 1960s, doctors treating **thalassemia** patients started to transfuse them with fresh red blood cells every month. This alleviated most of the childhood symptoms and led to a major improvement in survival. It is still used as a treatment today. However, since blood contains large amounts of iron, which the body cannot eliminate naturally, most patients died in their teenage years from damage caused by too much iron. Researchers later found that excess iron could be removed from the body by treatment with a drug called desferoxamine. This drug prevented iron-induced heart disease and helped patients live much longer. Recently, two oral

drugs have become available to remove iron. They have dramatically improved the quality of life of patients with iron overload from transfusions for thalassemia (Vichinsky '08).

A century ago, two French investigators reported that small amounts of plasma from anemic rabbits injected into normal animals caused an increase in red blood cell production (**erythropoiesis**) within a few hours. They referred to this activity as **hemopoietine.** Over time, as investigators became more convinced that this red-blood-cell stimulating activity was caused by a single protein in the blood plasma, they gave it a variety of names – erythropoietic-stimulating activity, erythropoietic-stimulating factor, and, ultimately, "erythropoietin." Refining the work of the French scientists in the 1950s and 60s, American investigators conclusively showed that a hormone stimulated red cell production, and that the kidneys were the primary source of erythropoietin, and that low oxygen was the main driver of erythropoietin production. Soon, researchers found that patients with anemia responded by increasing their levels of erythropoietin to stimulate increased red blood cell production. Patients who required an increase in red blood cells in order to make up for low oxygen levels in the blood (such as patients with lung disease living at high altitudes, or smoking more than a pack of cigarettes a day) also had elevated erythropoietin levels. In the early 1960s came the development of **hemodialysis**, a method of removing waste products from the blood when the kidneys are unable to perform this function, to sustain the lives of patients with end-stage kidney disease. As a result of this treatment advance, these patients were able to survive the underlying disease, but their damaged kidneys could no longer make erythropoietin, leaving them severely anemic and in desperate need of Epo therapy. In 1983, scientists discovered a method for mass producing a synthetic version of the hormone. Experiments were conducted to test the safety and effectiveness of the new drug, **Epo**, for treating anemia in patients with kidney failure. The results of these early clinical trials were dramatic. Patients who had been dependent on frequent blood transfusions were able to increase their red blood cell levels to near-normal within just a few weeks of starting therapy. Patients' appetites returned, and they resumed their active lives. It was the convergence of two technologies – long-term dialysis and molecular biology – that set the stage for anemia management in this group of patients. Since then, millions of patients worldwide have benefited from Epo therapy (Adamsom '08).

Blood transfusions are the transfer of blood, its components, or products from one person (donor) into another person's bloodstream (recipient). Every year in the U.S., more than 20 million units of red blood cells, platelets, and plasma are transfused to treat hematologic conditions such as severe anemia, leukemia, and sickle cell disease. Transfusions have long been associated with some risk to patients. The HIV epidemic during the 1980s was a major cause of fear; regular transfusions, especially of clotting factor concentrates, spread the virus quickly and nearly undetected. That outbreak prompted the development of biovigilance or hemovigilance: tracing and tracking transfusion-related adverse events and incidents, both infectious and non-infectious, that affect blood donors and recipients. Another of the most significant issues complicating transfusion safety has been bacterial contamination of blood products, particularly of platelets. However, steps have been taken in the last decade to avoid, detect, and eliminate this complication through improved donor selection, specialized preparation of the arm before needle insertion, and special screening techniques. Blood is regularly tested for infectious disease transmission, particularly for viruses such as Hepatitis B and C, HIV, and West Nile Virus. Serum tests have been replaced by molecular testing called nucleic acid amplification testing (NAT), which finds active viruses in the donor's blood to determine infection risk. If an active virus is found, the donor unit is discarded. Experts anticipate that new methods, including new molecular and microarray testing, which can identify many infectious agents rapidly and

accurately, will replace or augment serum studies and NAT in the near future. Blood transfusion has never been safer from known infectious risk than it is today (Luban '08).

Potential post-transfusion reactions include transfusion-related lung injury (TRALI), during which the donor's immune antibodies cause breathing problems in the recipient; transfusion associated cardiac overload (TACO), which is swelling caused by the increased blood volume; and post-transfusion iron overload, which is a buildup of iron in the body, usually caused by multiple or regular transfusions. Immune reactions, which happen when the body's immune system is affected by the donor blood, also pose several risks to transfused patients. Alloimmunization occurs when the recipient develops an allergic reaction to the donor's red blood cells: transfusion-related immune modulation (TRIM) can lead to increased risk of infections and cancer recurrence, post-transfusion graft-versus-host disease (GVHD, when the donor's immune system attacks the recipient's blood cells), and microchimerism (when a small amount of donor blood persists in the recipient's body, causing ongoing low-grade GVHD). Removing white blood cells or radiating blood to prevent white blood cell growth can reduce the likelihood that the recipient will reject the donor blood. New techniques can isolate specialized cell populations from blood – most importantly, hematopoietic progenitor cells (HPCs) that are used for stem cell transplantation. Because HPCs are easier to extract and the process is safer for donors, HPC transplantation has replaced bone marrow transplantation for many cancers and other diseases. Researchers are also using umbilical cord stem cells (UCSCs) as a source of HPCs. UCSCs are collected and processed in a method similar to whole blood and are a rich resource for transplantation therapy in pediatric and some adult patients. In the future, these cells may be grown and expanded for clinical use. Furthermore, researchers have isolated specialized cell types other than HPCs that play an important role in cellular therapy because they can modify proliferation and immune responses during the engraftment of transplanted cells (Luban '08).

By the early 1980s, **human blood**, plasma, and plasma-derived products were discovered to be transmitting potentially deadly blood-borne viruses, including hepatitis viruses and HIV. Manufacturers of plasma-derived clotting factor concentrates attempted to kill these viruses with dry heat, solvent-detergent treatment, and pasteurization, with varying degrees of success. By 1985, most patients with hemophilia in the U.S. had been switched to heat-treated concentrates, but many had already been infected with HIV and a large percentage of them succumbed to it. Eventually better screening methods for blood donors were developed, improving the safety of donated plasma. Screening of donors for the hepatitis B virus was already in place, and in 1989 the hepatitis C virus (HCV) was isolated, allowing HCV antibody testing of donors to begin in 1990. HIV was identified in 1984, and by 1985 a blood test for HIV antibodies was instituted in blood and plasma collection facilities. The successful cloning of the factor VIII gene in 1984 was a major breakthrough, allowing production of recombinant human factor VIII (r factor VIII). Clinical trials in humans began three years later, and this was truly an exciting time, especially for families who had lost loved ones to AIDS. By 1992, two pharmaceutical companies had licensed factor VIII products for use in hemophilia A. Cloning of factor IX was first reported in 1982, and a licensed r factor IX product (BeneFIX) became available for people with hemophilia B in 1997. Other significant advances that have been made in recent years include treatment for patients with inhibitors (antibodies that inhibit or interfere with the function of factor VIII or factor IX) and prophylaxis (treatment to prevent disease). Inhibitor antibodies develop in approximately 30-35 percent of people with hemophilia A and 1-3 percent with hemophilia B. Now that we have safer clotting factor replacement products, preventive (prophylactic) treatment

has gained acceptance as a means to preserve normal joint and musculoskeletal function in boys and young men with hemophilia (Lucher '08).

Decade-old heart attack scars healed after being injected with stem cells from a patients' own bone marrow. So far, eight patients have received the experimental treatment in an ongoing clinical trial. All eight had suffered heart attacks an average of 5 1/2 years prior; one of the patients had his heart attack 11 years earlier. All had dangerously enlarged hearts, with areas of scar tissue from their heart attacks. The researchers harvested bone marrow progenitor cells from four patients and adult stem cells from another four patients. Using a catheter, they then injected the cells into the walls of the patients' hearts. Within three months, the scarred areas of the patients' hearts began to work again. About six months after treatment, and for a year later -- the length of the study so far -- all eight hearts regained a more normal size. They shrank 15% to 20%, three times more than current treatments can achieve. Whether just plain old bone marrow or [adult stem] cells, injected into the scar, and three months later, the area that was completely dead started to contract again. Stem cells are being explored in the treatment of people with recent heart attack damage -- but the "landmark area" is the use of stem cells to treat end-stage heart failure. Stem cells actually reverses the enlargement and their propensity to get worse (DeNoon ’11) (Hare '11).

In 1868, two investigators from Prussia and Italy were the first to report that bone marrow generates blood cells in mammals. This observation was the starting point of intense efforts to replace malfunctioning marrow through the transplantation of blood-forming (hematopoietic) cells in humans. However, it took an entire century to develop reliable techniques to identify suitable donors, design potent antibiotics, and establish essential supportive care methods to successfully perform clinical **hematopoietic cell transplantation** (HCT) procedures. This important accomplishment would not have been possible without understanding issues related to graft rejection and the prevention of graft-versus-host disease (GVHD), a serious reaction caused by the donor’s immune cells attacking the recipient’s vital organs. In 1968, three patients in the United States and the Netherlands suffering from severe combined immunodeficiency syndromes, in which the ability of the body’s immune system to fight infections is compromised, were successfully transplanted and cured by HCT. Since then, the number of HCT procedures has risen to 50,000-60,000 per year, and the cumulative number of patients treated worldwide has now reached 800,000. The majority of HCT recipients are patients with leukemia, lymphoma, myeloma, myelodysplasia, bone marrow failure conditions, severe red blood cell disorders such as sickle cell disease or thalassemia, and certain solid tumors (Blume '08).

Hematopoietic cells can be obtained from suitably matched related or unrelated volunteer donors (allogeneic HCT) or from the patient’s own tissues (autologous HCT). Sources of hematopoietic cells include the bone marrow, blood, or umbilical cord blood. International unrelated volunteer donor banks containing information on approximately 12 million volunteers are interconnected by worldwide computer systems. Approximately 3,500 HCT procedures from unrelated donors are now performed annually, and almost 40 percent of such transplants involve a donor who is from a different country from the recipient. In parallel, umbilical cord blood banks are rapidly growing in size and usage. To date, some 10,000 HCT procedures with umbilical cord blood grafts have been performed. The choices of which type of HCT (allogeneic or autologous) and the source of the graft (bone marrow, blood, or cord blood) depend mainly on the patient’s underlying disease and whether it is in remission. Before transplant, the patient is treated with high-dose chemotherapy, with or without radiation therapy, to eradicate the cancerous cells (prior to both autologous and allogeneic HCT), and to suppress the patient’s immune system to

prevent it from attacking the donor hematopoietic cells (prior to allogeneic HCT). More recently, it has been established that less intensive pre-transplant treatment also allows successful transplantation, but with less severe side effects. Such "reduced intensity" transplants prevent later relapses by maintaining the body's ability to launch an immune attack by the new marrow against the cancer. This "graft-versus-malignancy effect" is a critical element for cure through allogeneic HCT. Reduced-intensity regimens have also made it possible to extend HCT to older patients (up to 75 years) and younger patients with health problems that make them ineligible for high-intensity regimens. Significant post-transplant problems can result from toxic effects related to the preparatory treatments, GVHD, infections, and relapse of the underlying disease. Continued research is leading to further improvements and better survival results. The long-term outcome of HCT procedures depends on whether or not the patient is in remission. While 50-80 percent of leukemia patients can be cured by allogeneic HCT if performed during first remission, the expectation for success is markedly reduced for those whose HCT is carried out in more advanced stages of their disease. Likewise, the long-term results of autologous HCT are strongly influenced by the amount of cancer in the patient's body at the time of transplantation, with relapse being the leading cause for treatment failure (Blume '08).

Before 1950 the inflexible fate of those with high blood pressure was a stroke, heart failure, or kidney failure, but today, thanks to the use of *Rauvolfia* extracts, an Ayurvedic treatment for schizophrenia, a large percentage of cases of hypertension can be controlled. Reserpine and other **Rauvolfia alkaloids** act on the sympathetic nervous system by depleting almost all the neurotransmitter substance, norepinephrine, from sympathetic nerve tissue. This neural blocking results in relaxation of the vessels and output of the heart, with subsequent reduction in blood pressure. By chance patients being treated for malaria with Cinchona bark containing quinine and other alkaloids were found to be free of arrhythmias. Subsequent investigation proved that quinine, and more importantly **quinidine**, regulated atrial fibrillation and flutter. Quinidine may suppress abnormal rhythms in any chamber of the heart but in other studies can cause certain dangerous arrhythmias. Allocryptopine from *Fagara coca* controls atrial arrhythmias and is said to be more effective than quinidine (Elvin-Lewis '77: 5, 187, 190-191). The ABC of adrenergenic blockers developed since the 1970s have been abused in the treatment of congestive heart failure and because these drugs have monopolized the literature pertaining to hypertension and cardiovascular drugs it seems fitting to first prescribe Rauvolfia alkaloids to minimize paranoia regarding the appropriate treatment of malignant hypertension for which medicine is essential. A daily dose of 12.5 mg hydrochlorothiazide (HCTZ) is the commonest and cheapest drug for treating high blood pressure. Drugs in the class called dihydropyridines, the largest group, tend to be the best at lowering blood pressure. The best value is felodipine, and if it is causing too many side effects, amlodipine may be better (Spence '05).

Adverse Effects of Hypertensive Drugs

Drug Class	Main Adverse Effects
ACE Inhibitors	Acute kidney failure in severe narrowing of both kidney arteries, cough in 8%, swelling of the face and tongue (angiodedema) 1 in 1,000
Beta-Blockers	
Beta 1 to reduce heart rate and contractility	Bradycardia and congestive heart failure
Beta 2 for vasoconstriction, bronchoconstriction, reduced insulin release, gluconeogenesis and fat metabolism	Cold extremities, reduced muscle blood flow, Raynaud's phenomenon, aggravation of asthma, Type II diabetes, hypoglycemia by

	insulin and hyperlipidemia
Calcium Channel Blockers	
Verapamil	Constipation, aggravation of congestive heart failure
Diltiazem	Slow heartbeat (bradycardia)
Dihydropyridines (nifedipine, felodipine, amlodipine)	Ankle swelling, fast heartbeat (tachycardia), headache

Source: Spence '05: Table 9.1, 9.3; pgs. 139, 145

Only about 25 percent of people with hypertension have it well controlled. **Thiazine diuretics** are the commonest and cheapest drug for treating high blood pressure is hydrochlorothiazide, a drug that is particularly effective in the elderly and people with African ancestors, it acts first as a diuretic; after six weeks or so, its main effect is to relax the small artery branches, the arterioles. The main issue with this drug is determining the correct dose: for most individuals a dose of 12.5 mg daily I enough, and for others 12.5 mg every other day. Hydrochlorothizide is usually available in tablets of 25 mg or more, so half of the smallest tablet is the optimal dose (Spence '05: 127). Drug therapy can now control about 80% of all cases of hypertension. Drugs do not cure, but their control of this disease marks a tremendous change in the outlook for patients whose inflexible fate until 1950 was a stroke, heart failure, or kidney failure (Elvin-Lewis '77: 189).

People taking long term diuretic therapy to rid their body of salt and water, often experience adverse effects related to the depletion of the number of ions. Often the rubric **hypokalemia** (low blood level of potassium) is used to characterize the problem. The problem is however not a low eve of potassium in the blood, it is potassium depletion in the cells throughout the body, including muscles, heart, brain, and elsewhere. Potassium supplements do not restore intracellular potassium unless magnesium is taken at the same time. Maintaining adequate intracellular potassium helps prevent toxicity of digoxin (a heart medication that can cause serious problems if the blood level is too high, or the potassium level in the cells is too low) and minimizes the adverse effects on diabetes and cholesterol. Taking diuretic causes the body to react by turning on hormone systems designed to retain salt and water. **Aldosterone** causes the kidney to retain sodium and excrete potassium and other ions; when potassium is eventually depleted, there is excretion of hydrogen ions, leading to an alkaline state in the blood (alkalosis). Most individuals with depleted potassium have a normal serum potassium. If taking a diuretic and feel tired, achy, have cramps in extremities, are impotent, and feel faint when standing up, presume depleted potassium. Usually when there is potassium depletion there is also depletion of magnesium, zinc, selenium, rubidium and other ions (Spence '05: 146). **Hydralazine** is the old standby among vasodilators, drugs that dilate arteries, which has recently been resurrected for the treatment of heart failure, particularly for African-Americans. When used alone, it causes the heart to speed up and tends to cause throbbing headaches, so it is usually used in combination with beta-blocker (Spence '05: 131).

Drugs that reduce production of aldosterone by the adrenal gland also are magnesium and potassium sparing. Drugs that block activation of angiotensin by **blocking angiotensin-converting enzyme**, ACE inhibitors such as captopril, enalapril, lisinopril or any drug with a proper name ending in –pril), or by blocking angiotensin II at its receptor angiotensin receptor blockers (ARBs) (losartan irbesartan, candesartan, or other drug ending in –sartan) will reduce urinary losses of potassium, magnesium and probably the other ions that are depleted by diuretics. Because potassium loss from the kidney is driven by exchange of potassium for

sodium as regulated by aldosterone, salt intake is an important concern. The more salt eaten, the more potassium lost. Every sodium ion reabsorbed from the renal tubule leads to excretion of a potassium ion; high sodium intake aggravates potassium losses, and when potassium is depleted, potassium ions are exchanged for hydrogen ions, leading to acid urine with alkaline blood. Blocking the effect of high renin – potassium and magnesium depletion – by blocking the effect of angiotensin II with angiotensin receptor blockers (ARBs) will prevent **secondary hyperaldosteronism**. This may be the best approach for people who have either congestive heart failure or secondary hyperaldosteronism from renal artery stenosis or other high-renin states. ACE inhibitors, also block formation of angiotensin II, but this effect wears off after a few weeks because there are other pathways for the formation of angiotensin II. If potassium-sparing diuretics and ARBs or ACE inhibitors are used together, there is a real risk of seriously increased levels of potassium in the blood (hyperkalemia). For **primary hyperaldosteronism** the specific treatment is blockers of aldosterone such as spironolactone and eplerenone; amiloride can also be used and is the specific treatment for hypertension due to abnormalities of the renal tubule such as Liddle's syndrome. The problem is not low levels of potassium in the blood (hypokalemia) but **potassium/magnesium depletion**; potassium supplements do not solve the problem because magnesium is required to restore intracellular potassium. A recommended approach is to: (1) reduce salt intake below 2-3 grams per day; (2) reduce the dose of diuretic, (3) use potassium/magnesium sparing diuretics to prevent losses or (4) use angiotensin blockers to reduce secondary hyperadlosteronism and thus prevent depletion of potassium and magnesium (Spence '05: 147, 148 152).

To **minimize potassium losses**, one can reduce salt intake; use angiotensin-receptor blockers (ARBs) to prevent angiotensin II from causing the adrenal cortex to release aldosterone; or block the effects of aldosterone on the kidney tubule by using potassium-magnesium sparing diuretics. A minority of patients with difficult to treat high blood pressure will require potassium and magnesium supplementation. Potassium depletion is usually managed by a combination of reducing salt intake, reducing the dose of diuretic and using either potassium/magnesium sparing diuretics or drugs that prevent excess aldosterone production such as angiotensin receptor blockers. For most individuals, particularly the elderly, a daily dose of 12.5 mg hydrochlorothiazide (HCTZ) is the commonest and cheapest drug for treating high blood pressure, is enough. Among diuretics that do not deplete the body's potassium and magnesium, amiloride is generally preferred for men, because men who take spironolactone often have sore nipples and sometimes breast enlargement. This does not appear to be a problem with eplerenone, a new aldosterone antabgonist. Avoid triamterene, because half the people who take it develop an abnormality in the urine (triamterene casts) and it is implicated in kidney inflammation (interstitial mephritis) and kidney stones. If a small does of one of the thiazide family of diuretics if required, a common ratio might be HCTZ 12.5 mg to amiloride 10-20 mg, or spironolactone 100 mg. For people with secondary hyperaldosteronism, overproduction of aldosterone because of high levels of renin and angiotensin - angiotensin receptor blockers are more effective (Spence '05: 149, 150).

Any **ACE inhibitor** will cause a cough in about 8 percent of people and swelling of the face and tongue (angiodedema) in about one in one thousand. One can avoid these adverse effects by switching to angiotensin blockers, which have benefits similar to those of ACE inhibitors. The first dose of any ACE inhibitor or angiotensin blocker can cause a severe drop in blood pressure, particularly in people taking diuretics. They can also cause acute kidney failure in people that have severe narrowing of both kidney arteries. This problem is rare except in very severe high blood pressure or heart failure. Among ACE inhibitors the main difference is due to the

presence of a sulfhydryl group in captropril, which is responsible for the loss of taste and a characteristic generalized rash that looks like measles. Both of these problems will disappear if the patient switches to another ACE inhibitor or to an angiotensin blocker. Captopril is very short acting and must be taken two or three times per day to achieve desired effects in all but the least severe cases. Lisinopril, quinapril, and some of the other ACE inhibitors are long acting enough to work well when taken once a day. Captopril is also the most expensive of ACE inhibitors (Spence '05: 145).

Beta-blockers block one of the two kinds of adrenaline receptor (a structure on the surface of cells that responds to adrenaline), the beta receptors. Beta receptors are of two types, beta-1 and beta-2. Stimulating beta-1 receptors causes the heart to speed up and beat more forcefully. Stimulating the beta-2 receptors causes the bronchi to dilate and the arteries that got to the muscles to dilate. **Alpha-blockers** block the second of the two kinds of adrenaline receptor, the alpha receptors: the alpha-1 receptor when stimulated causes the arteries to constrict, and the alpha-2 receptor when stimulated inhibits the sympathetic nervous system. Alpha-blockers are used selectively to block the alpha-1 receptors by preventing the arteries from constricting, they tend to lower blood pressure. They also have beneficial effects on cholesterol and diabetes, and are now commonly used for bladder symptoms from prostate gland enlargement. The main ones in use are prazosin, doxazosin, and terazosin. Compared with prazosin, the latter two are longer acting so can be taken less often, and they tend to cause less trouble with a faint feeling on standing. Doxazosin is the longest acting, and probably the best choice for that reason (Spence '05: 128, 129, 130).

Beta-blockers have issues in the different ways individual bodies handle the drugs (pharmacokinetics) and the way the drugs interact with adrenaline receptors (pharmacodynamics). Concerns include how drugs metabolize, how long the drug action lasts, how the drugs are absorbed into various body tissues, and how tightly the drug binds to receptors. Propranolol undergoes extensive metabolism during its first pass through the liver (first-pass metabolism); about 70 percent of an oral dose is broken down in the liver and never makes to the rest of the body. Both propranolol and metoprolol have a twenty-fold range in the blood levels achieved with a given dose that in different people can lead to blood levels that range from five to one hundred units. If propranolol and metoprolol don't work well at the dose prescribed hypertension can be controlled, at a much lower cost, with a beta-blocker that is excreted by the kidney or metabolized in a different way. Nadolol and atenolol are two beta-blockers that are excreted by the kidney, creating special problems for the elderly and for people with impaired kidney function. They can build up in the blood-stream, causing relatively slow heart action (bradycardia), and aggravate heart failure, which in turn aggravates the kidney function. If the heart rate has been getting slower and slower switch to a beta-blocker that is not excreted by the kidney, but metabolized by the liver (Spence '05: 140, 141).

The best and most convenient beta-blocker is **pindolol**, it has the most potent ISA, so it does not cause the adverse effects due to blockade of beta-2 receptors. (ISA, intrinsic sympathomimetic activity of drugs that block beta-1 receptors and stimulate beta-2 receptors.) Pindolol is also the best beta-blocker for people with diabetes, high cholesterol, or blocked arteries in the legs; it is less likely to aggravate cholesterol and diabetes, and less likely to cause fatigue and is the least likely to cause rebound hypertension if doses are missed. The downside of pindolol is that small proportion of people (about 5 percent) experience vivid dreams, tremor or anxiety because of the drug's greater penetration into the brain. Beta-blockers penetrate brain tissue to markedly varied extents because of difference in how well they dissolve in fat. These differences explain why

pindolol, with its extreme penetration into brain tissue, is the most likely beta-blocker to cause anxiety, tremors and vivid dreams, and why propranolol, which is also concentrated in the brain, is the most likely to cause subjective tiredness and hallucinations. Selective blockade of beta-1 receptors that speed up the heart and cause it to beat harder and stimulation of beta-2 receptors that cause dilation of the large air tubes in the lung and of the arteries that go to muscles. Nonselective drugs such as propranolol, nadolol and timolol are more likely to cause adverse effects due to beta-2 blockade. Drugs that stimulate beta-2 receptors will have a different profile again; pindolol, a relatively potent beta-2 stimulator, had beneficial effects on cholesterol, may benefit diabetes, and is least likely to cause problems with cold extremities and asthma (Spence '05: 141, 142, 144).

Calcium-channel antagonists, or **calcium-channel blocker**s, dilate arteries by interfering with the channels that permit calcium to enter cells; they are useful for both hypertension and angina. Calcium-channel antagonists, or calcium-channel blockers, dilate arteries by interfering with the channels that permit calcium to enter cells. Trouble with constipation or shortness of breath or other symptoms of heart failure, is often helped by changing from verapamil or diltiazem to another type of drug, or changing to a dihydropyridine (the largest class of CCBs) such as nifedipine, felodipine, or amlodipine. If the problem is a slow heart rate from diltiazem, changing to a dihydropyridine or another class of drug should help; if it doesn't, check out a pacemaker. Consumers of both diltiazem and a beta-blocker, may need to reduce the dose of beta-blocker. Those having a lot of angina on a dihydropyridine such as felopidipine, are helped by adding a beta-blocker (or switching to diltiazem for those who can't take a beta-blocker). If it doesn't help, find out about endartectomy, angioplasty or bypass surgery, and make sure that all the risk factors are optimally controlled. If the problem is ankle swelling, flushing, or headache, switching from nifedipine or felodipine to amlodipine or another class of drug should help. Diltiazem and verapamil are not very strong and are extremely expensive, so are not advised for treating high blood pressure: the main reason to use them. Verapamil is good for heart-rhythm disturbances such as atrial fibrillation and diltiazem is good for angina (chest pain brought on by exertion, due to narrowing of the coronary arteries) (Spence '05: 139, 140).

Drugs in the class called **dihydropyridines**, the largest group, tend to be the best at lowering blood pressure. Diltiazem is a somewhat weaker vasodilator in the peripheral arteries throughout the body, but it affects the coronary arteries and so may be better for angina. Verapamil is another relatively weak drug that may aggravate heart failure. The main dihydrpyrinidines are nifedipine, felodipine, amlodipine, nisodipine, and nicardipine. Nifedipine and felodipine are quite short acting, and the slow-release pills that have been developed are only partially effective in correcting the problem of peaks and troughs in blood pressure. Nifedipine is relatively expensive, but the best value is felodipine, and if it is causing too many side effects, amlodipine may be better. Nicardipine is very expensive and usually has to be taken several times a day, so it has little advantage. A special problem occurs when dihydropyridines are taken with **grapefruit juice** that reduce the metabolism of a number of drugs. Felodipine blood levels go up on average about 300 percent with grapefruit juice, nisodipine levels about 500 percent. A number of important interactions occur between grapefruit and other drugs such as cyclosporine, terfenadine (an antihistamine), and propafenone; based on the known metabolism of warfarin and the cholesterol-lowering drugs such as lovastatin and simvastatin, can be anticipated to be affected by grapefruit juice. As a rule of thumb any drug that should not be taken with erythromycin, ketoconazole or itraconazole, should not be taken with grapefruit juice (Spence '05: 162).

Grapefruit juice inhibits the metabolism of a number of drugs, whereby a large proportion of the drug is metabolized by oxidation to form another chemical, in the wall of the intestine. This oxidation is performed by a specific form of the family of oxidative enzymes (Cytochrome P450) called CYP3A4. Drugs that are largely metabolized during oxidation are said to have low bioavailability, because a low proportion of the drug is available to the body. When the metabolism of these drugs in the intestinal wall is inhibited, a much larger proportion of the drug is absorbed unchanged, and the blood levels of the drug are much higher. Dihydropyridine calcium-channel antagonists) drugs with high bioavailability such as amlodipine are not much affected by grapefruit juice; nifedipine, which is 60 percent bioavailable, has a 30 percent rise in blood levels when taken with grapefruit juice, and nisoldipine, which is 8 percent bioavailable, goes up on average fivefold up to ninefold. Interesting Florida orange juice has no such effect, although Seville orange juice and lime juice have some effect (though less powerful than grapefruit juice). Other drugs for which the grapefruit juice effect is important include the transplant anti-rejection drug cyclosporine (a tripling of blood levels); the AIDS drug squinovir (large effects); the sleeping pills midazolam and triazolam; and most importantly, the anti-histamine terfenadine. Both terfenadine and the gut-motility drug cisapride can cause serious heart-rhythm disturbances when their metabolism is inhibited, wherefore they are no longer on the market. Other drugs affected importantly by grapefruit include the anticoagulant warfarin and the heart-rhythm drug propafenone in some individuals, and the cholesterol-lowering drugs lovastatin and simvastatin. Blood levels of both lovastatin and simvastatin can be increased fifteen-fold by a glass of grapefruit juice. Atorvastatin is also affected by grapefruit, although to a much lesser degree, but pravastatin and rosuvastatin are not. A simple rule of thumb is that if a drug should not be taken with erythromycin, ketoconazole or itraconazole, it should not be taken with grapefruit juice. To be safe, don't drink grapefruit juice if taking one of the affected drugs (Spence '05: 162).

Angiogenesis is the formation of new blood vessels. This process involves the migration, growth, and differentiation of endothelial cells, which line the inside wall of blood vessels. The process of angiogenesis is controlled by chemical signals in the body. These signals can stimulate both the repair of damaged blood vessels and the formation of new blood vessels. Other chemical signals, called angiogenesis inhibitors, interfere with blood vessel formation. Normally, the stimulating and inhibiting effects of these chemical signals are balanced so that blood vessels form only when and where they are needed. Bevacizumab was the first **angiogenesis inhibitor** that was shown to slow tumor growth and, more important, to extend the lives of patients with some cancers. The FDA has approved other drugs that have antiangiogenic activity, including sorafenib (Nexavar), sunitinib (Sutent), pazopanib (Votrient), and everolimus (Afinitor). Sorafenib is approved for hepatocellular carcinoma and kidney cancer, sunitinib and everolimus for both kidney cancer and neuroendocrine tumors, and pazopanib for kidney cancer. Angiogenesis inhibitors are unique cancer-fighting agents because they tend to inhibit the growth of blood vessels rather than tumor cells. In some cancers, angiogenesis inhibitors are most effective when combined with additional therapies, especially chemotherapy. Angiosarcomas are usually treated with paclitaxel (Taxol), docetaxel (Docefrez, Taxotere), sorafenib (Nexavar), or bevacizumab (Avastin). Lymphangiosarcomas are more difficult to treat. Chemotherapeutic drugs such as paclitaxel, doxorubicin, ifosfamide, and gemcitabine exhibit antitumor activity. Recently, there has been interest in evaluating the effectiveness of anti-angiogenic drugs in the treatment of lymphangiosarcoma. Early evidence suggests that treatment with one such drug, Bevacizumab, may be effective in treating lymphangiosarcoma. Investigation of bevacizumab in combination with other chemotherapy agents is underway. Interferon-alfa was the first drug

specifically approved for the treatment of Kaposi's. It is of particular interest because of its antiproliferative, antiviral (anti-HIV), antiangiogenic, and immune-modulating properties.

Etoposide (VP-16) has been evaluated as both an oral and an intravenous treatment for Karposi Sarcoma (KS). As an oral agent, VP-16 has been evaluated primarily in patients who have undergone prior treatment with multiple cytotoxic agents. When VP-16 is given intravenously (150 mg/m^2 on days 1 to 3 every 4 weeks), high response rates (78%) have been reported in patients without prior treatment and with good prognosis (no history of opportunistic infection and no constitutional symptoms). The primary toxicity of this agent is myelosuppression, which may necessitate the use of colony-stimulating factors, particularly in patients with advanced disease receiving other myelosuppressive agents. Additionally, alopecia frequently occurs in association with etoposide therapy, and is a consideration for patients who are receiving treatment of their KS for primarily cosmetic purposes. In patients with KS of poor prognosis, bleomycin given intramuscularly (5 mg/day for 3 days) or as a 4-day continuous infusion (6 mg/m^2/day) produced a 48% partial response rate. Results of a small, single-institution study in which bleomycin was given as a 72-hour infusion (20 mg/m^2/day) to 17 patients indicated a partial response rate of 65%. Bleomycin toxicity appears to be acceptable, with neutropenia an infrequent complication. Doxorubicin (also known by its trade name Adriamycin) is a component of the most widely used combination regimen for HIV-associated KS. In one trial, however, weekly treatment with doxorubicin (25 mg/m^2) in patients with AIDS-related KS achieved a partial response rate of only 10%. The primary toxicity of weekly doxorubicin is myelosuppression, even with the relatively low doses prescribed for KS treatment. Alternating vincristine and vinblastine weekly achieves a response rate of 33%. Toxicity includes vincristine-induced neurotoxicity (which limits its usefulness as a single agent) and vinblastine-induced myelosuppression. Paclitaxel A partial response was reported in 13 of 20 patients (65%), with 5 of 6 patients with known pulmonary KS responding, as well as 6 previously treated patients with nonpulmonary KS achieving a partial response. In a second trial, of the 30 evaluable patients, 16 (53%) achieved a partial response. The time to response was short (median of three cycles of treatment). Dramatic improvement in symptomatic lymphedema was noted in 25 of 26 patients. Therapy was well tolerated. Vinorelbine, a semisynthetic vinca alkaloid with a favorable therapeutic index compared to other vinca alkaloids, was evaluated in previously treated patients with progressive AIDS-related KS. Thirty-five evaluable patients were treated with vinorelbine 30 mg/m2 every 2 weeks. Clinical complete and partial remissions were achieved in 43% of patients, with a median progression-free survival of 151 days. The agent was well tolerated, with neutropenia the most frequent dose-limiting toxicity. Two liposomal agents are currently approved for the treatment of KS: liposome-encapsulated daunorubicin (DaunoXome) and liposome-encapsulated doxorubicin (Doxil). Both agents are highly active against KS and have less toxicity than the nonliposomal anthracyclines. Myelosuppression, however, remains the dose-limiting toxicity.

Between 1949 and 1954, the first clinical trials that tested combinations of chemotherapy drugs methotrexate and corticosteroids, (and unfortunately 6-MP) for childhood **acute lymphoblastic leukemia** (ALL) were carried out. Patients lived longer with these new combinations of chemotherapy drugs, but all still died, usually within a year. Because ALL tended to come back in the central nervous system, a major advance was made by aggressively treating the brain and spinal fluid with radiation and drugs that markedly decreased this form of relapse so, one-half of the patients were cured of leukemia. The cure rate now approximates 80 percent and methotrexate is available by prescription for oral consumption (Simone '08). **Chronic myeloid leukemia** (CML) is one of the four main types of leukemia, affecting approximately 5,000

people per year in the United States. The disease can occur at any age but is primarily a disease of adults. CML is characterized by a massive over-production of white blood cells. A normal white blood cell count ranges between 4,000 and 10,000; in contrast, patients with CML typically have white blood cell counts ranging from 100,000 to as high as 500,000. Because the white blood cells mature and function normally, infections are not a common feature of CML. Rather, symptoms include fatigue due to anemia or abdominal discomfort due to an enlarged spleen. Historically, patients with CML lived no more than three to five years, during which time the disease would quickly transform from a chronic leukemia to an aggressive and fatal acute leukemia.

In 1960, Peter Nowell and David Hungerford, working in Philadelphia, described a shortened chromosome in the blood and bone marrow of patients with CML. This was the first consistent chromosomal abnormality associated with a human cancer. Then, in 1973, Janet Rowley showed that this abnormal chromosome, now called the Philadelphia chromosome, came about because of an exchange of genetic material between two chromosomes. In the 1980s, it was demonstrated that the consequence of this chromosome exchange was the production of an abnormal gene called *BCR-ABL* fueling the excess growth of white blood cells in CML. With the target identified, a drug discovery program was started, aimed at developing a drug to shut down the activity of *BCR-ABL*. The compound that became known as imatinib (Gleevec) was developed in 1992, and studies showed that this compound killed CML cells without harming normal cells. In 1998, the drug was tested in patients with CML who had exhausted standard treatment options and whose life expectancy was limited. Within six months of starting the clinical trials of imatinib, all of the patients had their blood counts return to normal. Remarkably, this once-a-day pill had minimal side effects. These unprecedented results were confirmed in much larger clinical trials, and imatinib was approved by the U.S. Food and Drug Administration (FDA) in 2001, less than three years from the start of the clinical trials. With longer follow-up, this once routinely fatal leukemia now has a five-year survival rate of 95 percent. Newer drugs (dasatinib and nilotinib) have been developed that can shut down most of the mutated forms of *BCR-ABL*, and have significant activity in patients with resistance to imatinib; these drugs are also FDA-approved (Druker '08).

Chemotherapy for Leukemia and Lymphoma

White Cell Disease	FDA Approved Drug
Multiple Myeloma and Plasma Cell Dyscracias	Oral Thalidomide, with dexamethasome, a corticosteroid. Others: Bortezomib, Carfilzomib, Clafen (Cyclophosphamide), Cyclophosphamide, Cytoxan (Cyclophosphamide), Doxil (Doxorubicin Hydrochloride Liposome), Doxorubicin Hydrochloride Liposome, Dox-SL (Doxorubicin Hydrochloride Liposome), Evacet (Doxorubicin Hydrochloride Liposome), Kyprolis (Carfilzomib), Lenalidomide, LipoDox (Doxorubicin Hydrochloride Liposome), Mozobil (Plerixafor), Neosar (Cyclophosphamide), Plerixafor Pomalidomide (Pomalyst), Pomalyst, Revlimid (Lenalidomide), Synovir (Thalidomide), Thalidomide, Thalomid (Thalidomide), Velcade (Bortezomib), Zoledronic Acid Zometa (Zoledronic Acid).
Waldenström macroblobuline mia	Fludara (fludarabine) and Leustatin (cladribine) first to try. Cytoxan (cyclophosphamide) may be added. Other commonly used chemotherapy drugs are Luekeran (chlorambucil) and prednisone, usually given together, or Adriamycin (doxorubicin). Rituxan (rituximab).

	Campath (alemtuzumab) has also been an effective treatment, as has Velcade (bortezomib).
Langerhans' cell histiocytoses	Oral methotrexate (20 mg/m^2) weekly for 6 months or Oral thalidomide 50 mg to 200 mg nightly, with prednisone are taken for low risk disease or vinblastine IV and prednisone for patients with more complicated cases requiring radiation and surgery
Acute Leukemias	
Acute lymphoblastic leukemia (ALL)	Abitrexate (Methotrexate), Adriamycin PFS (Doxorubicin Hydrochloride), Adriamycin RDF (Doxorubicin Hydrochloride), Arranon (Nelarabine), Asparaginase Erwinia chrysanthemi, Cerubidine (Daunorubicin Hydrochloride), Clafen (Cyclophosphamide), Clofarabine, Clofarex (Clofarabine), Clolar (Clofarabine), Cyclophosphamide, Cytarabine, Cytosar-U (Cytarabine), Cytoxan (Cyclophosphamide), Dasatinib Daunorubicin Hydrochloride, Doxorubicin Hydrochloride, Erwinaze Asparaginase Erwinia Chrysanthemi), Folex (Methotrexate), Folex PFS (Methotrexate), Gleevec (Imatinib Mesylate), Iclusig (Ponatinib Hydrochloride), Imatinib Mesylate, Marqibo (Vincristine Sulfate Liposome), Methotrexate, Methotrexate LPF (Methorexate), Mexate (Methotrexate), Mexate-AQ (Methotrexate), Nelarabine, Neosar (Cyclophosphamide), Oncaspar (Pegaspargase), Pegaspargase, Ponatinib Hydrochloride, Rubidomycin (Daunorubicin Hydrochloride), Sprycel (Dasatinib), Tarabine PFS (Cytarabine), Vincasar PFS (Vincristine Sulfate), Vincristine Sulfate, Vincristine Sulfate Liposome
Acute myeloblastic leukemia (AML)	Adriamycin PFS (Doxorubicin Hydrochloride), Adriamycin RDF (Doxorubicin Hydrochloride), Arsenic Trioxide, Cerubidine (Daunorubicin Hydrochloride), Clafen (Cyclophosphamide), Cyclophosphamide, Cytarabine, Cytosar-U (Cytarabine), Cytoxan (Cyclophosphamide), Daunorubicin Hydrochloride, Doxorubicin Hydrochloride, Neosar (Cyclophosphamide), Rubidomycin (Daunorubicin Hydrochloride), Tarabine PFS (Cytarabine), Trisenox (Arsenic Trioxide), Vincasar PFS (Vincristine Sulfate), Vincristine Sulfate, combination; ADE
Myelodysplastic syndromes	
Chronic myeloid leukemia (CML)	Bosulif (Bosutinib), Bosutinib, Clafen (Cyclophosphamide), Cyclophosphamide, Cytarabine, Cytosar-U (Cytarabine) Cytoxan (Cyclophosphamide), Dasatinib, Gleevec (Imatinib Mesylate), Iclusig (Ponatinib Hydrochloride), Imatinib Mesylate, Neosar (Cyclophosphamide), Nilotinib, Omacetaxine Mepesuccinate, Ponatinib Hydrochloride, Sprycel (Dasatinib), Synribo (Omacetaxine Mepesuccinate), Tarabine PFS (Cytarabine), Tasigna (Nilotinib)
Chronic lymphocytic leukemia (CLL)	Alemtuzumab, Ambochlorin (Chlorambucil), Amboclorin (Chlorambucil), Arzerra (Ofatumumab), Bendamustine Hydrochloride, Campath (Alemtuzumab), ChlorambucilClafen (Cyclophosphamide), Cyclophosphamide, Cytoxan (Cyclophosphamide), Fludara (Fludarabine Phosphate), Fludarabine Phosphate, Leukeran (Chlorambucil), Linfolizin (Chlorambucil), Neosar (Cyclophosphamide), Ofatumumab Treanda (Bendamustine Hydrochloride), combinations CHLORAMBUCIL-PREDNISONE, CVP

Meningeal Leukemia	Cytarabine, Cytosar-U (Cytarabine), Tarabine PFS (Cytarabine), Methotrexate
Hairy cell leukemia	Cladribine (2-chlorodeoxyadenosine, 2-CdA), Pentostatin
Polycythemia vera	Anagrelide (Agrylin), Ruxolitinib (Jakafi)
Lymphoma	
Hodgkin's lymphoma	Adcetris (Brentuximab Vedotin), Adriamycin PFS (Doxorubicin Hydrochloride), Adriamycin RDF (Doxorubicin Hydrochloride), Ambochlorin (Chlorambucil), Amboclorin (Chlorambucil), Blenoxane (Bleomycin), Bleomycin, Brentuximab Vedotin, Chlorambucil, Clafen (Cyclophosphamide), Cyclophosphamide, Cytoxan (Cyclophosphamide), Dacarbazine, Doxorubicin Hydrochloride, DTIC-Dome (Dacarbazine), Leukeran (Chlorambucil), Linfolizin (Chlorambucil), Lomustine, Matulane (Procarbazine Hydrochloride), Neosar (Cyclophosphamide), Procarbazine Hydrochloride, Velban (Vinblastine Sulfate), Velsar (Vinblastine Sulfate), Vinblastine Sulfate, Vincasar PFS (Vincristine Sulfate), Vincristine Sulfate, combinations; ABVD, ABVE, ABVE-PC, BEACOPP, COPP, ICE, MOPP, STANFORD and VAMP.
Non-Hodgkin's lymphoma	Abitrexate (Methotrexate), Adcetris (Brentuximab Vedotin), Adriamycin PFS (Doxorubicin Hydrochloride), Adriamycin RDF (Doxorubicin Hydrochloride), Ambochlorin (Chlorambucil), Amboclorin (Chlorambucil), Arranon (Nelarabine), Bendamustine Hydrochloride, Bexxar (Tositumomab and Iodine I 131 Tositumomab), Blenoxane (Bleomycin), Bleomycin, Bortezomib, Brentuximab Vedotin, Chlorambucil, Clafen (Cyclophosphamide), Cyclophosphamide, Cytoxan (Cyclophosphamide), Denileukin Diftitox, DepoCyt (Liposomal Cytarabine), Doxorubicin Hydrochloride, DTIC-Dome (Dacarbazine), Folex (Methotrexate), Folex PFS (Methotrexate), Folotyn (Pralatrexate), Ibritumomab Tiuxetan, Intron A (Recombinant Interferon Alfa-2b), Istodax (Romidepsin), Leukeran (Chlorambucil), Linfolizin (Chlorambucil), Liposomal Cytarabine, Matulane (Procarbazine Hydrochloride), Methotrexate, Methotrexate LPF (Methotrexate), Mexate (Methotrexate), Mexate-AQ (Methotrexate), Mozobil (Plerixafor), Nelarabine, Neosar (Cyclophosphamide), Ontak (Denileukin Diftitox), Plerixafor, Pralatrexate, Recombinant Interferon Alfa-2b, Rituxan (Rituximab), Rituximab, Romidepsin, Tositumomab and Iodine I 131 Tositumomab, Treanda (Bendamustine Hydrochloride), Velban (Vinblastine Sulfate), Velcade (Bortezomib), Velsar (Vinblastine Sulfate), Vinblastine Sulfate, Vincasar PFS (Vincristine Sulfate), Vincristine Sulfate, Vorinostat, Zevalin (Ibritumomab Tiuxetan), Zolinza (Vorinostat) and combinations CHOP, COPP, CVP, EPOCH, ICE, R-CHOP.

Source: FDA

The cure of Hodgkin lymphoma in the 20th century is another one of cancer's biggest success stories. Breakthroughs in radiation therapy and chemotherapy paired with careful clinical research transformed an invariably fatal disorder into one that is routinely cured. The recognition of late adverse effects from radiation therapy and chemotherapy in the form of second cancers, heart and blood vessel disease, and sterility shaped subsequent research efforts to maintain or improve cure rates with fewer complications, an important goal in a disease that primarily affects

individuals in their 20s and 30s. Today, as more than 80 percent of patients are cured after primary treatment. Sir Thomas Hodgkin is credited with the initial description of the clinical disorder that bears his name. In 1832, he reported on a group of patients with enlargement of lymph nodes and spleen that differed from the major known maladies of the day. The introduction of the linear accelerator (a radiation machine used to treat cancer) in the treatment of Hodgkin lymphoma at Stanford University resulted in cures of early-stage lymphoma. Meanwhile, a team at the National Cancer Institute safely combined four chemotherapy drugs (mustard, vincristine, procarbazine, and prednisone) known as the "MOPP" regimen and reported the first cures of advanced Hodgkin lymphoma in 1964. Steadily improving techniques for defining the extent and location of disease (staging) has allowed appropriate modalities of treatment to be selected for individual patients. The late 1970s and 80s presented new challenges in the recognition of adverse effects associated with MOPP and radiation therapy, some of which were not apparent for decades after treatment. This time period also featured another major advance in an alternative four-drug chemotherapy regimen (doxorubicin, bleomycin, vinblastine, and dacarbazine), known as "ABVD," that proved to be more effective than MOPP in treating advanced disease and had fewer side effects. In the 1990s, even more effective and less toxic treatments for early-stage lymphoma were devised by reducing the dose and area of the body treated with radiation therapy in combination with brief chemotherapy such as ABVD. The German Hodgkin Study Group introduced an intensive seven-drug chemotherapy program, "BEACOPP," to address the fact that approximately 30 percent of advanced Hodgkin's lymphoma was not cured with ABVD. Although associated with more severe early toxicity and sterility, a higher cure rate and improved survival were achieved with BEACOPP in a randomized clinical trial (Horning '08).

The development of the drug rituximab as a therapy for B-cell lymphoma (a type of cancer affecting cells of the immune system) provides an excellent illustration of how great improvements in patient care were made through the discovery of a therapy that destroys cancer cells without harming other cells in the body. The discovery of rituximab, an antibody that recognizes CD20, a target shared by malignant lymphoma cells from almost all patients, but also found on normal, immune B cells. Rituximab proved to be effective in treating B-cell lymphoma, and the elimination of normal B cells was surprisingly not harmful. Because rituximab does not affect other normal cells in the body, it can be combined with other therapies. Today, rituximab is part of the regular treatment for almost all patients with B-cell lymphoma, and it has prolonged the lives of many of them. Rituximab can also treat many non-cancerous diseases caused by overactive B cells of the immune system. Rituximab has been used to treat rheumatoid arthritis, multiple sclerosis, and a growing list of non-cancerous conditions (Levy, Malony & Miller '08).

Bone pain, known as myeloma, or multiple myeloma if there are multiple bone infections, is an extremely common serious complication because it is crippling and untreated infections can break through the bone to marrow causing leukemia or through soft tissue to the lymphatic system, causing lymphomas. Bone pain is the primary physical symptom of leukemia and is the most painful symptom in lymphoma. Oral Thalidomide, used in conjunction with dexamethsaome, a corticosteroid, are the first FDA approved chemotherapeutic drugs usually taken by people diagnosed with multiple myeloma and plasma cell dyscracias. Others include: Bortezomib, Carfilzomib, Clafen (Cyclophosphamide), Cyclophosphamide, Cytoxan (Cyclophosphamide), Doxil (Doxorubicin Hydrochloride Liposome), Doxorubicin Hydrochloride Liposome, Dox-SL (Doxorubicin Hydrochloride Liposome), Evacet (Doxorubicin Hydrochloride Liposome), Kyprolis (Carfilzomib), Lenalidomide, LipoDox (Doxorubicin Hydrochloride Liposome), Mozobil (Plerixafor), Neosar (Cyclophosphamide), Plerixafor

Pomalidomide (Pomalyst), Pomalyst, Revlimid (Lenalidomide), Synovir (Thalidomide), Thalidomide, Thalomid (Thalidomide), Velcade (Bortezomib), Zoledronic Acid Zometa (Zoledronic Acid). Radiation therapy may be done to relieve bone pain or treat a bone tumor. Two types of bone marrow transplantation may be tried: Autologous bone marrow or stem cell transplantation makes use of one's own stem cells. Allogeneic transplant makes use of someone else's stem cells. This treatment carries serious risks but offers the chance of improved survival. Many patients with myeloma develop bacterial infections that may be serious, and infectious complications remain the most common cause of death in myeloma patients. In the past, gram-positive organisms (eg, *Streptococcus pneumoniae, Staphylococcus aureus*) and *Haemophilus influenzae* were the most common pathogens. More recently, however, infections with gram-negative organisms, anaerobes, and fungi have become frequent. The increased susceptibility of patients with multiple myeloma to bacterial infections, specifically with encapsulated organisms, has been attributed to impairments of host-defense mechanisms, such as hypogammaglobulinemia, qualitative deficiency in immunoglobulin function, granulocytopenia, decreased cell-mediated immunity, and the prolonged use of steroids.

IV.7 Thoracic Surgery

Thoracic surgery has existed as a specific surgical discipline for more than a century. Initially, its main focus was surgery for tuberculosis and bronchiectasis. However, since 1940, rapid progress has been made in surgery for lung cancer, of the oesophagus and, most spectacularly, of the heart. After 1960, cardiac surgery became a separate subspecialty with an emphasis on coronary bypass surgery, valve surgery and congenital heart surgery. According to the latest data from the National Center for Health Statistics, 48 million surgical inpatient procedures were performed in the United States in 2009. Other surgical statistics for inpatient procedures, include a total of 23 million: Nervous system surgeries: 1.2 million, Eye surgeries: 69,000, Ear surgeries: 24,000, Nose, mouth, and pharynx surgeries: 289,000, Respiratory system surgeries: 1.3 million, Cardiovascular system surgeries: 7.3 million, Digestive system surgeries: 6.1 million, Urinary system surgeries: 1.1 million, Musculoskeletal system surgeries: 5.2 million, Integumentary (skin) system surgeries: 1.4 million. There are more inpatient cardiovascular system surgeries than on any other part of the anatomy. 7.3 million cardiovascular system surgeries comprise 32% and 1.7 million respiratory system (expanded definition) surgeries 7.4% of 23 million total surgical procedures. Combined 8.6 million thoracic surgeries, believed to split the sternum to enter the chest cavity, are 38% of total inpatient surgical procedures.

Mechanical ventilation is used to assist or replace spontaneous breathing. It is implemented with special devices that can support ventilatory function and improve oxygenation through the application of high-oxygen-content gas and positive pressure. The primary indication for initiation of mechanical ventilation is respiratory failure, of which there are two basic types: (1) hypoxemic, which is present when arterial O_2 saturation (SaO_2) <90% occurs despite an increased inspired O_2 fraction and usually results from ventilation-perfusion mismatch or shunt; and (2) hypocarbic, which is characterized by elevated arterial carbon dioxide partial pressure (PCO_2) values (usually >50 mmHg) resulting from conditions that decrease minute ventilation or increase physiologic dead space such that alveolar ventilation is inadequate to meet metabolic demands. The most common reasons for instituting mechanical ventilation are acute respiratory failure with hypoxemia (acute respiratory distress syndrome, heart failure with pulmonary edema pneumonia, sepsis, complication of surgery and trauma), which accounts for +/- 65% of al ventilated cases, and hypercarbic ventilatory failure – e.g. due to coma (15%) , exacerbations of chronic obstructive pulmonary disease (COPD; 13%), and neuromuscular disease (5%). The

primary objectives of mechanical ventilation are to decrease the work of breathing thus avoiding respiratory muscle fatigue, and to reverse life-threatening hypoxemia and progressive respiratory acidosis (McCance '14: 1740).

There are two basic methods of **mechanical ventilation**: non-invasive ventilation (NIV) and invasive (or conventional mechanical) ventilation (MV). NIV has gained acceptance because it is effective in certain conditions, such as acute or chronic respiratory failure and is associated with fewer complications, namely pneumonia and traheolaryngeal trauma. Experience from several randomized trials has shown that, in patients with ventilatory failure characterized by blood pH levels between 7.25 and 7.35. NIC is associated with low failure rates (15-20%) and good outcomes, as judged by low intubation rates. Despite its benign outcomes, NIV is not useful in the majority of cases of respiratory failure and is contraindicated in patients with the cardiac or respiratory arrest, severe encephalopathy, severe gastrointestinal bleed, hemodynamic instability, unstable angina and myocardial infarction, facial surgery or trauma, upper airway obstruction, high-risk aspiration and/or inability to protect airways, and inability to clear secretions. Once the patient has been intubated, the basic goals of MC re to optimize oxygenation while avoiding ventilator-induced lung injury due to overstretch and collapse/re-recruitment. Whichever mode of mechanical ventilation use din acute respiratory failure, the evidence from several important controlled trials indicates that a protective ventilation approach guided by the following principles is safe ad offers the best chance of a good outcome (1) set a target tidal volume close to 6 mL/kg of ideal body weight. (2) Prevent plateau pressure (static pressure in the airway at the end of inspiration) exceeding 30 mc H_2O). (3) Use the lowest possible fraction of inspired oxygen (FIO_2) to keep the SaO_2 at greater than or equal to 90%. (4) Adjust the PEEP to maintain alveolar patency while preventing over-distention and closure/reopening. With the application of these techniques, the mortality rate among patients with acute hypoxemic respiratory failure has decreased to +/- 30% from close to 50% a decade ago (Mcance '14: 1738, 1739, 1743).

The **nasal cannula** is the most common form of oxygen delivery for people with chronic respiratory conditions. They are inexpensive, relatively comfortable, provide a great deal of flexibility, and allow you to pursue daily activities. You can talk, eat and cough while wearing them. A nasal cannula has two small prongs in the nose attached to a tube coming from an oxygen source. Two to six liters of oxygen per minute can be administered, but consistent use of more than three liters per minute may dry the lining of the nose and lead to sinusitis. Bubbling the oxygen through a humidifier before delivery at the nose moistens the gas. At low oxygen glow rates of one or two liters per minute, or with a conserving cannula, it may not be necessary to moisten the gas. A nasal cannula may produce some irritation around the ears. **Face masks**, called the Venti-mask, for oxygen delivery are not often used outside a hospital. **Transtracheal** oxygen delivery is efficient, cosmetically more acceptable for some people, promotes continuous use of oxygen, and reduces breathlessness during eating. For example, a person needing two liters per minute with a regular cannula may need only one liter per minute with a transtracheal catheter. This lengthens the amount of time for one E cylinder from five hours to ten. The system requires a surgical procedure. There are standard methods for inserting a catheter (small tube) through the skin at the front of the neck into the windpipe to enable the direct delivery of oxygen into the trachea. A needs is inserted through the cricothyroid membrane. Then a catheter is introduced through the needle and remains in place after the needle is withdrawn. The oxygen source is connected to the small tube. In order to prevent infection, the catheter needs attention and cleaning on a daily basis (Tucker et al '01: 96, 97, 100).

Intubation, is the insertion of plastic endotracheal tube in the windpipe during anesthesia or to ventilate a patient. Intubation should only be put into place in the patients throat by an anesthesiologist or skilled practitioner because one must be very careful not to damage the airways, and many patients are displeased with the tracheolaryngeal trauma or die from pneumonia. The purpose of the endotracheal tube is to provide a safe and secure airway during surgery and general anesthesia and, in some cases, to control ventilation after surgery or while in the intensive care unit (ICU) with a respiratory disease. In 1920, rubber tubes designed to deliver inhaled anesthetic gases directly into the trachea were introduced. These tubes were called "endotracheal tubes" to denote their position within the trachea. The end of the endotracheal tube coming out of the mouth is connected to the anesthesia breathing circuit. A low-pressure cuff (balloon) on the outer portion of the endotracheal tube is positioned inside the trachea and is inflated to form an airtight seal between the endotracheal tube and the trachea. This airtight seal prevents any stomach contents fluids or secretions from entering into the trachea or the lungs. The **laryngeal mask airway** (LMA), is another device used to secure a patient's airway. It is inserted in the throat and rests above the vocal chords. The LMA is made of soft rubber and is inserted via the mouth into the back of the throat and rests above the vocal cords after you are asleep (Sweeney '03: 75, 77, 78, 80).

The **American Society of Anesthesiologists (**ASA) physical status score is a grading of general health coming to surgery. Patients with a physical status score of 3 or greater may have a several-fold higher incidence of complications during and after surgery when compared to ASA 1 and 2 patients. This needs to be applied to invasive mechanical ventilation involving intubation to ensure patients adequately try corticosteroids and oxygen by nasal cannula before declaring an emergency and calling in an anesthesiologist to intubate the COVID-19 patient in acute respiratory distress. The number-one factor correlating with complications or mortality associated with surgery was an ASA score of 3 or greater. When "E" (for emergency") is added on the physical status score there is a severalfold increase in risk. Emergency surgery on the patient with a physical status score of ASA 3 or higher can be associated with prohibitive risk. The U.S. **surgical death rate** is estimated that 1.14 percent of patients who go in for surgery never leave the hospital. Researchers in the United Kingdom looked at more than 46,000 patients in 28 European countries who underwent non-cardiac surgery. They found that 4 percent of them died before they could make it out of the hospital. Nearly 75 percent of patients in Europe who died did not get admitted to an intensive care unit (ICU). The surgery death rates that the researchers found in other countries ranged from Latvia, which at 21.5 percent had the worst death rate, to Iceland with a rate of 1.2 percent (Padel '12).

American Society of Anesthesiologists (ASA) Physical Status Scoring System

ASA Score	Physical Status
ASA 1	A normal, health patient
ASA 2	A patient with mild to moderate systemic disease
ASA 3	A patient with severe systemic disease that is not incapacitating
ASA 4	A patient with incapacitating illness that is a constant threat to life
ASA 5	A moribund patient who is not expected to survived twenty-four hours with or without surgery
ASA 6	Organ donor. Brain dead patient for organ harvesting. Included in the physical status scoring system is the

	designation “E” for emergency.

Source: Sweeney ’03: 42

More than 3 million children receive anesthesia in operating rooms in the United States each year. Infants and young children are at significantly higher risk of a serious complication or death associated with anesthesia than older children and adults. Infants and small children have substantially higher metabolic rates and oxygen demand. The infant has much smaller lung volumes, a smaller airway that is more prone to obstruction, and far less respiratory reserve. The epiglottis is relatively large and floppy; minor airway irritation or infection (croup, epiglottitis) may result in swelling that can cause dangerous narrowing or even closure of the airway. Infants are prone to cold stress, which may lead to cardiovascular instability, decreased oxygen levels in the blood, and bleeding disorders. These physiological conditions present in infants and small children make them far more prone to life-threatening complications, including hypoxemia (low oxygen level in the bloodstream) and cardiac arrest. Anesthesia for infants and small children requires specialized equipment and skill set. Studies who that the “occasional” pediatric surgeon has substantially higher complication rates, including death, than the surgeon who regularly performs surgery on children (Sweeney ’03: 37, 38, 40, 43).

Upper airway obstruction must be differentiated from respiratory distress caused by pulmonary, neurologic, cardiovascular and esophageal disorders. Upper airway obstruction in adults tends to be inflammatory or neoplastic, whereas in children it tends to be inflammatory or congenital. While the narrowest part of the adult airway is the glottis, in children it is the subglottis. Newborns are obligate nasal breathers because they have a high riding larynx. Any nasal obstruction can produce cyclical cyanosis. The baby cries once the cyanosis becomes uncomfortable and is able to breath through the mouth. The character of noisy breathing in relation to the respiratory cycle helps localize the site of obstruction. Treatment centers on relief of the airway obstruction. If airway support is indicated, the safety of intubation versus tracheotomy must be determined. If complete airway obstruction occurs and intubation is not possible, **emergency cricothyrotomy** may be the simplest way of achieving an airway. This procedure can be performed through a small horizontal or vertical incision made directly through the skin, subcutaneous tissues and cricothyroid membrane, preferably with a single stab. Care is taken not to enter the esophagus or the posterior wall of the trachea. An endotracheal tube, tracheostomy tube, or other instrument is inserted atraumatically. Bleeding is controlled with digital compression of the vessels. The patient should then be transported to the operating room for more definitive treatment. Cricothyrotomy should not be attempted on young children, because the cricothyroid space is too small to accommodate a tube large enough for ventilation. (Wynn & Goldsmith '04: 257, 260, 261).

Tracheostomy is one of the most ancient operations and has long been used for the emergency management of upper airway obstruction. In the past two decades, tracheostomy has been increasingly employed to control secretions in severely ill patients. More recently, tracheostomy has provided a route for ventilator support in respiratory insufficiency. A spectrum of lesions, principally associated with its use has been identified. Tracheostomy often cnnot be avoided in organic upper airway obstruction, although sometimes a tube may be slipped past an obstruction transiently until definitive treatment is provided. Patients with respiratory insufficiency or impening failure are usually supported by respirator with an endotracheal tube for varying lengths of time. If it appears that more than a day or so of support will be required, a nasotracheal tube is generally preferred for patients' comfort. If it becomes clear that long-term support will be needed, a tracheostomy is usually done as an elective procedure within 5 to 7

days. Such a transfer becomes necessary because of the dangers of tube obstruction, the discomfort to the patient of a nasal or oral tube, and the considerable damage to the larynx that may result from prolonged intubation. Tracheostomy is only rarely an emergency procedure.

The safest way to establish an emergency airway is by insertion of an **endotracheal tube**, or, failing that, introduction of a ventilating bronchoscope. The simplest emergency surgical airway, an opening in the superficially located crico-thyroid membrane is rarely required. Tracheostomy may be done under local anesthesia, with the patient supine and the neck hyperextended. The speedily made vertical cutaneous incision for emergency tracheostomy has been replaced by a carefully placed horizontal incision. This avoids the late tethering scars that may follow the vertical incision. Palpation of the extended neck always reveals the position of the cricothyroid membrane and the cricoid cartilage below this. The incision is placed at the level of the second tracheal cartilage and carried through the platysma. The strap muscles are separated vertically in the midline with minimal bleeding. The lower border of the cricoid cartilage is clearly defined, and the incision between the strap muscles and its subjacent fascia is carried down to a point below the thyroid isthmus. The thyroid tissue on either side is controlled with mattress sutures. Exact levels of the cartilaginous rings must be determined. The first cartilage must be left intact, and the opening in the trachea must be placed so that there will be no tendency for the tube consequently to erode the first ring or the adjacent cricoid cartilage by upward pressure. The second and third cartilages and all or part of the fourth if necessary) are incised vertically in the midline to avoid the potential danger of upward pressure by the outside of the elbow of the tube. There is little controlled work to prove the superiority of the vertical incision over the cruciate or the horizontal incision.

The longer-term **complications of tracheostomy** present largely in three ways (1) sepsis, (2) hemorrhage, or (3) obstruction of the airway. Additional complications are tracheoesophageal fistula and persistence of the stoma. In general, the longer a tracheostomy is in place (especially with an inflated cuff) the greater is the chance that complications will occur. All tracheostomies are clinically contaminated and *Staphylococcus aureus* (often a resistant strain), *Pseudomonas aeruginosa*, and a variety of other bacteria such as *Escherichia coli* and *Streptococcus* can be cultures. Sepsis should be treated preventatively in post-tracheostomy patients with prescriptions for oral erythromycin, doxycycline and/or metronidazole. Two hundred seventy-nine patients with post-intubation tracheal injuries were submitted to surgical reconstruction at the Massachusetts General Hospital from 1965 to 1982. Two hundred and twenty-five patients has good to excellent results, and in 25 the results were clinically unsatisfactory including five deaths (Grillo '86: 2000-2005).

Because of abnormalities with breathing any surgery is a problem. If the disease is mild, it may not increase the risk of surgery much, if at all. If disease is severe, the person is not likely to survive long just because of the severity of the lung problems, then surgery is probably not an option. To decide how bad the lung situation is, **lung function** is measured. Categorizing lung function as mildly, moderately or severely abnormal is generally based on the FEV_1 test, the amount of air exhaled in the first second of blowing. The worse the abnormality in lung function, the higher the surgical risk. Maximal voluntary ventilation is measured by what the person can actually breathe with a major effort. This is determined in the laboratory by how much air can move in and out by really hyperventilating, breathing hard and fast for several seconds, at maximal effort. Some surgeons prefer to have the person exercise while they watch. If lung function measurements indicate that the person has moderate or severe disease, then arterial blood gases are drawn so the lungs' ability to get rid of carbon dioxide can be evaluated.

Getting rid of carbon dioxide is a measure not only of lung function but also of the brain's activity in signaling the lung muscles to take a breath. Arterial blood gases are also measured for oxygen in the blood, an important number to guide the anesthesiologist in the operating room (Tucker et al '01: 198).

How much **risk surgery** carries in people with COPD depends on what part of the body is to be operated on and the type and amount of surgery, as well as quality and quantity of lung function. An operation on the lower leg or neck is unlikely to be very risky, even in someone with severe disease, because the surgery itself will not interfere with the ability of the lungs to breathe, or with coughing. Lung disease does not become worse as a result of such surgery. A short procedure where an intestinal specialist looks into the swallowing tube and stomach, is not risky. When a lung specialist looks into the windpipe and bronchial tubes, the risk is usually low, though wheezing and increased shortness of breath may occur. Operations done high up in the abdomen or in the chest itself, can interfere with the ability to cough and clear out phlegm because of pain causing a reluctance to breathe deeply. For abdomen or chest surgery, the extent of the surgery is very important. Heart surgery, done by splitting apart the sternum (the hard center cartilage in the front of the chest) is less risky than lung surgery done by making a long incision between the ribs. Getting into the chest by cutting between the ribs, cuts through a lot of nerves and also the lung will have to collapse to let air into the chest. The sternum lacks nerves and causes much less pain when it is split. One operation thus causes a lot more pain than the other, difficulty coughing, deep-breathing and clearing out phlegm. However, new anesthesia techniques have cut the risk in this procedure. In general, procedures done under local anesthesia, where the anesthesiologist only deadens the area to be operated on, or with regional anesthesia, where only the nerves leading to the surgical site (usually an arm or leg are deadened, are not risky for those with lung disease. Procedures where the person is sedated enough to prevent the procedure from being frightening or painful, but where the person is still awake, also carry a very low risk. Operations which can be done with low spinal anesthesia, such as some procedures below the waist, carry a low risk as they don't interfere with lung function after the surgery. Higher risk procedures are those done with spinal anesthesia where the anesthesia has to go above the waist, and those done with general anesthesia. General anesthesia means the patient is put completely to sleep, and a tube is placed in your windpipe for breathing. For most of the operation you are in a coma and cannot breathe for yourself so the anesthesiologist has to do it for you. The risk increases because the anesthetic techniques interfere with breathing and with the normal ability of the lungs to clear out mucus. Even a very skilled anesthesiologist cannot clear out phlegm as effectively as deep breathing and coughing. After procedures done with this type of anesthesia, a breathing machine may be needed for temporary life support, which may also increase the risk of complications (Tucker et al '01: 199).

Lung Function and Surgical Risk

Lung Function	FEV_1 as a percent of normal value	Surgical risk
Normal	More than 80%	Not increased
Mild	60-805%	Not increased
Moderate	40-60	Somewhat increased
Severe	Less than 40%	Very increased

Source: Tucker et al '01: Table 24

For someone with lung disease it is very important to decide before surgery **whether they can tolerate the removal of any lung tissue**, and if so, how much. For example, if the patient already has moderate COPD and gets short of breath with ordinary activity, removing any good lung tissue at all may leave the patient completely disabled. If too much is removed, the patient may not be able to breathe well enough after surgery to come off the life-support breathing machine. Because of these problems, lung doctors attempt to figure out before surgery how much lung function will be left after surgery. A decision has to be made whether the remaining lung function will be enough to get by on, and whether the surgery is worth the risk of ending up a respiratory cripple. Deciding about the effect of lung removal is done by performing a combination of tests. First, breathing function is measured with spirometry, usually after using a bronchodilator to open the bronchial tubes as much as possible. The FEV_1 is calculated. Then a test called a lung scan shows where in the lung the blood flow goes. A tiny amount of radioactive material is injected into the arm. How much blood flow goes to the right lung and how much to the left is calculated, and how much is in the lower half of the lung and how much in the upper. These two tests are put together to figure out what will happen after surgery. For, example, if one has lung cancer in the lower part of the right lung, to remove all the cancer requires removal of half the right lung. FEV_1 is 2.0 liters, 50% of expected. The lung scan shows that 50% of the lung function is in each lung. In the right lung, 50% of the function is in the lower half. This means that the surgeon would expect you to lose 25% of the total function by taking out the lower right lung, or half of the 50% on the right. After surgery, FEV_1 would be expected to be 1.5 Liters (2.0 Liters x 75%). The patient should be able to breathe well enough after surgery that the cancer can be surgically removed. On the other hand, suppose that FEV_1 is only 1.0 Liter, 25% of expected. In order to remove the lung tumor, one half of the right lung has to come out. If the blood flow in the lung is going half to the right and half to the left, and in the right lung half of its flow is in the bottom, FEV_1 will be only 0.75 Liters after surgery. This is probably not enough to breathe well enough to live independently. Surgery should not be performed. The decision may be to treat the lung cancer with radiation or chemotherapy (Tucker et al '01: 199, 200).

Patients with **head and neck cancer** are often nutritionally deficient because they have difficulty eating animal products, bread and protein. The patient should be brought into positive nitrogen balance to reduce postoperative complications and improve tolerance to radiotherapy and/or chemotherapy (Jacobs '89: 214). The extent of surgical resection is dictated by the extent of tumor at staging. The primary lesions should be widely excised leaving negative margins. Primary closure of the surgical defect is preferable, but local or regional skin flap should be utilized when required. In the oral cavity a composite resection includes the primary, part of the mandible (if necessary) and cervical nodes. For patients in whom tumor approaches, but does not grossly involve, adjacent bone, a partial mandibulectomy may be performed. Gross bone invasion demands segmental mandibular resection, the extent of which depends on the degree of clinical involvement. In the oropharynx, if the lesion is below the level of the arytenoids, a total laryngectomy is recommended because of aspiration. In the supraglottic larynx a supraglottic laryngectomy can be performed if the cancer is confined to the supraglottic region and the forced expiratory volume (FEV) is more than 60%.

A total **laryngectomy** should be done if (1) tumor extends to the commissures, artyenoids, thyroid cartilage, or glottis, (2) there is impaired mobility or fixation of vocal cords. In the larynx, hemilaryngectomy is appropriate to T_{1-2} failures of radiation. For patients with known neck disease, a standard radical neck dissection should be performed. This includes the superficial and deep cervical fascia with its enclosed lymph nodes, the sternocleidomastoid and omohyoid muscles, the internal and external jugular veins, the spinal accessory nerve, and the submaxillary gland. . For patients with cancers of the oral cavity, oropharynx, and supraglottic larynx in whom surgical management of the neck is chosen, a functional neck dissection should be performed. This leaves the sternocleidomastoid, the internal jugular vein and the spinal accessory nerve intact. In addition to the post-operative problems with postoperative infections and bleeding the long term problems include the following (1) cosmetic deformities, (2) speech impediment, (3) aspiration pneumonia and (4) shoulder droop and pain resulting from accessory nerve dysfunction following neck dissection (Jacobs '89: 216).

For **parotid cancers** that are low-grade and involve only the superficial lobe, a superficial parotidectomy may be performed. For all others, a total partodiectomy is recommended. The facial nerve can often be preserved, but if it is involved and needs to be sacrificed, a nerve graft may preserve function. At the time of the surgery, if peri-parotid nodes are positive, a radical neck dissection should be performed. Treatment of minor salivary gland cancers includes a wide excision. Most would recommend postoperative radiation for patients with high-grade cancers, positive margin, perineural invasion, deep lobe involvement, and regional lymph node metastases, at a minimum dose of 5000 cGy to 5500 cGy or 6600 cGy for positive margins. Primary radiotherapy is reserved for inoperable patients (Jacobs '89: 220, 221). Almost all tumors of the nasopharynx are managed primarily by means of radiation therapy. However, almost all tumors of the salivary glands are managed primarily with surgical excision (Schwartz, Har-El & Aziz '04: 453-457).

Lung cancer is the most common fatal neoplasm in the United States in both women and men. It has replaced tuberculosis as the major pulmonary cause of death. Approximately 150,000 new cases were diagnosed in 1988. Over the past 40 years, long-term survival after the diagnosis of lung cancer has shown little or no improvement. The overall 5-year survival rate is approximately 10% to 15%. Chemotherapy for small cell lung cancer has advanced significantly, resulting in prolongation of life but few long-term survivors. Operative mortality has decreased from 10% to 3%. The incidence of discovery of unresectable tumor at the time of thoracotomy has decreased from 25% to 5%. Because of the disappointing results of surgical therapy for lung cancer treatment lies in prevention, through smoking cessation (Miller & Johnston '89: 319-321). Most patients with benign lesions do not need an operation. Non small cell lung cancer (NSCLC) - squamous (epidermoid) carcinoma, adenocarcinoma and large cell carcinoma of the lung comprise approximately 75% of all cases of lung cancer in the United States. Squamous cell carcinoma is most clearly related to cigarette smoking, and possibly candidiasis. Surgical therapy is offered as the best chance for cure in non-small cell carcinoma of the lung. For patients with non-small cell lung cancer who are not surgical candidates radiation therapy can be effective, particularly for palliation of symptoms of bronchial obstruction, bone pain, superior vena cava syndrome, or spinal cord compression. Radiotherapy has occasionally been curative, but most patients suited for cure by radiation are also surgical candidates and receive surgery. Potentially curative doses of radiation will cause loss of pulmonary function, which is often comparable to loss from resection (Miller & Johnston '89: 328, 332). Surgical resection is integrated into the management of some intra-thoracic Stage III NSCLC with advanced primary tumors and absence of mediastinal node involvement with a 5 year survival as

high as 20% to 35% (Ihde '89: 192-194). Patients with stage I, II, or IIA disease are usually assigned surgical therapy, whereas those in stages IIIb and IV are generally not believed to be candidates for curative surgery. (Miller & Johnston '89: 328-331). Patients with Small Cell Lung Cancer (SCLC) are markedly more responsive to chemotherapy than are patients afflicted with other lung cancer cell types. Effective combination therapy has led to four- to fivefold improvement in median survival compared to untreated patients and a small fraction apparently enjoying a long-term cure (Ihde '89: 195).

Lobectomy, pneumonectomy, segmentatectomy or wedge resection, sleeve resection, decortication or thymectomy may be indicated by the surgeon's intra-operative findings. The chosen procedure will remove all of the tumor with adequate margins of resection and maximum conservation of normal lung tissue. Postoperative mortality of 3% for lobectomy and 5% to 8% for pneumonectomy can be anticipated. The five year survival rate following complete resection of Stage I NSCLC is 40% to 50% and for State II 15% to 30%. Surgeons must take precautions that they do not remove too much parenchymal tissue to cause respiratory insufficiency. The predicted postoperative FEV_1 should exceed 800 ml. Loss of pulmonary function is roughly proportional to the percentage of total lung resected. The five year survival rate by clinical stage is as follows I (45-50%), II (25-30%), IIIa (15-20%), IIIb (5%), IV (2%). Patients with stage I, II, or IIA disease are usually assigned surgical therapy, whereas those in stages IIIb and IV are generally not believed to be candidates for curative surgery. Metastasis to contralateral mediastinal or hilar nodes places a patient in a nonsurgical category. Direct chest wall extension and selected instances of mediastinal invasion in the absence of mediastinal nodal metastasis are potentially surgically curable. Cervical mediastinoscopy is a minor procedure that is usually performed under general anesthesia. A small incision is made in the suprasternal notch, and the pretracheal space is entered. An instrument similar to a laryngoscope is inserted and advanced into the middle mediastinum. Paratracheal, high parabronchial and subcarinal lymph nodes can be routinely sampled. Since the trachea lies posterior to the aortic arch and main pulmonary arteries, the surgeon does not have access to the anterior and superior mediastinum. Mediatinoscopy carries a less than 2% complication rate and changes the clinical staging in 30% of lung cancer patients. It is the most important factor in increasing the resectability rate to well over 90% in patients undergoing exploratory thoracotomy (Miller & Johnston '89: 328-331).

Lung transplants are much more dangerous than heart transplants with a 50% and 90% 3 year survival rate respectively. Between 1963 and 1980, approximately 25 patients had one lung replaced and a few patients had transplantation of one pulmonary lobe. One patient in 1970 had transplantation of both lungs. The longest survival from this era was 10 months. In the 1980s, using cyclosporine plus other immune-suppressants, the Toronto lung transplant group resumed single lung, and occasionally double lung, transplantation in patients with end-stage primary lung disease, with promising results in more than 20 patients. The single lung transplant is used for end-stage pulmonary fibrosis, and the double lung transplant for non-fibrotic end-stage disease such as emphysema. The three main problems for the early lung transplant patients were suboptimal quality of cadaver donor lung, disruption of bronchial anastomoses, and graft rejection. Combined heart-lung transplantation was undertaken initially at Stanford University in the 1980s for patients with end-stage pulmonary hypertension. The combined heart-lung transplant is much more complex and less successful than transplantation of the heart alone; nevertheless it is more than 50% successful for at least 3 year as performed in experienced centers (Weill '89: 601). Although lung transplantation remains a high-risk procedure, survival results have improved over the past decade. Five-year survival is now about 50% overall, but more experienced centers now regularly report 5-year survival figures in the region of 70%

However, long-term survival remains low compared with transplantation of other solid organs, due to chronic infection and rejection leading to bronchiolitis obliterans syndrome (BOS), which remains the Achilles' heel of lung transplantation.

Trauma is the leading cause of death and disability among Americans younger than 40 years. In the United States more than 150,000 violent deaths occur each year and more than 500,000 trauma victims are left with permanent disabilities. It is estimated that more than $100 billion are spent annually on trauma situations. Primary causes of death from trauma are related to laceration of the brain, brainstem, high spinal cord, heart, aorta, or other large vessel (Ovchinsky & Turk '04: 314). **Head and neck surgery** is well-recognized subspecialty of otolaryngology. The anatomic and physiologic complexity of the head and neck makes it one of the most challenging regions of the body. All five senses function in this region, with four of them (vision, hearing and balance, taste and smell) limited to the head and neck region. In addition, crucial functions such as breathing, swallowing, coughing and speaking depend on intact anatomy and physiology of the head and neck (Har-el '04:196). **Rhinoplasty** is the surgical correction of congenital or acquired defects of the nose. **Rhytidectomy** and meloplasty are technical terms for a face lift. **Brow lift** is a procedure aimed at surgical rejuvenation of the upper third of the face, also known as the forehead-glabella-brow unit. **Blepharoplasty** is a surgical correction of eyelid deformities. **Otoplasty** is the surgical alteration of the appearance of the auricle, usually for outstanding (lop) ears. **Cutaneous laser surgery** involves use of high-intensity light either in continuous wave or pulsed form (Ovchinsky & Turk '04: 333-337).

Parathyroid gland surgery is performed if **s**ome calcium stones are caused by overactive parathyroid glands, which are located on the four corners of your thyroid gland, just below your Adam's apple. When these glands produce too much parathyroid hormone (hyperparathyroidism), calcium levels can become too high and kidney stones may form as a result. Hyperparathyroidism sometimes occurs when a small, benign tumor forms in one of the parathyroid glands or another condition leads these glands to produce more parathyroid hormone. Removing the growth from the gland stops the formation of kidney stones. Or a doctor may recommend treatment of the condition that's causing your parathyroid gland to overproduce the hormone. Surgery is the most common treatment for primary hyperparathyroidism and provides a cure in at least 90 percent of all cases. A surgeon will remove only those glands that are enlarged or have a tumor (adenoma). If all four glands are affected, a surgeon will likely remove only three glands and perhaps a portion of the fourth — leaving some functioning parathyroid tissue. Surgery may be done as an outpatient procedure.

Heart surgery is used to correct heart problems. Cardiac surgery is the most invasive and perhaps the most risky of all operations. To accomplish heart surgery, you may be subjected to incredible physiological derangements, like induced cardiac arrest, and placement on a heart-lung bypass machine. To monitor cardiac surgery patients, high-tech and invasive monitors are used. These monitors may be placed directly on the heart (the Swan-Ganz monitor) or in the esophagus (transesophageal echocardiography) to monitor heart function during and after surgery. Scientific literature suggests that surgical results may be substantially better when performed at a facility doing more than 200 open-heart operations per year (Sweeney '03: 37, 38, 40, 43). The operative risk rate in a good center is around 5 percent or less. Although there has been a trend toward operation on sicker and more elderly patients results continue to improve with overall mortality rates for otherwise healthy individuals of less than 3% (Heger et al '04: 263). Risk of dying during bypass surgery 4.6 – 11.9 percent. Risk of permanent brain damage from bypass surgery 15-44 percent. Recipients of bypass surgery for whom it prolongs life 2

percent. Risk of death during angioplasty 0.4 – 2.8 percent. Risk of major complications developing during angioplasty 10 percent. Studies that have found that angioplasty prolongs life or prevents heart attacks but serious mechanical complications can result from trying to threat a tube through an artery. Patients undergo bypass and angioplasty operations primarily to relieve angina and improve blood flow to the heart. Yet there is however a 25 to 50 percent likelihood that within six months their blood vessels will again be blocked, and their chest pain will recur, assuming they continue to eat a meat-based diet (Robbins '01: 23). Opening up blocked arteries via either surgery on the carotid (neck) artery or stenting (inserting a metal expanding sleeve into a narrowed artery to hold it open) reduces stroke risk substantially: in persons in whom the carotid artery is narrowed by 70 percent or more and who have had warning symptoms of stroke, surgically removing the inner layer of the artery with the plaque that is blocking the artery (endarterectomy) – reduces stroke or death by two-thirds over two years. (For patients with a narrow carotid artery who have not yet had warning symptoms of a stroke, surgery is only for those at high risk of stroke, as evidence by the particles breaking off the plaque (microemboli) that can be detected by ultrasound of the brain arteries (transcranial Doppler). Patients need to follow their diet, quit smoking and take medication (Spence '06: x, 72).

Heart surgery can be done to: correct a congenital heart defect, repair abnormal or damaged arteries and structures in the heart; repair or replace valves that control blood flow through the heart; Implant medical devices that regulate heart rhythms or blood flow; or replace a damaged heart with a healthy heart from a donor (heart transplant). Traditional **open heart surgery**, is done by opening the chest wall to operate on the heart. Almost always, the chest is opened by cutting through a patient's breastbone. Once the heart is exposed, the patient is connected to a heart-lung bypass machine. The machine takes over the pumping action of the heart. This allows surgeons to operate on a still heart. Heart surgery is done to correct problems with the heart. More than half a million heart surgeries are done each year in the United States for a variety of heart problems. For very ill people with severe heart problems, heart surgery can reduce symptoms, improve quality of life, and increase lifespan (Sanders '08: 20). Ferdinand Sauerbruch (1875-1951) was a German surgeon who introduced a new era into the surgery of the pleural cavity. As a result of the **differential pressure procedure** he invented it became possible to open the thorax in a low-pressure chamber, without the lung collapsing and respiration ceasing. Today the differential pressure procedure has been replaced by endotracheal narcosis and artificial bronchial respiration. Through the creation of the **heart-lung machine**, the most difficult heart operations, such as the artificial replacement of the heart-valve, have become possible, today thousands of people are walking around with artificial heart-valves made of Silastik, synthetic material that is not rejected by the living organism. **Electrical pacemaker** machines are set into the pleural cavity to govern the constant stimulation or regulation of the disturbed activity of the heart (Venzmer '71: 341, 342). At the end of 1967 Professor Christian Barnard, a surgeon in Cape Town, South Africa, succeeded in transplanting the heart of an accident casualty into a patient whose own heart was on the point of failing. In 1968 other **heart transplants** were undertaken with varying success in the U.S.A. Japan and in Europe. Once the immunity barrier is conquered and the rejection reaction arrested, a whole new era of medicine dawned (Venzmer '71: 341, 342, 345, 346). Approximately 20,000 operations of the heart and circulation in patients with congenital heart disease are performed each year in the United States. Nearly 80% of the first-year survivors live to reach adulthood. The trend in cardiac surgery for congenital heart disease has gone from palliative to staged anatomic correction to single-stage total repair (Heger et al '04).

The most common type of heart surgery for adults is **coronary artery bypass grafting** (CABG). More than 500,000 operations were completed in 2000 (Heger et al '04: 263). Bypasses are done using grafts of either autologous reversed saphenous vein or internal mammary artery (usually the left internal mammary artery is used owing to the proximity to the heart). The long-term patency of saphenous vein grafts is 60% or less at 10 years, owing to pathologic changes, including thrombosis (usually occurs early), intimal thickening (which usually occurs several months to several years postoperatively) and atherosclerosis in the graft, sometimes with superimposed plaque rupture, thrombi or aneurysms (usually more than 2 to 3 years). In contrast the internal mammary artery has a greater than 90% patency at 10 years (Schoen '94: 515). The clinical performance of a **vascular graft** depends primarily on its type and location. Large-diameter (>10 cm) Dacron grafts in current use function well in high-flow, low resistance locations such as the aorta. In contrast, small-diameter fabric vascular grafts (<6 to 8 mm in diameter) perform less well. The most widely used small vessel replacements are autologous saphenous vein (the patient's own vein, dissected free, reversed in direction, and transplanted to a different site) and expanded-polytetrafluoroethylene (ePTFE), essentially a spongy Teflon fabric. Failure of small-diameter vascular postheses (<6 mm diameter) is most frequently due to thrombotic occlusion or intimal fibrous hyperplasia, either generalized (in vein grafts) or anastomotic (in synthetic grafts). The ability to endothelialize cardiovascular prostheses is limited in humans and full endothelialization of clinical grafts is unusual. Luminal coverage develops relatively slowly and incompletely, formation of neointima (a surface covered by endothelial cells, is generally restricted to a 10 to 15 mm zone near the anastomosis and the remainder of the graft surface constitutes a pseudointima (thrombus or cells other than endothelial cells) (Schoen '94: 514). It has been recognized for many years that the left internal mammary is the optimum coronary artery bypass conduit, with a patency rate of more than 90% at 10-year follow-up. During CABG, surgeons use healthy arteries or veins taken from another part of the body to bypass (that is, go around) blocked arteries. CABG relieves chest pain and reduces the risk of heart attack. Minimally invasive techniques allow surgeons to perform single and sometimes multiple coronary bypass operations through small anterior thoractotomy incisions instead of the traditional median sternotomy. The left internal mammary artery is anastomosed to the left anterior descending artery with the heart beating, thus avoiding the risks of cardiopulmonary bypass and cardiac arrest. There is however concern regarding the long term patency of minimally invasive procedures (Heger et al '04: 263).

Surgery for patients with end-stage congestive heart failure currently is limited to **heart transplantation**, frequently after a period of left ventricular assistance with a mechanical device. Transplant surgery makes use of the super-cooled foreign organs of people who have died in accidents, is complicated by the defense mechanism of the organism against foreign albumen. The number of heart transplants performed in the United States each year is limited to approximately 2,000 (2,500 worldwide) because of the shortage of donor organs. Patients older than age 60 have been shown to have similar early mortality ad length of hospitalization as younger groups. Five year survival ranges from 71% in older patients to 82% in younger patients. The major current limitation to the long-term success of cardiac transplantation is late, progressive diffuse stenosing intimal proliferation of the coronary arteries (graft arteriosclerosis), which is a problem because denervated hearts feel no chest pain, and congestive heart failure or sudden death is the usual outcome. Hypercholesteremia affects 60-80% of recipients and may contribute to coronary vasculopathy. Statins reduce the level of cholesterol and appear to have the added advantage of decreasing the incidence of cardiac rejection. The outlook is good with a 1-year survival of 70 to 80% and 5 year survival of more than 60% Transplant atherosclerosis is responsible for many later deaths (Heger et al '04: 264). Three major factors contribute to the

widespread success of cardiac transplantation; (1) better selection of candidates, (2) improved maintenance immunosuppression (including the use of cyclosporine A, along with steroids and azathioprine) and (3) early histopathologic diagnosis of acute allograft rejection by sequential endomyocardial biopsy. When myocardial injury is not extensive, the rejection episode is usually successfully reversed by increased immunosuppressive therapy. Advanced rejection may be irreversible and fatal often as the result of infection and development of malignancies, particularly lymphomas (generally related to fungus or the Epstein-Bar virus in the presence of profound chronic therapeutic immunosuppression) (Schoen '94: 580).

In **catheter ablation** a long thin medical device called an ablation catheter is inserted by hand through a blood vessel and then is guided into the heart using x-ray or mapping equipment to find and treat abnormal rhythms. The success rate of catheter ablation is 90 percent or greater for superventricular tachycardia, such as atrial flutter, atrial tachycardia, AV node, AV node reentrant tachycardia, Wolff-Parkinson-White syndrome, 50 to 85 percent for atrial fibrillation, 50 to 75 percent for ventricular tachycardia from coronary artery disease and 90 percent or greater for focal ventricular tachycardia (Cohen '10: 87, 89). Although the risks vary depending on the case, cardiac catheterization in a stable patient at a catheterization laboratory carries a less than 1% probability of morbidity, with major complications such as stroke, myocardial infarction, major bleeding, less than 0.5% and overall mortality less than 0.2% (Heger et al '04: 93. The solution for dysrhythmia is often an implanted battery-powered pacemaker which will jolt the heart to keep it in line. An **implantable cardioverter defibrillator** (ICD) is connected to at least one wire, which is typically inserted through a blood vessel into the heart. A doctor may prescribe an ICD if there might be a high risk for sudden cardiac death without one. An ICD helps to treat lethal arrhythmias such as ventricular tachycardia and ventricular fibrillation (Cohen '10: 16, 28). When the heart rate is too slow, a person may develop symptoms and may need to have a **pacemaker** surgically implanted to correct the problem. Disease inside or outside the specialized cardiac conduction tissue can also result in fast heart rhythm problems that might require treatment with medications, catheter ablation (a procedure that identifies the heart rhythm abnormality and destroys specific tissue to cure the rhythm problem) or an implantable device such as a defibrillator (Cohen '10).

A **pacemaker pulse generator** is used to treat slow heart rhythms. One, two or three leads may be attached to the device depending on the number of heart chambers that are required to receive pacing therapy. **ICDs** were developed in the early 1980s and are very similar to pacemakers. ICDs help regulate both fast rhythms (tachycardias) and slow rhythms (bradycardias). Simply put, ICDs monitor the heart rate, and if it is greater than a predetermined (or programmed) value, the ICD may deliver therapy to treat the arrhythmia. Ventricular tachycardia or ventricular fibrillation may be treated by the delivery of a shock (defibrillation) or rapid pacing (also called antitachycardia pacing). This ability to deliver a shock to the heart to terminate tachycardias is one important difference between and ICD and a simple pacemaker. **Implantable cardiac monitors** are useful in identifying very rare or infrequent abnormal cardiac rhythms that may result in light-headedness, dizziness, or loss of consciousness. The term **pacemaker dependent** is used when a patient is completely dependent on the pacing function from the device and has little or no underlying heart rhythm. (Cohen '10: 106, 109, 117, 126). In the United States, medical devices are regulated by the Food and Drug Administration (FDA). The FDA issues three classifications of recall. The most serious is class I recall, in which the device problem may severely impair the safety of the patient and has the potential for severe injury, including death. A class II recall might also have a risk for injury or death, but these outcomes are much

less likely to occur. A class III recall is for a problem that is not likely to harm the patient, though there is a very remote chance of injury (Cohen '10: 127).

Replacement of damaged cardiac valves with prostheses has become a common and often lifesaving mode of therapy. **Artificial valves** fall primarily into two categories – mechanical prostheses using different types of occluders, such as old style caged balls, tilting disks, or hinged flaps and tissue valves usually bioprostheses consisting of chemically treated animal tissue, especially porcine aortic valve tissue, which has been preserved in a dilute glutaraldehyde solution and subsequently mounted on a prosthetic fram (called a "stent") or cryopreserved aortic homografts offer durability in younger patients without the need for anticoagulation. The Medronic-Hall valve is a pivoting disk mechanical prosthesis that is extremely low profile. The St. Jude and Carbomedics valves are hinged, bileaflet valves that are popular among cardiac surgeons becaue of the excellent hemodynamics and ease of implantation. Cryopreserved **aortic homografts** from deceased human organ donors offer durability in younger patients without the need for anticoagulation. They require special techniques for procurement, storage and implantation and are particularly applicable for patients with native or prosthetic valve endocarditis and the patience to wait for a donor. The Ross procedure is particularly effective in young patients with aortic valve disease. This technique involves replacing the patient's diseased aortic valve with his or her own pneumonic valve and reimplanting the coronary arteries. The pulmonary valve is then replaced with a pulmonary homograft. The Ross procedure offers superior longevity over bioprostheses in younger patients, as well as the advantage of not requiring anticoagulation. **Bioprotheses** continue to the valve replacement of choice in older patients, especially those older than age 70. Three popular bioprotheses are available in the United States: The Hancock and Carpentier-Edwards valves, which are both porcine bioprostheses, and the Bacter pericardial valve, which is constructed from bovine pericardium. Bioprostheses are not composed of living tissue; they are a combination chemically treated biologic tissues and artificial materials. In general, these valves have a low incidence of thromboembolisms, especially in the aortic position. Many patients can go without anticoagulation, but anticoagulation still is advisable for patients with atrial fibrillation, atrial clots, or previous thromboembolism. The primary concern of bioprosthetic valves is valve durability. They are susceptible to primary valve failure as a result of calcification and structural deterioration, which tends to be accelerated in patients under the age of 40 (Heger et al '04). Approximately 60% of substitute valve recipients have a serious prosthesis-related problem within 10 years postoperatively. The most frequent valve-related complications include (1) thromboembolism (local occlusion of the prosthesis by thrombus or distant thromboemboli), (2) partial dehiscence (separation) of the suture line anchoring the valve leading to a paravalvular leak, (3) infective endocarditis, (4) durability problems caused by structural deterioration, and (5) intrinsic (design-related) obstruction to forward flow.

Thromboembolic complications constitute the major problem with mechanical valves. This necessitates long-term anticoagulation. Hemorrhagic side-effects, such as stroke or gastrointestinal bleeding, may arise. Infective endocarditis is an infrequent but serious potential complication developing in about 6% of patients within 5 years of valve replacement. Bioprosthetic valves may develop vegetations that directly involve the prosthetic valvular cusps and can embolize. The major contaminating organisms are staphylococcal skin contaminants (e.g. *S. aureus, S. epidermidis*) early (less than 1 month) postoperatively and streptococci later. Within 10 years postoperatively, at least 30% of tissue valves require replacement for calcification, often with tearing. Other complications, such as hemolysis induced by high blood shear, mechanical obstruction to flow by mechanical valves and dysfunction due to ingrowth of

fibrous tissue, may be serious (Schoen ’94: 556, 557). Surgical approaches the pareserve the mitral apparatus result in substantial improvement in left ventricular function compared to replacement procedures in which the subvalvular apparatus is disrupted. Ideal patients for mitral valve repair are those with concalcified valves and mitral regurgitation. Valve repair can include partial resectin of leaflets, lengthening, shortening, transposition, or replacement of chorda tenineae, and placement of valvuloplasty rings to decrease the dize oth e mitral annulus. In 1996 **minimally invasive valve surgery** began with new technology using smaller incisions, transeosophageal echocardiography (TEE) to assess the competency of the operating room repair, newer perfusion techniques and is as safe or safer than convention open sternotomy cases (Heger et al '04: 265, 266).

An **endarterectomy** is an operation in which a surgeon removes the inner lining of an artery, along with the plaque attached to it. In the case of blockage in the carotid artery, the surgeon makes an incision along the length of the neck, exposing the artery, and clamps the artery above and below the area that needs to be cleaned out. The artery is then opened lengthwise, and the inner lining and plaque are removed. The artery is then sewn closed, the clamps removed and the skin sutured. Some teams routinely put in a shunt. Some medical centers are better than others and it is wise to have a carotid endarterectomy performed in a center where such operations are routine, with a complication rate, established by audit, of 3 percent or less. This surgery should be done by experts with lots of practice, and if a surgeon claims a complication rate of zero, you should assume the complication rate has not been audited and find another surgeon. Until 1991, nobody knew whether this operation produced better results than medical therapy, even though the surgery had been done in about a million individuals. In general surgeons believed that the operation was beneficial, and neurologists had some doubts. In 1991 a major study found that for individuals with severe narrowing of the carotid arteries and symptoms, the benefit of endarterectomy was so clear that the study was stopped after two years, when only 691 individuals had been enrolled. In persons with narrowing of 70 percent or more, stroke and death were reduced from 26 percent to 9 percent over two years; in other words with surgery, they were nearly three times better off. The actual risk at the tie of surgery was a 1 percent risk of death and a 1 percent risk of a severe stroke, with a 4 percent risk of lesser complications. Another clinical trial in Europe produced similar results. In persons with less severe narrowing of the arteries, the benefit of surgery is much less. It is now clear that there is no benefit from surgery in individuals with narrowing less than 50 percent, with narrowing between 50 percent and 70 percent, the benefits depend on other risk factors such as ulceration of the artery, the specific symptoms (ocular vs. hemispheric) sex and associated conditions such as diabetes. The number of patients who need to be treated with surgery (carotid endarterectomy) to prevent 1 stroke in 2 years is estimated for symptomatic narrowing of the carotid artery >70% at 1 patient in 6, for symptomatic moderate narrowing 50-70% 1 patient in 15 and asymptomatic narrowing >60% 1 patient in 67 (Spence ’06: 60, 61, 62, 63).

At one time, **aortic dissection** was almost invariably fatal, but the prognosis has markedly improved. The development of surgical procedures involving the aortic wall and the early institution of intensive antihypertensive therapy permit salvage of 65 to 75 percent of patients (Schoen ’94: 500, 504). Treatment recommendations for aortic aneurysms are based on the size of the aneurysm. Small aneurysms found early can be treated with "watchful waiting." If the diameter of the aorta is small-less than 3 centimeters (cm)-and there are no symptoms, "watchful waiting" and a followup screening in 5 to 10 years may be all that is needed, as determined by the doctor. If the aorta is between 3 and 4 cm in diameter, the patient should return to the doctor every year for an ultrasound to see if the aneurysm has grown. If the aneurysm is between 4 and

4.5 cm, testing should be repeated every 6 months. If the aorta is larger than 5 cm (2 inches around or about the size of a lemon) or growing more than 1 cm per year, surgery should be considered as soon as possible. Two main types of surgery to repair aortic aneurysms are open abdominal or open chest repair and endovascular repair. The traditional and most common type of surgery for aortic aneurysms is open abdominal or open chest repair. It involves a major incision in the abdomen or chest. General anesthesia is needed with this procedure. The aneurysm is removed and the section of aorta is replaced with an artificial graft made of material such as Dacron® or Teflon®. The surgery takes 3 to 6 hours, and the patient remains in the hospital for 5 to 8 days. It often takes a month to recover from open abdominal or open chest surgery and return to full activity. Open abdominal and chest surgeries have been performed for 50 years. More than 90 percent of patients make a full recovery. The risk of rupture for a small abdominal aortic aneurysm (less than 4 cm) is about 2%, aneurysms larger than 5 cm are the most dangerous, with a risk 5 to 10% per year. Timely surgery is key, operative mortality for untreated aneurysms is approximately 5% whereas emergency surgery after rupture carries a mortality rate of more than 50% (Schoen '94: 500).

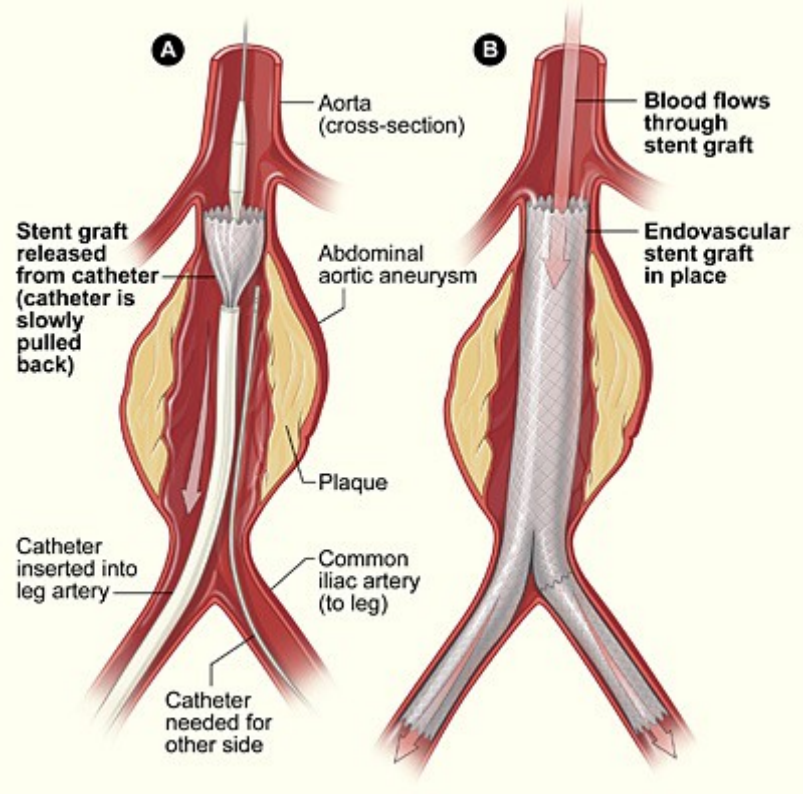
Coronary angioplasty is a medical procedure in which a balloon is used to open a blockage in a coronary (heart) artery narrowed by atherosclerosis. This procedure improves blood flow to the heart. Angioplasty is done on more than 1 million people a year in the United States. Serious complications don't occur often, but can happen no matter how careful your doctor is, or how well he or she does the procedure (Sanders ’08). For arteries that are causing trouble because they are too narrow a stiff-walled balloon on the tip of a catheter can be used to dilate the artery, a procedure called angioplasty. This method is most useful where the problem is due to reduced blood flow in the heart, leg arteries or kidney arteries. In the brain, however, because there are so many backup arteries, the problems from blocked arteries are mainly due not to reduced blood flow but to emboli, that is chunks of artery wall or of plaque. For that reason angioplasty is not very useful at preventing strokes. The process of balloon dilatation of an atherosclerotic vessel characteristically causes plaque fracture, often with accompanying localized hemorrhagic dissection of the adjacent arterial wall. The plaque splits at is weakest point, which is not necessarily the area most severely obstructed. Uncommonly, abrupt reclosure follows the angioplasty. Nevertheless, most patients improve symptomatically following angioplasty, thereby avoiding the need for aortocoronary bypass graft surgery at that time. The long term success of angioplasty is limited by the development of proliferative restenosis that occurs in approximately 30 to 40% of patients within the first 4 to 6 months following angioplasty (Schoen ’94: 513, 514).

Percutaneous transluminal coronary angioplasty (PTCA) has changed extensively since it was developed in 1977. Initially, PCTA was limited to single-vessel lesions in patients with coronary artery disease (CAD) who were symptomatic and undergoing medical therapy. Later this evolved into a much broader spectrum of patients undergoing this nonsurgical technique, including those with multi-vessel CAD, patients with previous CABG surgery and stenosis of the native or graft vessels, patients with acute myocardial infarction who present early in the course to a properly equipped facility, patients with total occlusion, and certain high-risk surgical cases (elderly patients with renal failure, systemic disease, and some with severe left ventricular dysfunction). In experience hands, PTCA is a low-risk procedure with 1% or less mortality and approximately 5% morbidity, including myocardial infarction, infection, bleeding and the need for emergency CABG because of dissection or acute closure. The success rate for experienced operators is 90% per vessel dilated. The major pitfall is that restenosis which occurs in 30 to 50% of cases and to a variable degree in virtually all lesions. Acute gain is difference in lumen

diameter before and immediately after intervention and is the result of arterial expansion or plaque removal. Late loss is the difference in lumen diameter after intervention and at follow-up; late loss is the result of intimal hyperplasia, elastic recoil and vascular remodeling. Restenosis presents as recurrent angina not myocardial infarction or sudden death because the restenotic lesions are less prone to rupture and acutely thrombose. Stenting has had an enormous impact in lowering restenosis rates, accounting for a 30 to 50% decrease. Stenting prevents elastic recoil and constrictive remodeling and are used in more than 80% of interventions (Heger et al '04: 93, 94).

In coronary and other arteries that do not stay open after a simple angioplasty to dilate them, it is necessary sometimes to place a metal frame or stent, like a self-expanding sleeve over the balloon used in angioplasty. When the balloon is inflated, the stent opens up and holds itself in place against the artery wall, so that it stays there when the balloon is deflated. Because a stent in essence covers the artery wall with a mesh preventing chunks from embolizing a stent in the carotid artery or possibly the aorta is likely to be useful for preventing strokes. Aortic stents would have to be huge and could likely be put in place with an operation that involves entering the aorta with a large catheter that could be passed through a needle. At present, stents available are not perfect for the carotid arteries: they can kink when you turn your neck. So far, several clinical trials have shown that angioplasty of the carotid arteries carries a much higher risk than carotid endarterectomy (cleaning out the interior artery wall) (Spence ’06: 71).

Placement of an Endovascular Stent Graft



Credit: American Heart Association

To place an **endovascular stent graft** in an aortic aneurysm a catheter is inserted into an artery in the groin (upper thigh). It is then threaded up to the abdominal aorta, and the stent graft is released from the catheter. The stent graft allows blood to flow through the aneurysm. To

perform endovascular repair, the doctor first inserts a catheter into an artery in the groin (upper thigh) and threads it up to the area of the aneurysm. Then, watching on x ray, the surgeon threads the graft (also called a stent graft) into the aorta to the aneurysm. The graft is then expanded inside the aorta and fastened in place to form a stable channel for blood flow. The graft reinforces the weakened section of the aorta to prevent the aneurysm from rupturing. Endovascular repair surgery reduces recovery time to a few days and greatly reduces time in the hospital. The procedure has been used since 1999. Not all aortic aneurysms can be repaired with this procedure. The exact location or size of the aneurysm may prevent the stent graft from being safely or reliably positioned inside the aneurysm (Sanders '08).

In 1868, two investigators from Prussia and Italy were the first to report that bone marrow generates blood cells in mammals. This observation was the starting point of intense efforts to replace malfunctioning marrow through the transplantation of blood-forming (hematopoietic) cells in humans. However, it took an entire century to develop reliable techniques to identify suitable donors, design potent antibiotics, and establish essential supportive care methods to successfully perform clinical **hematopoietic cell transplantation** (HCT) procedures. This important accomplishment would not have been possible without understanding issues related to graft rejection and the prevention of **graft-versus-host disease** (GVHD), a serious reaction caused by the donor's immune cells attacking the recipient's vital organs. In 1968, three patients in the United States and the Netherlands suffering from severe combined immunodeficiency syndromes, in which the ability of the body's immune system to fight infections is compromised, were successfully transplanted and cured by HCT. Since then, the number of HCT procedures has risen to 50,000-60,000 per year, and the cumulative number of patients treated worldwide has now reached 800,000. The majority of HCT recipients are patients with leukemia, lymphoma, myeloma, myelodysplasia, bone marrow failure conditions, severe red blood cell disorders such as sickle cell disease or thalassemia, and certain solid tumors (Blume '08).

Hematopoietic cell transplant (HCT) can be obtained from suitably matched related or unrelated volunteer donors (allogeneic HCT) or from the patient's own tissues (autologous HCT). Sources of hematopoietic cells include the bone marrow, blood, or umbilical cord blood. International unrelated volunteer donor banks containing information on approximately 12 million volunteers are interconnected by worldwide computer systems. Approximately 3,500 HCT procedures from unrelated donors are now performed annually, and almost 40 percent of such transplants involve a donor who is from a different country from the recipient. In parallel, umbilical cord blood banks are rapidly growing in size and usage. To date, some 10,000 HCT procedures with umbilical cord blood grafts have been performed. The choices of which type of HCT (allogeneic or autologous) and the source of the graft (bone marrow, blood, or cord blood) depend mainly on the patient's underlying disease and whether it is in remission. Before transplant, the patient is treated with high-dose chemotherapy, with or without radiation therapy, to eradicate the cancerous cells (prior to both autologous and allogeneic HCT), and to suppress the patient's immune system to prevent it from attacking the donor hematopoietic cells (prior to allogeneic HCT). More recently, it has been established that less intensive pre-transplant treatment also allows successful transplantation, but with less severe side effects. Such "reduced intensity" transplants prevent later relapses by maintaining the body's ability to launch an immune attack by the new marrow against the cancer. This "graft-versus-malignancy effect" is a critical element for cure through allogeneic HCT. Reduced-intensity regimens have also made it possible to extend HCT to older patients (up to 75 years) and younger patients with health problems that make them ineligible for high-intensity regimens. Significant post-transplant problems can result from toxic effects related to the preparatory treatments, GVHD, infections,

and relapse of the underlying disease. Continued research is leading to further improvements and better survival results. The long-term outcome of HCT procedures depends on whether or not the patient is in remission. While 50-80 percent of leukemia patients can be cured by allogeneic HCT if performed during first remission, the expectation for success is markedly reduced for those whose HCT is carried out in more advanced stages of their disease. Likewise, the long-term results of autologous HCT are strongly influenced by the amount of cancer in the patient's body at the time of transplantation, with relapse being the leading cause for treatment failure (Blume '08).

The indication for **kidney transplantation** is end-stage renal disease (ESRD), regardless of the primary cause. This is defined as a glomerular filtration rate <15ml/min/1.73 sq.m. Common diseases leading to ESRD include malignant hypertension, infections, diabetes mellitus, and focal segmental glomerulosclerosis; genetic causes include polycystic kidney disease, a number of inborn errors of metabolism, and autoimmune conditions such as lupus. Diabetes is the most common cause of kidney transplantation, accounting for approximately 25% of those in the US. The majority of renal transplant recipients are on dialysis (peritoneal dialysis or hemofiltration) at the time of transplantation. However, individuals with chronic renal failure who have a living donor available may undergo pre-emptive transplantation before dialysis is needed. There is good evidence that kidney donation is not associated with long-term harm to the donor. In some cases of male living donors a hydrocele may occur in the scrotum related to the side of the nephrectomy. Traditionally, the donor procedure has been through a single incision of 4–7 inches (10–18 cm), but live donation is being increasingly performed by laparoscopic surgery. This reduces pain and accelerates recovery for the donor. Operative time and complications decreased significantly after a surgeon performed 150 cases. Live donor kidney grafts have higher long-term success rates than those from deceased donors. Since the increase in the use of laparoscopic surgery, the number of live donors has increased. Any advance which leads to a decrease in pain and scarring and swifter recovery has the potential to boost donor numbers. In January 2009, the first all-robotic kidney transplant was performed at Saint Barnabas Medical Center through a two-inch incision. In the following six months, the same team performed eight more robotic-assisted transplants. In 2004 the FDA approved the Cedars-Sinai High Dose IV Immunoglobulin (IG) therapy which reduces the need for the living donor to be the same blood type (ABO compatible) or even a tissue match. The therapy reduced the incidence of the recipient's immune system rejecting the donated kidney in highly sensitized patients. In 2009 at the Johns Hopkins Medical Center, a healthy kidney was removed through the donor's vagina. Vaginal donations promise to speed recovery and reduce scarring. Since medication to prevent rejection is so effective, donors do not need to be genetically similar to their recipient. Most donated kidneys come from deceased donors; however, the utilization of living donors in the United States is on the rise. In 2006, 47% of donated kidneys were from living donors. This varies by country: for example, only 3% of kidneys transplanted during 2006 in Spain came from living donors.

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