ED'S PATHOLOGY MELTDOWN
Part I -- General Pathology

[These notes are intended for students who have already learned the material in a course in general and systemic pathology and who are now preparing for an exam. They showcase related words, without explaining their meanings or their relationships, and without pictures. If you don't already know the "why"'s, you'll never really learn any of this. When you've mastered these notes, go back and enjoy a real textbook. These notes are more current, and "Boards" may be, too.

Clinical correlations follow from the pathology. If you're studying for the USMLE, you'd better be able to go, without thinking, from "necrosis of a large portion of the heart" to "cardiogenic shock" to "shortness of breath, a cold feeling, a weak pulse, and pallor" without even thinking.

You would be stupid to use these while you are actually trying to learn. You would be even stupider to use these as a substitute for your own doctor's advice.

Pathologists talk about suffering without showing much emotion. These notes reflect this. By no means are we an unfeeling lot. For me, the key is this: Science gives us the power to overcome disease and diminish (but never eliminate) human misery. Brackets [] mark stray thoughts added for your enjoyment, rather than for testability.

We also talk about death as inevitable. This is true. But death's not something to be sought, especially while you still have the potential to work, to play, and to love others -- my definition of health. Especially, suicide is almost always a bad idea. Among physically healthy folks who attempted and failed, 99% are happy, one year later, that they failed.

If you've used these notes, then drop me an E-mail message (erf@alum.uhs.edu) and tell me what you think. I claim copyright, which as far as I'm concerned means you can share these notes freely in any medium so long as they're never altered, and never sold for a profit.

The notes are dedicated to my students. Everything that I now do right as a teacher, I've learned how to do from them. Health and friendship.

* * *

Now I lay me down to study

I pray the Lord I won't go nutty;
And if I fail to learn this junk
I pray the Lord that I won't flunk.
But if I do, don't pity me at all
Just lay my bones in the study hall;
Tell my teacher I did my best
Then pile my books upon my chest.
Now I lay me down to rest,
I pray I'll pass tomorrow's test.
If I should die before I wake
That's one less test I'll have to take.
-- Author unknown!]

["Where there is love of medicine, there is love
of humankind."
-- Hippocrates]

[The philosophic basis for pathology comes up often enough on rotations and with patients and families. Famous pathology theorists: Hippocrates (disease of whole persons), Morgagni (disease of organs), Virchow (disease of cells, disease as the result of politics), Pauling (molecular basis of disease). Today the trend is to integrate all five of these understandings, never forgetting the focus on "whole persons".]

Disease: My definition is "things on and under the skin which interfere with a person's ability to work, to play, and/or to love others." There really are a lot of distinct diseases, and when you understand how they arise, it's easy to figure out how to treat them. Etiology: "Cause" of a disease. It is stupid to think of any disease having a single cause; for example, you need a HIV virus to get AIDS, but the causes of the epidemic also include patient vulnerability, patient behavior, and even social problems. Pathogenesis: The story of how a disease arises. Symptom: What the patient tells the doctor. Sign / finding: What the doctor finds to help with the diagnosis. Morphology: altered shapes in disease. Pathognomonic: Occurs only in one disease, enabling you to make the diagnosis. Pathogen: By custom, a micro-organism that causes disease. Diathesis: A stupid word for a systemic problem without a gross anatomic lesion; the favorite use is "bleeding diathesis". Organic disease: The pathologist can exhibit a clear lesion. Functional disease: The pathologist cannot exhibit a clear lesion (migraine, fibromyalgia, "I slept on my neck wrong"). Psychosomatic: Anything about the mind-body interface; much (if not most) of what you've heard about "stress causing disease" and "emotional basis for disease" isn't true.

Health: Having the physical and mental equipment to make you able to work, to play, and to love others (my definition). Pathology: Applying science to disease and the human experience of disease. ["Nosos" is Greek for "disease", "Pathos" is Greek for a range covering "human experience and human suffering."] Hence, "pathology" never loses touch with human experience. General pathology: Mechanisms common to disease regardless of location. Systemic pathology: Studying disease organ-by-organ. Anatomic pathology: The hospital autopsy, cytology, and biopsy services. Clinical pathology: The rest of the lab, mostly liquid specimens. Nosology: Naming diseases.

[Doctor literally means "teacher-understander", i.e., you bring science to the diagnosis and treatment of disease. Science: The serious

business of trying to understand the world, and make predictions about it, taking elaborate resources against self-deception. Our most powerful tool in predicting, and ultimately controlling, our world. Science cannot teach us about matters of ultimate human concern, but the best way to make a bad decision is to base it on emotionally-appealing make-believe (ideology) instead of looking squarely at reality. Scientific physicians are probably the most humane and decent people you'll meet, and it's a credit to you that you've chosen science over fantasy. Theory: An explanation which has shown predictive power and has not yet been falsified. Predictive value is the criterion for scientific truth (i.e, oat-cell carcinoma will respond to chemotherapy; you'll never find a modern human skull in dinosaur strata). Testability (falsifiability) is a criterion for scientific statements.]

Hypoxia: cell can't do oxidative phosphorylation. Intracellular ADP increases, glycolysis increases greatly, lactic acid builds up and drops the cell pH, and proteins denature. This lets water, sodium and calcium into, and potassium and various marker enzymes (LDH, SGOT, or whatever, depending on the cell) out of, the cells. Water-and-lipid phases separate as layers ("myelin figures", dumb name). The cell and its rough-endoplasmic-reticulum may swell with water ("cloudy swelling"). This is still reversible. When hypoxia is bad enough, the calcium precipitates the phosphates in the mitochondria ("mitochondrial densities") which kills the cell (irreversible injury). If that doesn't happen, then sometimes the change in pH or whatever lets calcium that's tied-up by proteins loose in the cytoplasm, where it activates phospholipases. Lysosomes may burst, and freed fatty acids can act as detergents. A neuron is probably permanently damaged by zero-blood-flow in about 15 seconds, i.e., it's lost spines. A neuron is likely to die if deprived of oxygen for 3 minutes. Heart muscle cells last 30 minutes. Liver and kidney epithelial cells last maybe 2 hours. Glia may last a few hours. A leg can last maybe six hours. Histotoxic hypoxia: The cytochromes are inactivated, i.e., cyanide. Anemic hypoxia: Not enough hemoglobin to carry oxygen. Hypoxic hypoxia: Low arterial pO2. Ischemic hypoxia: Not enough blood to the area. Reperfusion injury: When blood is restored to an ischemic area, more calcium and oxygen (etc.) get into the cells and hurts them worse.

The causes of hypoxia:

Ischemia ("ischemic hypoxia"; "stagnant hypoxia"): Loss of arterial blood flow (literally, "holding back the blood")

Local causes

-- Occlusion of the arteries that bring in fresh blood

-- Occlusion of the veins which allow blood to leave, so that fresh blood can flow in

-- Shunting of arterial blood elsewhere ("steal

syndromes"; "Robin Hood" syndromes)
Systemic causes
-- Failure of the heart to pump enough blood
Hypoxemia: Too little oxygen in the blood
Oxygen problems ("hypoxic hypoxia")
-- Too little oxygen in the air
-- Failure to properly ventilate the lungs
-- Failure of the lungs to properly oxygenate the blood
-- Failure of the heart to pump enough blood through the lungs
-- Tremendously increased dead space (i.e., pulmonary thromboembolus)
Hemoglobin problems ("anemic hypoxia")
-- Inadequate circulating red cell mass ("anemia")
-- Inability of hemoglobin to carry the oxygen (carbon monoxide poisoning, methemoglobinemia)
-- "High affinity" hemoglobins that will not give up their oxygen to the tissues
Failure of the cytochromes ("histotoxic hypoxia")
Cyanide poisoning
Rotenone poisoning
Dinitrophenol poisoning
Other curious poisons

I wish I had time to review blood gases here....

Cytopathic virus: Causes morphologic change when it hijacks the genome. Cytolytic virus: Destroys the cell. Inclusion body: Any new kind of intracellular structure, visible by light microscopy, that results from disease. Viral inclusions are masses of viruses getting made.

Herpes simplex & zoster swollen nuclei (often several in one cell) with a single, large intracellular inclusion.

Cytomegalovirus huge cells with one enormous intranuclear inclusion and often several small intracytoplasmic inclusions.

Rabies eosinophilic intracytoplasmic Negri bodies

Measles multinucleated epithelial giant cells with herpes-like inclusions in the nuclei (Warthin-Finkeldey cells)

Free radical: Has an unpaired electron, capable of setting off a chain reaction which damages many molecules. They cross-link unsaturated fat, mutate genes, cross-link sulfhydryls. Hydroxyl radicals result from ultraviolet rays hitting water. Iron turns H2O2 into two hydroxyl radicals. White cells generate free radicals to kill bacteria. Our own drug-metabolizing systems turn some molecules (acetaminophen, carbon tetrachloride) into free radicals. Too high an oxygen concentration damages the lungs using superoxide. Endogenous antioxidants include melatonin, vitamins C and E, glutathione, glutathione peroxidase, selenium, ceruloplasmin, transferrin, and the enzyme superoxide dismutase.

Apoptosis: "Shrinkage necrosis"; "individual cell necrosis"; "cell suicide." A cell activates a program that slices-and-dices its DNA ("endonuclease"), cross-links its proteins ("transglutaminase"), and dissolves its cytoskeleton ("calpain"). Embryogenesis, skin-cell and gut-epithelium shedding, a woman's monthly cycle, elimination of autoreactive or no-longer-useful immune cells, all forms of atrophy, suicide on a T-cell's instructions (hepatitis, graft-vs.-host, many others), suicide of a cell with an injured genome (p53-mediated), hypoxia or cell injury insufficient to produce frank necrosis of a large group of cells. This is the only kind of necrosis in which there is no inflammation. "Apoptotic bodies" are eaten by macrophages (in liver these are "Councilman bodies"). The fas receptor in cell surfaces, when stimulated, activates the suicide program. This is the only kind of necrosis where there's not going to be any inflammation.

Poison: Some of the less-subtle ones include mercury and arsenic (bind sulfhydryl groups), cyanide (binds cytochromes, instant hypoxia), carbon monoxide (binds hemoglobin so oxygen cannot be carried by it), and molecules which are turned into free radicals by the body (acetaminophen overdose, carbon tetrachloride). First law of pharmacology: "All drugs are poisons, all poisons are drugs."

Necrosis is visible evidence of cell death. In hypoxic injury, the cell is dead long before necrosis is visible. The nucleus shrivels and darkens until there is no more euchromatin (pyknosis), then fragments (karyorrhexis), then vanishes (karyolysis).

Coagulation necrosis: The usual pattern of necrosis in poisoning or hypoxia. Cytoplasm becomes hyper-eosinophilic, and the nuclear changes appear. The cells persist as cell ghosts.

Liquefaction necrosis: The cytoplasm liquefies, at least in a few days. (1) Hypoxia of the brain, provided it's been severe enough to kill the

glia as well as the neurons; (2) gas gangrene, i.e., clostridial infection with bacterial enzymes hydrolyzing the tissues; (3) bacterial infections that bring so many neutrophils to an area that their enzymes hydrolyze the tissue. Situation (3) is called "suppuration" and the result is "pus".

Caseous necrosis: Dead cells crumble into a pasty powder ("cheesy"). Effected by tumor necrosis factor on the body's tissues, in the presence of waxes from certain micro-organisms, notably the tuberculosis bacillus and some fungi (histoplasmosis, blastomycosis).

Enzymatic fat necrosis: Lipase from damaged pancreas digests triglycerides; freed fatty acids precipitate with calcium as hard-water soap (like in my bathtub ring).

Traumatic fat necrosis: misnomer for what happens after a blow disrupts a group of fat cells; likely to scar up and calcify.

Fibrin: The body's sealant. Fibrinoid: A mix of fibrin and other proteins, typically immunoglobulin and complement, pushed into the walls of injured arteries when the endothelium is perforated. Fibrinous: made mostly of fibrin. Fibrous: Made of collagen. "Fibrin is a scab. Collagen is a scar."

Collagen types to know:

- I: Dense collagen
- II: Cartilage
- III: Reticulin
- IV: Basement membrane

Gangrene: Necrosis that somebody can see grossly and that looks ugly. Wet gangrene: It's infected by clostridia that are hydrolyzing, phew. Dry gangrene: It's dried up and cannot be hydrolyzed. Autolysis: Tissues self-destruct because of no blood flow, i.e., after death. Heterolysis: Tissues get digested by another cell, usually neutrophils. Putrefaction: Bacteria digest dead tissue.

Aplasia / agenesis: Never grew at all. Hypoplasia: Never grew to its normal size. Local gigantism: Self-explanatory, but usually mysterious. Syn-: Fused. Holo-: Never divided. Atresia: The hole never formed. Stenosis: The hole is too narrow. Occlusion: Something is blocking the hole. Ectopia: Good stuff, but in the wrong place. Choristoma: An ectopia that actually forms a visible mass. Hamartoma: The right tissue components, but scrambled (birthmarks, cartilage hunks, etc.) Fistula: An abnormal, epithelialized communication between two surfaces. Sinus: An (abnormal) opening onto a surface.

The Law of Epithelium: It does not tolerate a free edge. Diverticulum: All three layers of the wall of a hollow organ are outpouched. Pseudodiverticulum: The mucosa outpouches through a weak spot in the muscular wall ("diverticula" of the colon and upper esophagus, Rokitansky-Aschoff "sinuses" of the chronically inflamed gallbladder). Cyst: abnormal, fluid-filled, epithelially-lined, and closed. Spasm: Inappropriate, prolonged contraction of any muscle.

Atrophy: The organ shrank, because (1) the cells shrank (typical of endocrine-sensitive or work-responsive tissue like gland and skeletal muscle) and/or (2) the cells died off (apoptotic, typical of brain); lack of blood supply can cause either kind of atrophy. Aplastic anemia: A bad term for marrow cells dying off. Cachexia: Wasting of body tissues, muscle more than fat, typically as a result of cancer or any disease with overproduction of certain cytokines. Hyperplasia: An organ became larger because of increase in the number of normal cells; many examples. Hypertrophy: An organ became larger because its cells became larger; only a few examples (athletes' hearts, hypertensive folks' hearts, aortic valve stenosis, weight-lifters). Hypertrophy and hyperplasia together: The pregnant uterus, an overstimulated endocrine gland. Metaplasia: Transformation of one good cell type into another. Dysplasia ("intra-epithelial neoplasia"): Replacement of a normal type of tissue (usually epithelium) with bizarre cells which are not invading. Carcinoma-in-situ: Bad dysplasia. Anaplasia: Bizarre cells, typically lying topsy-turvy, with dark nuclei, frequent mitoses, and high nuclear-cytoplasmic ratio; whether or not they are invading (cancer) or not invading (dysplasia, "carcinoma in situ"). Neoplasia = tumor: A new, worthless organ, i.e., a clone of abnormal cells has figured out how to induce its own connective tissue stroma and blood supply. Benign tumor: It will stay localized. Malignant tumor: It has the ability, now, to spread to another site, and set up a metastasis. A pathologist distinguishes benign from malignant tumors by several means, including the presence of anaplasia in, and only in, the latter.

	Anaplastic?	A mass?
Dysplasia	yes	no
Cancer	yes	yes
Benign tumor	no	yes

Nowell's law / "tumor progression" / clonal evolution: Tumors arise from selection of mutated clones with a tendency to overgrow their neighbors. This happens again and again, so a tumor is a clone derived from a clone derived from a clone derived... The genes that mutate are the proto-oncogenes (mutated="activated" into oncogenes, one copy being sufficient to turn a cell bad), and the antioncogenes = "tumor suppressor genes", both copies of which must be destroyed="inactivated"

to turn a cell bad. Hypertrophy, hyperplasia, and atrophy typically are mediated by these genes, functioning as they should. Metaplasia can result either from these genes reacting properly to stimuli (hormones, tobacco smoke), or being mutated, or having their products inactivated by viruses (human-papilloma virus effect, for example). Dysplasia indicates some serious genetic damage.

Consistency

Soft: Like your earlobe. Think of fat, lung, edematous loose connective tissue, pus, tumor with scanty stroma ("small blue cell" tumors, sarcomas)

Firm: Like your strongest, leanest muscle when you flex it. Most pathology specimens are mostly firm.

Hard: Like your knuckle. Think of bone, other calcified tissue, over-fixed dense connective tissue.

Color

Red: Fresh blood or fresh myoglobin
Red-orange: Bilirubin; hemosiderin (sometimes)
Orange: Carotene
Yellow: Lipid (adipose tissue; adrenal cortex; most necrosis); elastic fibers (vessels; yellow ligaments)
Green: Biliverdin
Blue: Something non-white seen through a reflective surface (blood in your veins through your skin; carbon pigment under the pleura; blue iris; cornea in osteogenesis imperfecta).
Purple: ???
White: Tumor; granuloma; collagen (fibrous tissue; scar; etc.); calcium flecks
Gray: Lung alveolar tissue
Brown: Feces; hemosiderin; lipofuscin; melanin; cytochromes (as in the liver); formalin-fixed or stale hemoglobin/myoglobin; debris
Black: Carbon ("anthracotic pigment"); very abundant melanin; homogentisic acid ("alkapton"); formalin-fixed hemoglobin turns dark brown or black

Hematoxylin stains nucleic acid (nuclei, abundant rough endoplasmic reticulum), bacteria, and calcium blue. Eosin stains protein (arginine and lysine) molecules pink. PAS stains insoluble carbohydrates (glycogen, cartilage, fungi, mucin, basement membrane, alpha-1 protease

inhibitor, a few others not-so-strong) magenta; d-PAS stain is used to prove something PAS-positive is, or is not, glycogen. Acid-fast stains selectively stain mycobacteria. Sudan and oil-red stains demonstrate lipid phases. Mucicarmine is for epithelial mucin. Trichrome stains dense collagen blue. Immunostains turn a particular protein brown (immunoperoxidase) or fluorescent (immunofluorescence).

Glycogen accumulates in various organ in glycogen storage disease, in the nuclei of hepatocytes of those with hyperglycemia, and in the renal tubules of those with heavy-duty glycosuria.

Fatty change is too much fat in business cells which shouldn't ordinarily accumulate it; it's a sign that the cell is sick. The liver in alcoholism, ischemia, and a variety of poisonings. The heart in diphtheria (homogeneously yellow; toxin ties up carnitine) and severe anemia (tiger-stripe). Fatty ingrowth is extra fat cells in an organ where they don't usually belong. Cholesterol needles (really, plates) are frequent findings; in semi-living tissue, think of atherosclerosis.

Hemosiderin is iron storage pigment. You diagnose it using the Prussian Blue stain. Hemosiderosis is excess hemosiderin, at sites of repetitive minor trauma, on the ankles of folks with varicose veins, and so forth. Hemochromatosis is enough iron on board to make you sick. Primary hemochromatosis usually results from a combination of genetics (duodenum absorbs iron too well), diet (remember Bantu beer), and being male (i.e., no menstruation, no pregnancy). Secondary hemochromatosis results from some other disease, or from needing lots of red cell transfusions. Ferruginous body: asbestos fiber coated with iron. Hemozoin: malaria pigment, made by the bug to protect itself from free radicals. Hematin: another iron-rich pigment in the spleen, from hemolysis of any origin.

Alkapton: homogentisic acid polymer, typical of alkaptonuria (ochronosis), premature-arthritis with the stuff in cartilage, which is blackened.

Melanin is the familiar skin pigment. You diagnose it because it loses its color on being exposed to hair bleach. Melanin is a tyrosine-based polymer designed to keep you from getting skin cancer and vitamin D toxicosis. Melanosis coli pigment usually results from heavy use of cascara laxatives. Albinism is lack of melanin.

Bilirubin pigment generally occurs with bile plugs or bile lakes in the liver. Jaundice: Excess bilirubin in the blood. Kernicterus: Brain damage from high bilirubin; only babies seem to get it, and the bilirubin must rise to maybe 20 mg/dL. Unconjugated ("indirect")

bilirubin is elevated in hemolysis and in conjugation defects. Conjugated ("direct") bilirubin is elevated when most of the biliary tree has become obstructed. Both are elevated in liver cell disease. Gilbert's non-disease is a forme-fruste of Crigler-Najjar which affects 5% of folks and gives mildly-increased unconjugated bilirubin. The yellow patient with jaundice has elevated blood bilirubin; if it's uremia, the history and physical exam will tell you; if it's hyper-carotenemia (i.e., eats carrots), palms and soles are most yellow.

Lipofuscin is an inert, wear-and-tear pigment. You diagnose it by its location, or by process of elimination. Lots of lipofuscin in an organ means brown atrophy.

Dystrophic calcification results from disease at the site of calcification, i.e., in scars, in caseous necrosis, in psammoma bodies of tumors, in scleroderma-CREST, in atherosclerotic plaques, and so forth. Some stuff calcifies as you age (costal arches, pineal, respiratory cartilages). Nowadays calcium gets electroplated onto collagen during torture, a key finding in investigating human-rights abuses. A lithopedion is a dead unborn child who calcified. Metastatic calcification results from disease remote from the site of calcification that has caused elevated blood calcium or phosphate; calcium deposits in the lung alveoli, on the far-side of gastric parietal cell, around the renal tubules, and perhaps in the elastica of blood vessels.

Hyaline is a generic term for masses of acellular, amorphous protein. It includes most viral inclusions, amyloid, fibrinoid, Russell bodies (constipated plasma cells), fibrin, Mallory bodies, giant mitochondria (alcoholism), super-dense collagen (keloids), excess basement membrane (diabetes).

Mallory's hyaline is a mix of keratin and ubiquitin, usually in liver cells, usually in response to lots of alcohol in a short time (marker for "alcoholic hepatitis"). It's very chemotactic for neutrophils

Amyloid is beta-pleated anything. You diagnose it using Congo Red staining, which stains it intense brick-brown; polarization shows apple-green flashes.

Myxoid change: extra ground substance. Myxedema: generalized myxoid change, usually from hypothyroidism. Barlow's syndrome, a common banal problem, features myxoid change in the mitral valve posterior leaflet.

Mitochondrial abnormalities:

All very swollen:	Reye's

Parking-lot crystals	Mitochondrial myopathy (AZT, genetic)
Too many	Hurthle cell (oncocyte)
Giant	alcoholic's liver

Hereditary cytoskeleton problems:

Spherocytosis	fragile red blood cells; lack spectrin, ankyrin, or protein 4.1
Chediak-Higashi	phagocytes show poor chemotaxis, giant lysosomes

Storage diseases which will produce huge cells....

Gaucher's:	glucocerebroside
Tay-Sachs':	ganglioside
Niemann-Pick's:	sphingomyelin
Hunter's: \	mucopolysaccharide
Hurler's: /	
Fabry's:	ceramide trihexose

The crumpled-kleenex ("watered silk") cells of Gaucher's are worth being able to recognize.

Inflammation is the body's way of making war, and the analogies are obvious. It's a stereotyped response of vascularized tissue to injury, with specialized combat units, bystander casualties, and general misery and havoc. Immunity nowadays means the activity of B-cells ("humoral immunity") and T-cells ("cellular immunity"). Don't confuse inflammation with infection, i.e., invasion by harmful bugs. -itis: inflammation of. -osis: "full of" (in spite of what anyone else may tell you).

Edema: Extra fluid outside the vessels. Unqualified, it means among the cells. Effusion: Edema fluid in a body cavity. Transudate: Low-protein edema, due to (1) plugged lymphatics (cancer, surgical, filaria) and/or (2) too much total-body water (kidney failure, sodium retention, iatrogenic) and/or (3) low plasma oncotic pressure (i.e., low protein as in liver failure, nephrotic syndrome, kwashiorkor, others) and/or (4) increased venous hydrostatic pressure (varicose veins, heart failure, occluded veins, others). Exudate: High-protein edema, due almost always to inflammation (less often, to leaky vessels in a cancer). Empyema: pus filling a body cavity. Hyperemia: increased blood flow through an area because the vessels dilated, i.e., the reason things turn red and throb. Congestion: Increased blood in an area because the veins aren't emptying, i.e., the reason things turn blue and swell up. Nutmeg liver: Congested; liver is almost always

congested if the heart has suffered a few weak beats prior to death. Anasarca: Horribly bad total-body edema.

Scratch yourself, and after the initial few seconds of reflex vasoconstriction ("Have I been deeply gashed? I guess not..."), you can observe the triple response of Lewis. (1) A red scratch, from histamine. (2) A flare around the scratch, from a nerve reflex. (3) Edema in the area, from histamine. This is how we discovered locally-acting tissue molecules.

Acute inflammation: Vasodilatation and increased vascular permeability to protein, plus invasion by neutrophils. Almost entirely stereotyped. How much vessels leak depends how badly they are hurt. Mild injuries release only albumin, producing edema which washes nasty things away. Moderate injuries release immunoglobulin antibodies for more chemical warfare. The worst injuries release fibrinogen, which seals damaged vessels as fibrin.

Three ways of making vessels leak in inflammation.... Immediate-transient response: Leaky vessels, due to histamine and prostaglandins and leukotrienes and bradykinin and stuff. Starts right away, done in about 30 minutes after the injurious situation is gone; immediate-sustained-prolonged: Leaky vessels because they've been damaged, lasts until thrombosis or healing occurs; delayed-prolonged: Leaky vessels because the cells have undergone apoptosis (sunburn, x-rays, thermal burn).

Rubor (red) from the hyperemia. Dolor (pain) from the damage and mediators. Calor (heat) from the hyperemia (heart's blood is warm). Tumor (swelling) from edema.

Neutrophils ("polys") marginate, adhere ("adhesion molecules"; "integrins") to endothelium, and emigrate. Chemokinesis is increased neutrophil random movement. Chemotaxis is directed movement.

We can't review bacterial killing by neutrophils here; you might want to do this on your own. Same for the prostaglandins and leukotrienes, both products of cyclo-oxygenase, and therefore suppressible by aspirin and NSAID's.

Leaky vessels:	histamine, bradykinin, leukotrienes, PGE2
Chemotaxis:	Leukotriene B4; C5a; kallikrein, bugs
Opsonization:	Ig, C3b
Histamine release:	C3a, C5a ("anaphylatoxins")
Membrane attack:	C5-9

Thromboxane A2, from platelets, is for when you need hemostasis. It constricts vessels, makes platelets stick. Prostacyclin (PGI2), from endothelium, is for when you do not need hemostasis. It dilates vessels and makes the platelets not stick.

Prostaglandin E2: Dilates vessels, mediates fever in the hypothalamus, mediates the ability of bradykinin to cause pain.

Memory: The following all both dilate vessels, and make them leak... histamine, serotonin, prostaglandin E2, C3a, C5a, and bradykinin. Warning: You'll go nuts if you try to memorize every inflammatory mediator.

Neutrophil granule contents worth remembering:

Specific granules	collagenase, alkaline phosphatase
Azurophil granules	elastase, myeloperoxidase, acid hydrolases
Both kinds	lysozyme

The collagenase and elastase are there, of course, to digest your own tissues in pursuit of bacteria. They will form pus. In a confined space that the polys made, this is an abscess; in a normal hollow cavity, it's an empyema. Hydrolysis of tissue in this situation leads to tremendous osmotic power, hence the ripening and pressure buildup in a pimple. A surgeon should drain pus.

Which white cell comes out for which bug?

Neutrophils	Most bacteria, chlamydia, rickettsia
Lymphocytes	Viruses, autoimmunity, whooping cough
Macrophages	Typhoid, mycobacteria, fungi
Plasma cells	Spirochetes (Lyme disease, syphilis)
Eosinophils	Worms (their cationic proteins are our strongest weapon against worms); lots of different "mysterious immune diseases" with rashes
Nothing	Prions, gas gangrene, severe immunosuppression

In lymphogranuloma venereum, cat scratch fever, brucellosis, plague, tularemia, glanders-melioidosis, and yersinia infection, there will be a plentiful mix of neutrophils and epithelioid histiocytes.

Acute phase reaction: "Just being sick". Interleukin 1 and interleukin 6 are released from phagocytizing macrophages. Interleukin 1 goes to the hypothalamus and tells it (via PGE2 supposedly) to raise the body temperature ("maybe we will have an advantage over the germs better at a different temperature"). Interleukin 6 changes the relative amounts of protein produced by the liver, so in a few weeks there is

Less: Albumin, transferrin, and transthyretin, and
More: Fibrinogen, complement components, alpha-1 protease inhibitor (antitrypsin), and (from plasma cells) immune globulin.

The more-cationic plasma proteins mask the zeta potential on red cells, so red cells stack ("rouleaux") and thus are more streamlined and settle more rapidly (increased sedimentation rate).

Macrophages (monocytes in tissue, histiocytes), lymphocytes (B, T), and plasma cells are the principal actors in most chronic inflammation.

Granulomas are angry macrophages (i.e., influenced by gamma-interferon) that have stuck together ("epithelioid cells"), typically to wall something off (i.e., foreign body) and/or just because they're angry (mycobacteria, fungi, sarcoid, Crohn's, beryllium, less often the syphilitic gumma). Spot granulomas by the purple rice-crispies on a frayed pink tablecloth gestalt. The purple is the reticulated, long-oval, indented nucleus. The pink is the abundant cytoplasm without clear borders. While you're learning, look for the "giant cells" to spot granulomas; they're macrophages that have tried to eat each other. Langhans giant cells have nuclei arranged as a horseshoe; foreign-body giant cells have nuclei evenly dispersed; the distinction means exactly nothing. Chronic granulomatous disease results from neutrophils unable to kill staphylococci, hence macrophages must do it.

Ulcer: A portion of epithelium, and at least a bit of its underlying lamina propria, has died and been lost. Ulcers are always inflamed, and the crater is, of course, fibrin. Pseudomembrane: A very broad, very shallow ulcer; of course the strength of the "membrane" is fibrin. Look for pseudomembranes in diphtheria (throat) and C. difficile colitis.

Tissue injury is almost always accompanied by inflammation. There are a few exceptions: some infections in the very immunodeficient, yellow fever (generalized apoptosis of the liver cells), prion disease, and some of the diseases in which neurons just die off. (If you want to count getting your hair cut as "tissue injury"... but let us not be silly.)

Inflammation may resolve, i.e., so trivial there was no loss of local cells, or there may be a need for healing. The terminology is a bit confusion and not altogether standard. Regeneration refers to the replacement of local cells by division. Labile cell populations are continuously turning-over (epidermis, gut epithelium, marrow,

lymphocytes). Stable cell populations can divide when their neighbors vanish (liver epithelium, kidney tubules). Permanent cell populations don't replace (striated muscle, neurons, glia).

Scarring is laying-down of dense collagen (type I), which you will usually see in chronic inflammation ("transforming growth factor beta" effect) and wound healing. "Chronic -itis" in kidney, pancreas, and gall bladder can refer merely to scarring, an unfortunate misnomer. In healing of a nasty injury, the fibrin meshwork is ingrown by baby capillaries (angioblasts) and fibroblasts (attracted by "fibroblast growth factor" from platelets); they're here to "organize" it. Plasmin, of course, competes with the scar-formers to break down the fibrin; this is sometimes good, sometimes bad. Unless the plasmin is the total winner, the fibroblasts and angioblasts show as soft, mushy, red granulation tissue, which gradually is transformed into mature scar as the fibroblasts make collagen and ground substance. As they finish up, the fibroblasts grow little sarcomeres ("myofibroblasts") and the scar contracts. If a wound is nice and clean and the margins well-approximated and it heals by primary intention. Otherwise, it heals by secondary intention. Both are dumb names but the idea is important. Adhesions mark the site of old fibrin-rich inflammation in body cavities; bands of dense collagen now bind surfaces together.

Timetable for "the best possible wound" (i.e., a clean, protected one with edges apposed, in a well-nourished patient with good blood vessels):

minutes: Fibrinogen from the severed vessels is activated via one or the other arms of the clotting cascade, forms a meshwork, and stops the bleeding. The meshwork also contains platelets.

24 hours: Polys have entered the fibrin meshwork
Epithelial cells are regenerating from the edges of the wound surface, etc.

3 days: The fibrin meshwork is extensively invaded by macrophages.
Granulation tissue is appearing at the edges of the incisions.
A thin layer of epithelial cells now covers the wound surface.

5 days: Granulation tissue fills the entire wound, and there is abundant collagen.

2 weeks: Fibroblasts continue to multiply, and collagen continues to accumulate.

4 weeks: The overlying epidermis is now normal, though it will not re-grow adnexal structures.
Capillary involution and scar contraction is well underway, and the red scar is turning white.
The wound is still growing stronger, though it will never have the tensile strength of uninjured tissue (sorry).

Exuberant granulation tissue: "proud flesh" on a good healer. Keloid: heals so well that the collagen weaves as dense as osteoid; dark-pigmented folks often have this happen.

Bad for healing: poor blood supply, lack of zinc (for collagen-strengthening enzymes), lack of vitamin C, infection (dirt and foreign bodies promote infection), glucocorticoid excess, weak connective tissue (Ehlers-Danlos), anemia, too few polys, fibrin problem.

Names for surgical operations:

"-tomy": The surgeon cut something.
"-ectomy": The surgeon cut something out.
"-ostomy": The surgeon cut something to make a mouth. If one organ is named, the mouth opened to the outside of the patient. If two organs are named, the mouth connected two organs.
"-plasty": The surgeon changed the shape of an organ.
"-pexy": The surgeon moved the organ to the right place.

Types of pain...

Aching pain: Probably periosteum, tooth, dura, or some circuit inside your own brain is involved

Burning pain: Either (1) the integrity of a mucosal surface has been breached, or (2) the nerve or its immediate environment has been damaged (probably a depletion of substance P; "causalgia" from nerve injury, thermal burns, sunburns, leprosy, epidermal necrolysis, capsaicin.

Crampy pain (gas, labor, kidney stones): A hollow organ is being distended

Stabbing ("lancinating") (pleuritis, pericarditis, peritonitis):

If you haven't really been stabbed, then one of your serosal membranes is hurting.

Not really any of these: ischemia, common inflammation (everything from bee-sting to plague)

Edema of systemic disease. Heart failure (purists: right-sided heart failure) edema is most likely to start in the feet, since the primary problem here is increased venous hydrostatic pressure, and venous hydrostatic pressure is highest here due to gravity). Kidney failure edema is most likely to start around the eyes, since there's excess total-body water and often low plasma oncotic pressure, and the tissue spaces are loosest around the eyes. Liver failure edema is typically in the peritoneal cavity, since portal venous pressure is usually greatly increased in liver disease.

Cerebral edema results from cloudy swelling of the neurons, which they'll do on the slightest injury; it's bad because the expanding brain has no place to go except out of the skull. Hydrocephalus: Too much cerebrospinal fluid for any reason. Angioedema is a curious result of C1-esterase deficiency, with sudden, grotesque swelling of bodyparts (weird feedback). Lymphedema results from plugged lymphatics (cancer, surgery, filaria) and tends to be denser and more "woody" if longstanding; bad cases produces dermal and epidermal thickening (elephantiasis). Ascites: Effusion in the peritoneal cavity. Hydrocele: Effusion in a man's tunica vaginalis. Hydrosalpinx: Effusion in an oviduct, usually from old gonorrhea or something similar. Hydrothorax: Watery effusion in the pleural cavity. Hemarthrosis: blood in a joint. Melena: Passing digested (black, tarry) blood in the stool. Hematochezia: Bright red blood out the rectum. Effusion: Edema fluid from any cause in a body cavity. Loculated effusion: Fibrin in an exudate divides the effusion into smaller compartments; eventually the fibrin is likely to be replaced by scar. Ileus: The gut is filled with extra water, typically because it isn't moving.

Hemorrhage: Blood outside the circulatory system. Hemoptysis: Coughing up blood. Hematemesis: Vomiting blood. Petechia: A little bleed in the tissues, under a millimeter maybe. Ecchymosis: Fancy word for a bruise. Purpura: Purple blotches where you've bled into tissue.

Clot: Solid blood, generally used loosely. Hematoma: Solid blood outside the circulatory system but in the tissues. Thrombus: Blood has turned solid inside the circulatory system; all thrombi are variable mixes of red cell, platelets, and (the basic component) fibrin. Ante-mortem thrombi are easy to recognize by their lamination, i.e., layers

telling the story of their formation, the lines of Zahn (fudge-ripple ice cream). Post-mortem thrombi feature a layer of red-cell-poor clot ("chicken fat") and a layer of red-cell-rich clot ("current jelly"), since the red cells sediment before the blood clots. Thrombi propagate because their surface itself causes blood to clot. Vegetation: A thrombus, typically small, on the endocardium of the heart at a site of disease. Mural thrombus: A big thrombus overlying damaged myocardium. Thrombi recanalize by turning ("organizing") into granulation tissue, growing new channels, then having these channels pulled open by scar contraction. Less often, plasmin destroys a clot; nowadays, physicians can destroy them using therapeutic agents.

"Virchow's triad" is the most important concept in general pathology. Here are the causes of thrombosis:

- Injured endothelium
  - Myocardial infarcts
  - Myocarditis sites
  - Cardiac jet lesions (abnormal flow)
  - Inflamed or prosthetic cardiac valves
  - Ruptured atherosclerotic plaques
  - Vasculitis syndromes
  - Radiation injury
  - High blood pressure itself (?)
  - Cigaret smoke (?)
  - Invasion of vessel by tumor
    - (think of renal cell, hepatocellular, or follicular thyroid carcinomas)
  - Iatrogenic
    - Sclerotherapy for varicose veins
    - Indwelling lines, etc.
- Altered blood flow ("turbulence and stasis")
  - Myocardial infarcts (dead wall balloons out)
  - Quivering ("fibrillating") cardiac atria
  - Over big ruptured atherosclerotic plaques
  - In dilated cardiac chambers (valve or muscle disease)
  - In weakened arteries which have ballooned ("aneurysms")
  - Over-viscous blood
    - Sickle cell disease
    - Polycythemia (too much red cell mass)
    - Cryoglobulins (proteins that tend to precipitate)
    - Macroglobulinemia (too much IgM)
  - Vascular malformations
  - Prolonged bed-rest or immobilization
- Hypercoagulable blood
  - Congenital factor deficiencies

- Lack of antithrombin III
- Lack of protein S
- Lack of protein C (even heterozygotes) or its curious cofactor
- High blood homocysteine

- Pregnancy and after childbirth
- Tissue damage
  - After severe trauma or burns
  - After surgery
- Nephrotic syndrome
  (glomerular leakage of protein; probably because small anti-coagulant proteins such as protein S are selectively lost)
- Secretion of thrombogenic factors by tumors
  (notably adenocarcinomas, notably of the pancreas; "Trousseau's other sign")
- Presence of "lupus anticoagulant" (paradoxical)

Arterial thrombi (i.e., formed in an artery) are usually less rich in red cells (i.e., they flow past in the fast stream). Look for thrombi atop cracked atherosclerotic plaques.

Disseminated intravascular coagulation means that the clotting cascade is getting activated in your bloodstream. You can expect bleeding (depleted clotting factors), reopening of recent fibrin scabs (i.e., your venipuncture, the effect of plasmin activation), thrombocytopenia, fragmented red cells (schistocytes, etc.), little infarcts (maybe; the glomeruli get it bad in DIC), and death unless the disease is treated.

Causes of DIC worth mentioning now....

- Things that release thromboplastin into the blood
  - Large infarcts
  - Massive intravascular hemolysis (remember bad malaria)
  - Acute promyelocytic leukemia
  - Various obstetrical catastrophes
  - Disseminated cancers
  - Snakebite
- Things that damage endothelium
  - Rickettsial diseases
  - Meningococcemia
  - Other infections
  - Vasculitis syndromes
  - Toxemia of pregnancy (fibrin thrombi in placenta)
- Things that do both
  - Shock
  - Gram-negative sepsis (mystery)

Major surgery
Burns
Massive trauma
Heat stroke

Fibrinolysis fills your vessels up with fibrin split products.

Emboli are anything that moves in the circulation, from one place to another, that shouldn't. Most emboli are thromboemboli (they do not cease to be thrombi). Paradoxical emboli: A thrombus from a systemic vein went through a patent foramen ovale (note that right atrial pressure must exceed left atrial pressure to allow this), and then to the systemic circulation. Pulmonary emboli typically arise from the deep veins of the legs, less often the right atrium. Systemic emboli usually arise in the left atrium or ventricle.

Amniotic fluid emboli result from abnormal communication between the contents of the amnionic sac (fetal urine, fetal hair, fetal skin debris, and more unsavory stuff) and the veins of the womb. This can wipe out the pulmonary vasculature and produce DIC, and is bad.

Air emboli can result from iatrogenic mishaps, stab wounds, caisson disease (decompression sickness of divers) or weird practices. Listen for the waterwheel murmur. Talc emboli slowly kill drug-injectors. Fat emboli are most often from a broken heelbone; nobody really knows why fat embolization makes you so sick ("fat binds platelets, damages lung and brain endothelium, etc., etc."). Red marrow emboli are typically found in the lungs after vigorous but futile CPR, from broken ribs and breastbones. Atheroemboli are crud from plaques of atherosclerosis. Tumor emboli are not unheard-of in cancer patients. Therapeutic emboli are squirted into sick organs by radiologists, to destroy them.

Infarcts result from death of an organ (while the rest of the body is still alive) from loss of its blood supply. ("Death is a total body infarct.") Arterial infarcts result from emboli (i.e., wipe out one arterial bed) or generalized circulatory insufficiency (i.e., appear between arterial beds). Venous infarcts result from obstructed veins (twisting, clots, mechanical problems.) Infarcts are white (pale, anemic) if (1) they are caused by arterial insufficiency and (2) there is no collateral circulation or reperfusion to flow slowly into the dead vessels afterwards. Infarcts are red (hemorrhagic, bloody) if (1) they result from occluded veins or (2) collateral circulation or reperfusion.

Kidney & spleen These organs have no collateral circulation

(WHY not?) Infarcts are usually arterial, white, and pyramid ("wedge")-shaped.

Lung — Difficult to infarct due to its dual blood supply. Emboli cause infarcts when shock or heart failure compromises the bronchial arterial flow. Infarcts are always hemorrhagic, and are pyramid-shaped.

Brain — Variable, but never wedge-shaped. Watershed infarcts appear in the expected locations.

Heart — Variable, but never wedge-shaped. Watershed infarcts are the familiar "subendocardial infarcts".

Gut — Red. Never wedge-shaped. Arterial infarcts are likely to be due to dopamine or digitalis diverting the blood from the gut, in a setting of underlying shock.

Liver — Difficult to infarct due to its dual blood supply. Occluding a branch of the portal vein produces a wedge-shaped area of atrophy ("Zahn infarct").

Extremity — "Milk leg" is a venous infarct from a deep post-partum strep infection of the leg.

Septic infarcts: The bacteria found it and are having a heyday.

Shock: You cannot perfuse your body adequately. Eventually, this develops into a vicious cycle. Causes of shock that you must understand....

- Cardiogenic shock (i.e., pump failure)
  - Massive myocardial infarct
  - Rupture (ventricle, valve)
  - Diphtheria
  - Bad rhythm disturbances ("arrhythmias", a misnomer)
  - Certain poisons (remember massive nicotine ingestion)
  - Extrinsic compression (i.e., tamponade)
- Hypovolemic shock
  - Heavy bleeding (4 or more of your 10 pints]
    - Externally
    - Internally (remember GI bleeds, hemoperitoneum)

- Other fluid loss
  - Sweating
  - Vomiting
  - Diarrhea
  - Burns
  - Third-space losses (i.e., into effusions or ileus)
- Loss of vascular tone (i.e., all vessels opening)
  - Septic shock (i.e., from bacterial breakdown products)
  - Anaphylaxis (generalized mast-cell degranulation)
  - Neurogenic
    - Certain poisons (notably war gases)
    - Profound anaesthesia
    - Spinal cord injury
    - Vasovagal (i.e., extreme pain, emotion)
- Pulmonary embolism

In shock, the liver enzymes go up (underperfused liver), anaerobiosis causes lactic acidosis (which is bad), and a huge host of chemicals get released which further interfere with physiologic function. Histamine, serotonin, leukotrienes, cachectin, interleukin 1, C3a, C5a, and many other substances dilate vessels, inviting blood to pool in venules (rightly called "congestion"), and/or make small vessels permeable, causing blood to leak out. Some people even blame endorphins. Damaged cells can release thromboplastin, producing DIC. Ischemia of the heart produces the familiar subendocardial infarcts, which doesn't help the pump.

Compensated shock: Blood pressure is maintained in the arms, but you're probably not perfusing your kidneys, gut ("I have stress ulcers!"), skin ("I'm cold"), or muscles. Progressive / decompensated shock: You're dropping your pressure and getting lactic-acidotic. If the cause of your shock is treatable, you will probably survive; your kidneys may be "off" for a few weeks, and "shock lung" may or may not supervene in a few days. Less-fortunate people may have brain damage (if the brain was underperfused), subendocardial heart infarcts, Irreversible shock means your body's been sufficiently damaged by low-flow that you won't recover, period. If your brain's being perfused, you will probably still be lucid, and can talk sensibly, which is a good thing at such a time.

Septic shock (i.e., from bacteria getting a foothold and growing in your bloodstream) is a major mystery of medicine. Nobody really understands what's happening. Lipid A ("endotoxin") dilating vessels and making them leak is part of the problem, but not all. The body's own chemical defenses play some role too.

[If you were hatched from a swan's egg, it doesn't matter that you may have begun life in a chicken coop.

--Hans Christian Anderson

When you see a person who has been given more than you in money or beauty, then look to those who have been given less.

-- Mohammed]

In talking about genetic disease, watch what you say, especially when you make a prediction about behavior. Common sense and common humanity is the order of the day. I got an E-mail once from desperate parents who knew their unborn child was XYY -- I sent my congratulations....

Genetic disease is the price we pay for the ability of our genes to mutate, which has been important in the history of our species. Yet "genetic disease" is almost impossible to define. My best shot: Disease that is determined, more or less, when sperm meets egg. Congenital disease: Present at birth. (How is THIS different from genetic disease?) Familial disease: Runs in families. (How is THIS different from genetic disease? Think of the cycle of abuse affecting an adopted child.) Polygenic inheritance: Several genes are operating. Multifactorial: What isn't?

Hopefully you can explain genes, the genetic code, alleles, chromosomes (autosomal and sex), mitosis and meiosis, haploid and diploid cells (exact multiples of the haploid number are euploid; others are aneuploid), mutations (and the environmental problems that cause them), centromeres, and the basic biology of nucleic acids. You also understand classic Mendelian and sex-linked inheritance, homozygosity, heterozygosity, hemizygosity, and consanguineous mating. Also, sex-linked, sex-limited and lyonization, as well as penetrance, variable expressivity of a single allele, genetic heterogeneity (same effect, different loci). If any of these terms are unfamiliar, please review. If you don't know what restriction fragment length polymorphism is all about, ask a molecular diagnostician -- it's important. Know classic genetic research (sequence the protein and find the gene) and reverse genetics (find the gene, then find the protein). Remember that germ line mutations are present in the sperm or the egg, while somatic mutations are acquired after fertilization. "New mutations" (i.e., two normal parents gave birth to an achondroplastic dwarf) indicate a somatic mutation or a gamete or early-conception mutation. A few diseases (notably McCune-Albright) cannot be passed from parent to child, and always result from a mutation in the early unborn child (post-zygotic mutations), being lethal to the fertilized egg.

Imprinting: Genes from Mom and Dad are labelled differently, and have slightly different effects. Triplet repeat mutations: Big topic, these elongate with successive cell divisions, and make those diseases in which they are etiologic more severe with each generation (Huntington's, fragile-X, myotonic dystrophy); this is called genetic anticipation.

Be sure you are absolutely confident about the meaning of each of these categories:

- Cytogenetic disorders
  - Autosomal disorders
  - Sex chromosome disorders
  - Parental imprinting problems
- Single-gene disorders
  - Autosomal dominant disorders
  - Autosomal recessive disorders
  - Sex-linked disorders
- Mitochondrial gene disorders
- Polygenic disorders

Cytogenetic disorders: From nondisjunction or anaphase lag.

Rules:

(1) Autosomal monosomy or no "X" chromosome causes early loss of the embryo.

(2) All trisomies except trisomy 21 produce infants who will usually die during the first few months of life; around half of early spontaneous abortions has a trisomy.

(3) Unless a parent carries a balanced translocation, or when advanced parental age is a factor, there is no real tendency for these problems to recur.

Trisomy 21: Down's. 1 kid in 700, more with advanced maternal age. Flattened face. Open mouth, big tongue with no central crease. Slanting palpebral fissures and epicanthic folds ("mongolism"). Mental retardation (IQ 25-50). Lack of muscle tone at birth ("floppy baby"). Low-set or funny-looking ears. Single palmar crease ("simian crease"). Radiographic abnormalities (middle phalanges, pelvis). "Brushfield's spots" on iris. Heart defects (40%, notably endocardial cushion defects). Gentle, shy demeanor. Hypothyroidism (untreated, doesn't help intellectual function). Conductive hearing loss (untreated,

doesn't help learning). Bad respiratory infections (we don't know why). Various leukemias (very common in these children). Alzheimer's disease (always develops in patients surviving to age 40 or so).

Trisomy 18 is Edward's syndrome. Remember tiny jaw ("micrognathia"), prominent occiput, low-set ears, overlapping fingers, and rocker-bottom feet.

Trisomy 13 is Patau's syndrome. Remember tiny head ("microcephaly"), arhinencephaly ("abnormal limbic system"), tiny eyes ("microphthalmia"), cleft palate, polydactyly, and scrambled viscera. The worst cases are cyclopses.

Deletion of the short arm of chromosome 5 (i.e., 5p-) is cat-cry ("cri du chat", "Is there a cat in the nursery?") syndrome. Children are profoundly retarded, but some survive into adulthood.

Imprinting problems are a major topic of fascination right now. Prader-Willi and Angelman syndromes are the prototype.

Prader-Willi: a little bit dull, crossed eyes and almond-shaped epicanthic folds, floppy babies, small hands and feet, growth delay, short stature, and hypogonadism.They overeat, incorrigibly stealing and hiding food, and become very obese ("the commonest known cause of genetic obesity"). Docile and cute, until they get really upset, when they are likely to become extremely violent. (Remember the fat, jelly-donut-hiding kid in "Fill Metal Jacket"? True story.) The cause is lack of a normal gene at 15q11-13 from Dad, i.e. uniparental disomy or a mutation in Dad's copy.

Angelman: "happy (?) puppets", severely retarded, microcephaly and huge jaws. They have jerky, puppet-like movements, and laugh a lot. The cause is lack of a normal gene at 15q11-13 from Mom, i.e., uniparental disomy or a mutation in Mom's copy.

Microdeletion syndromes probably account for a variety of other cases of severe dysmorphism; this is a hot topic.

Sex chromosomal disorders

Rules:

(1) A Y-chromosome is necessary and sufficient to make a phenotypic male, provided the body can also make and use testosterone.

(2) The more extraneous X-chromosomes, the more abnormal the person.

(3) You will usually miss the diagnosis at birth, and may only make it late in adult life.

Klinefelter (XXY or sometimes XXXY etc.) One man in about 850. Tall (delayed epiphyseal closure), small penis, limited body-hair, sterile, gynecomastia, high voice, smell better than most men, gentle demeanor, sometimes kind-of-simple-minded, diminished economic striving.

XYY (supermale). One man in maybe 1000. Tall, acne, wiry (even Marfanoid), uncoordinated, bad temper. "Look for the guy with the most pimples on the prison basketball team." Often pectus, squint, "kinda different".... Your lecturer, who fits the actual phenotype nicely, plans to get checked when insurance reform becomes a reality; anyway, he's always known he's a bad man trying to be good.

Turner's: One X, no Y. About 1 woman in 2000. Webbed neck, short, shield-shaped chest, cubitus valgus, primary amenorrhea, failure of secondary sex characteristics. The eggs are gone by age 2, leaving streak gonads. Lymphedema and/or coarctation of the aorta are additional troubles. A person of either gender can have Noonan's, a Turner phenotype without Turner's. A woman I know worked for five years in a six-man OB-Gyn department before mentioning, "I'm 24, do you think I'll ever get a period?" Only then did they notice that this tiny woman had a webbed neck and...

Multi-X: Superfemales. XXX (one woman in a thousand) is usually normal, XXXX and more might be retarded.

Intersex! Your genetic sex (or should be) is whether or not you have testis-determining factor (usually on the Y-chromosome, and not on the X-chromosome; but there are exceptions, as in families where the men are XX, or where the women include XY's). Chromosomal sex: Do you have a Y-chromosome? Gonadal sex: Do you have ovary, testis, both (true hermaphrodite), or neither? Streak gonads, i.e., scar tissue: Woman with Turner's, some folks without testis determining factor or its receptor. Ductal sex: Did the muellerian (woman) or wolffian (man) ducts develop? Phenotypic sex: What he/she look like? Pseudohermaphrodite: Only one type of gonadal tissue, that does not match the body phenotype. Male pseudohermaphrodite: Looks like a woman with groin testes, no uterus. Female pseudohermaphrodite: Women with enlarged clitoris, maybe some labial fusion. Being a parent is the ultimate proof of which gender you are.

XXY	Klinefelter phenotype
XO	Turner phenotype
No testis-determining factor	Woman, may be sterile
Testis-determining factor on X	Man, may be sterile
No testis-determining factor receptor	Woman, may be sterile
XY that lost TDF on a clone	true hermaphrodite (?)
XX with Y on an autosome	true hermaphrodite (?)
XX /XXY mosaic	true hermaphrodite (?)
No muellerian-regression factor gene	male pseudohermaphrodite
No testosterone receptor	male pseudohermaphrodite
No five-alpha reductase	male pseudohermaphrodite
Too much testosterone for any reason	female pseudohermaphrodite

Don't confuse any of these with gender-dysphoria (seems to be wired in the hypothalamus, side of the "bed" nucleus....), cross-dressing, or homosexuality / bisexuality; the genetic basis for these conditions (they do NOT meet my definition of "disease", nor most others) remains obscure.

Autosomal dominant disease

Rules:

When a person has only one good gene where most people have two, the person can expect to make 50% as much of the good protein as do most other people. Sometimes, that isn't enough. Therefore, the known autosomal dominant diseases fall into five categories.

(1) Problems with the quantity or arrangement of large structural proteins

(2) Problems with regulator proteins and receptors, which permit relatively good quality of life.

(3) Deficiency in proteins which are in short supply even in health.

(4) Anti-oncogene deletion syndromes, in which a "second hit" on the normal allele of a normal cell turns it to a tumor cell. More about this last category later.

(5) The mutant gene makes a harmful protein. Today, the best-understood of these are the prion-related diseases, in which an altered protein begins a terrible chain reaction that can even be transmitted to genetically

normal creatures, even across species lines.

The common autosomal dominant diseases do not kill or disable until the patient has had a good chance of having a family. Why? Hint: Most genetic diseases do not result from new mutations. The major exceptions are Von Recklinghausen's neurofibromatosis and achondroplastic dwarfism (both are genes with very high mutation rates).

The autosomal dominant disorders are mostly of variable penetrance and/or expressivity, since they are modulated by other genes and/or environment. Two doses of a bad autosomal dominant gene produces some severe exaggeration of the single-dose syndrome, or else death in the womb. Obviously, consanguinity does not play a role in autosomal dominant disease.

The major autosomal dominant disorders which you'll meet in this course:

Structural proteins
- -- Marfan's syndrome family
- -- Many Ehlers-Danlos variants, and plain old familial double-jointnedness
- -- Hereditary spherocytosis
- -- The not-so-bad kinds of epidermolysis bullosa (abnormal keratin in intermediate fibers)
- -- Familial hypertrophic cardiomyopathy (some; Reggie Lewis, mutant beta-myosin chain)
- -- Achondroplastic dwarfism (fibroblast growth factor receptors, maybe others)
- -- Hereditary hemorrhagic telangiectasia (presumptive)
- -- Osteogenesis imperfecta (collagen)
- -- Pelger-Huet's non-disease (presumptive)

Receptor problems:
- -- Familial hypercholesterolemia
- -- Benign familial tremor (presumptive)
- -- Glucocorticoid-suppressible aldosteronism (ACTH turns on aldosterone)

Short-supply protein deficiency syndromes
- -- Von Willebrand's disease
- -- Maturity onset diabetes of the young (glucokinase)
- -- Acute intermittent porphyria
- -- Familial amyotrophic lateral sclerosis (superoxide dismutase)

Anti-oncogene deletion syndromes
- -- Retinoblastoma gene syndrome
- -- Neurofibromatosis I & II
- -- Familial polyposis coli

(including its variant Gardner's syndrome)
-- Lynch's hereditary non-polyposis colon cancer
-- Multiple endocrine neoplasia syndrome I, IIa & IIb
-- Li-Fraumeni cancer syndrome
-- Tuberous sclerosis (presumptive)
-- Von Hippel-Lindau disease (presumptive)
-- Familial dysplastic nevus syndrome (?)
-- Peutz-Jegher's syndrome (presumptive)
-- Adult polycystic kidney disease
-- BRCA-1 breast-and-ovary cancer syndrome
-- more

Harmful proteins
-- Prion diseases (more about these later!)
-- Hereditary amyloidosis C
-- Gilbert's (harmless unconjugated hyperbilirubinemia; the mutant gene product ties up the good copy)
-- Familial dysplastic nevus syndrome (? the melanin generates, rather than protects from, free radicals)

Molecular biology being worked out
-- Huntington's disease ("Huntington's chorea")
-- Friedreich's ataxia
-- Familial psoriasis
-- Treacher-Collins (variably malformed face, "Johnny Handsome")
-- Waardenburg's (deafness, different-colored eyes, white forelock)
-- Stein-Leventhal (probably)

Semi-diseases, heterozygotes for bad diseases
-- beta-thal minor
-- sickle-cell trait
-- hemoglobin C trait
-- one-dose hemochromatosis
-- alpha-thal is special, since there are four loci.

Marfan's syndrome: A heterogeneous group of genetic disorders with connective tissue problems. Marfan patients are tall, with very long extremities, and long fingers ("arachnodactyly"). The arm span exceeds the height. Joints are hyper-extensible. Double-jointed. Chest-deformities. Funny-looking face. Bones slim, muscles wiry, body habitus slender. "Ectopia lentis" of eye (lax suspensory ligaments). Elongate globe, flat cornea (progressive myopia). Weak central area of thoracic aortic media predispose to aortic dissection ("cystic medial necrosis"). Barlow mitral valve. Lax ligament around aortic valve, causes regurgitation later in life. One gene is fibrillin, a connective tissue protein. Semi-Marfan's abound. Related to Marfan's: (1) Lathyrism, from feeding sweet peas to turkeys and resulting in fatal aortic dissection, results from á-aminopropionitrile inhibiting

lysine oxidase, which cross-links collagen and elastin fibers. (2) Menke's kinky hair disease, on the X-chromosome, which prevents normal handling of copper, prevents function of lysine oxidase. (3) Stickler's, a common Marfan variant, results from a premature termination codon on the type II procollagen gene.

Ehlers-Danlos syndrome ("rubber man", "human pretzels") is a family of variably-inherited diseases which leave a person with poorly-woven collagen; easy to hurt, poor healers. Some have overly-extensible (even "cigaret-paper") skin; most have overly-mobile joints which often slip out of place. Type IV: various problems with type III collagen ("reticulin"); colon and arteries often rupture. Type VI: reduced lysyl hydroxylase (autosomal recessive), ruptured corneas, detached retinas. Type VII: inability to turn type I procollagen into collagen.

Familial hypercholesterolemia: Very common. Most of these patients lack enough good apoprotein B-100 ("LDL") receptors. Therefore, they have trouble with (1) hepatic clearance of VLDL leftovers ("IDL's") for recycling, leaving them in the plasma to turn into LDL's; (2) hepatic clearance of LDL's from the plasma, leaving high plasma LDL levels; (3) receptor-mediated uptake of LDL's by other cells (do you remember "coated pits"?), leaving more around to be taken up by the mononuclear phagocytes by their receptor-independent method (which doesn't burn LDL's very well). Xanthomas. Precocious atherosclerosis.

Stein-Leventhal syndrome is a mysterious very common woman's problem. The combination is (1) secondary amenorrhea; (2) hyperandrogenism. Usually also (3) relative tissue resistance to insulin; (4) big ovaries with thick fibrous capsules ("polycystic ovaries"; the cysts are follicles that could not rupture). The male phenotype is the super-hairy guy who goes bald very early.

Autosomal recessive disease

Rules:

> Many body proteins are in such abundant supply that if a person has only half as much of that protein (i.e., has one good gene where most people have two), there is no obvious problem. However, if a person has no good gene where most people have two, the person is sick. Therefore, the known autosomal recessive diseases are either
>
> (1) deficiencies or defects in highly specialized proteins (enzymes, transport proteins), or

(2) hemoglobinopathies requiring more than one dose of a gene

In contrast to autosomal dominant diseases, autosomal recessive diseases:

-- often result from consanguineous matings.

-- are often apparent at, or shortly after, birth;

-- have unknown mutation rates;

-- generally show complete penetrance (if there are several alleles, expressivity may vary; the most conspicuous exception is à1-protease inhibitor deficiency);

Heterozygote advantage accounts for the success of these diseases in Darwin's world in certain ethnic groups. Sickle cell and some of the other hemoglobinopathies protect heterozygotes from malaria. Hemochromatosis heterozygotes are protected from iron deficiency. Cystic fibrosis protects from cholera and other bacterial diarrheas. Tay-Sachs protects from TB.

The major autosomal recessive disorders which you'll meet:

Deficiencies or defects in highly specialized proteins

Known proteins

-- Cystic fibrosis ("mucoviscidosis")
-- Phenylketonuria
-- Galactosemia (two kinds)
-- Adenosine deaminase deficiency (immunodeficiency)
-- à1-protease inhibitor ("antitrypsin") deficiency
-- Common albinism
-- The lysosomal storage diseases (except Fabry's)
-- Most glycogen storage diseases
-- Alkaptonuria
-- Really bad von Willebrand's variants
-- Abetalipoproteinemia (missing apoprotein B; spiny red cells, malabsorption):
-- The bad kind of epidermolysis bullosa (bad type VII collagen, therefore bad anchoring fibers)
-- Chediak-Higashi
-- hereditary fructose intolerance (aldolase B)
-- homocystinuria (cystathione synthetase)
-- hereditary tyrosinemia (fumarylacetoacetate hydrolase)
-- Various inborn errors of hormone metabolism
-- metachromatic leukodystrophy (arylsulfatase A)
-- Krabbe's (galactosylceramidase)

Proteins awaiting discovery
-- Werdnig-Hoffman ("floppy baby") disease
-- Wilson's family of copper problems
-- Unusual albinism syndromes
-- Some Ehlers-Danlos variants
-- Around 16 different familial deafness syndromes
-- Hartnup (can't absorb tryptophan well from gut)
-- At least two malignant hyperthermia genes (neurochemists and anesthesiologists take note)

Major hemoglobin problems
-- Sickle cell anemia
-- Hemoglobin C disease
-- á-thalassemia major
-- Three and four-dose à-thalassemia syndromes
-- Combinations of the above

Albinism: Can't make melanin. Twelve or so different loci. The best understood is tyrosinase deficiency.

Alkaptonuria ("ochronosis"): lack of homogentisic acid oxidase. Precocious osteoarthritis, black urine, black cartilage (check those ears).

Lysosomal storage diseases, of course, result from failure of catabolism of large molecules within lysosomes, which accumulate.

Tay-Sachs disease ("amaurotic, i.e., blind, familial idiocy"): lack of hexosaminidase A, causing accumulation of GM2-ganglioside. Mostly neurons. Born normal, become retarded, blind, floppy. Head becomes huge. Cherry spot on macula is normal red seen amidst cloudy neurons.

Niemann-Pick disease: lack of any one of several proteins required to break down sphingomyelin molecules. Many types. Lipid-laden, foamy-looking affected cells. Electron microscopy shows lamellar lipid masses ("zebra bodies", other forms).

Gaucher's disease: Lack of glucocerebrosidase. Several types. Type I is a semi-disease with a big spleen and liver; pancytopenia (hypersplenism) and bone fractures are a problem. Type II is the kiddie form; replacement enzyme is $400,000 per year for life. In either form, pathologists see "Gaucher cells", huge reticuloendothelial cells bloated with glucocerebroside.

The mucopolysaccharidoses: Problems degrading glycosaminoglycans ("mucopolysaccharides", such as heparan sulfate, dermatan sulfate, keratan sulfate, chondroitin sulfate, and/or others). These include

the very severe Hurler's syndrome ("gargoyle" children with progressive mental retardation) to the variable Sanfilippo (severely mental deterioration, near normal-looking) and Morquio (dwarves with bad aortic valves and normal intelligence) syndromes. Hunter's (MPS-II) is sex-lined, but all the others are autosomal recessives. Expect mild to severe accumulation of mucopolysaccharides in the spleen, liver, etc. Pathologists see PAS-positive material in affected cells.

Metachromatic leukodystrophy: deficiency of arylsulfatase A; galactosyl sulfatide accumulates; brain deteriorates after infancy.

Krabbe's globoid cell leukodystrophy: deficiency of galactocerebroside B galactosidase; galactocerebroside accumulates; brain deteriorates in infancy.

Adrenoleukodystrophy ("Lorenzo's oil", etc.): a family of diseases, some X-linked, with problems breaking down long-chain fatty acids; both white matter and adrenal cortical problems. "Lorenzo's oil" was a heroic failure.

Glycogen storage diseases: The clinical application of a "Biochemistry" unit. Type I (Von Gierke's disease, glucose-6-phosphatase deficiency): Big livers, hypoglycemia. A mild disease. Type II (Pompe's disease, lysosomal glucosidase deficiency, "acid maltase" deficiency): All organs, and die young of heart disease. Type III (Cori's disease, limit dextrin disease, de-branching enzyme deficiency); Rare, patients have liver storage problems. Type IV (branching enzyme deficiency): accumulation of abnormal glycogen in all organs, including the brain; death in infancy. Type V (McArdle's disease, muscle glycogen phosphorylase deficiency): Patients are poor athletes, and get bad cramps and muscle damage when they try. Glycogen is deposited beneath the sarcolemma. Type VI (liver glycogen phosphorylase deficiency): Big liver, hypoglycemia, mild disease. There are others.

X-linked dominant diseases: The only well-known one is familial vitamin-D resistant rickets, a renal phosphate-wasting syndrome. Manic-depression (nowadays, "bipolar disorder") probably has a locus here.

X-linked recessives: Expressing the phenotype requires one dose for hemizygous men, two for women.

Rules:

X-linked diseases:

-- affect all males with the gene

-- affect a woman only if (1) she had two affected X-chromosomes, i.e., she had an affected father and a carrier mother (possible if we're just dealing with color blindness, most unlikely if we're dealing with Duchenne's muscular dystrophy); (2) she suffers from really unfortunate lyonization; (3) the disease is expressed when individually lyonized cells are affected (i.e., G6PD deficiency, in which half the red cells hemolyze and half don't; or some cases of fragile X syndrome); (4) she has Turner's syndrome (XO) or testicular feminization (XY).

-- generally produce many affected family members, once the new mutation has been propagated.

The major X-linked disorders

Familiar proteins

-- Hemophilia A (factor VIII deficiency)
-- Hemophilia B (factor IX deficiency)
-- G6PD deficiency ("favism"; several alleles)
-- Lesch-Nyhan syndrome
-- Duchenne's muscular dystrophy (Jerry's kids)
-- Chronic granulomatous disease
-- Hunter's mucopolysaccharidosis
-- Fabry's disease
-- Common red-green color-blindness
-- Testicular feminization (common type)
-- Nephrogenic diabetes insipidus (hADH receptor in collecting duct)

[-- Unnamed allele for monoamine oxidase A that correlates strikingly with horribly aggressive misbehavior; this new, major discovery caused a political flap...]

Being worked-out

-- Bruton's agammaglobulinemia
-- "David the Bubble Boy"'s immunodeficiency
-- Several other immunodeficiency syndromes
-- Some adrenoleukodystrophy genes
-- Some cases of agenesis of the corpus callosum (alexithymia)
-- Ehlers-Danlos type IX
-- Mencke's kinky hair (a real "kink" in copper metabolism)

Fragile X chromosome

Fabry's disease ("angiokeratoma corporis diffusum universale"; deficiency of the enzyme that breaks down ceramide trihexose). Glomeruli, maybe brain; lamellar bodies on EM.

Fragile X syndrome: About half of cases of familial mental retardation. One guy in 1500, mildly to moderately dim. Enormous testes. Difficulty counting things. Maxilla gets longer as you hit the teenaged years. Dr. Bell, the discoverer, was a famous lady astronomer before turning to medicine.

Y-linked inheritance: Passed father-to-son. Two are known: Testis-determining factor (i.e., being a man), and having hair grow on your ears when you get old.

Mitochondrial inheritance: From Mom. All are progressive and affect cells non-uniformly, i.e., there's a growth advantage for the defective mitochondria. These diseases include Leber's hereditary optic atrophy, (a cytochrome oxidase problem), Kearns-Sayre disease (progressive external ophthalmoplegia, retinal pigmentation, heart block, cerebellar ataxia) and its variants progressive external ophthalmoplegia, myoclonus epilepsy with ragged red fibers, and some others. The "ragged red fibers" of mitochondria look that way because of proliferated, dysfunctional mitochondria packed around their edges. Electron microscopy shows creatine kinase crystals looking like parking lots.

Polygenic inheritance is operating when family and adoption studies show a strong genetic tendency but you can't find a single gene. [Be extremely skeptical when anybody gets doctrinaire about a particular problem, especially when race or politics gets involved.]

[Genetic disease is extremely political. Reasonable people will differ about the issues within limits; there are plenty of charlatans on both the right and the left who are ready to make political capital off the public's misunderstandings. It will fall to you, the physician, to help your community sort this all out.]

Tumor means the same as neoplasm. These are mutant clones of cells that have acquired the ability to grown their own blood supply and connective tissue matrix. They do no good and often great harm. Benign tumors do not invade or spread to remote sites, but can compress healthy structures, make hormones, or cause mechanical or cosmetic troubles. They are usually round like balls, and lack microscopic anaplasia. Malignant tumors are the same as cancers. They invade the surrounding tissue, and most (exceptions: gliomas, basal cell carcinomas) can metastasize. They tend to look like cauliflowers ("exophytic growth", the various bumps representing overgrowing clones and areas between dieback), ulcers (the mass of the tumor has died off), or diffusely replace their parent organ. Differentiation of a malignant tumor tells how well, or how poorly, it resembles its cell of

origin. Well-differentiated tumors show little anaplasia and tend to be non-aggressive. Poorly-differentiated tumors show much anaplasia, and tend to grow and spread rapidly. Any cancer will ultimately kill the patient if not treated.

Carcinomas are cancers of epithelial origin. They tend to metastasize via lymphatic vessels to the regional lymph nodes. (Exceptions: hepatocellular carcinoma, renal cell carcinoma, and follicular cancer of the thyroid tend to spread by vein.) Sarcomas are of cancers of connective tissue origin. They tend to metastasize by veins to the lungs.

Under the microscope, recognize cancers by their anaplasia (bizarre nuclei, cells helter-skelter, high nuclear-cytoplasmic ratio, dark nuclei with bumps on the membranes, and so forth), by mitotic figures (especially bizarre ones), and by hemorrhage and necrosis ("invade, rather than outgrow, their blood supply"); you may also see genuine invasion.

Squamous cell carcinoma features keratin pearls (attempts to make hair), intercellular bridges (desmosomes), and/or single-cell apoptosis (i.e., thinks it's an old surface cell falling off the skin), plus tonofilaments on electron microscopy.

Adenocarcinomas feature bizarre glands, either as tubules or papillary structures (fronds, inside-out glands, with the connective tissue growing like the branches of a tree); look especially for glands-within-glands, stainable secretory product, signet-ring cells (the product forms one large vacuole), or just cohesive nests. (Of course, adenomas feature non-anaplastic glands). Many sarcomas are spindle-cell tumors. Leukemias and lymphomas feature non-cohesive cells that resemble blood cells or precursors.

Immunostains to learn (sometime):

CEA:	adenocarcinomas
CLA:CLA:	tumors of white cells ("common leukocyte antigen")
desmin:	myosarcomas
EMA:	adenocarcinomas ("epithelial membrane antigen")
Factor VIII:	endothelium
GFAP:	glial tumors ("glial fibril acid protein")
NSE:	oat cell CA, isletomas, APUDomas ("neuron-specific esterase")
keratin family:	most epithelial neoplasms

S-100 melanoma, schwannoma, brain, dendritic macrophages, histiocytosis X

vimentin: mesenchymomas, melanomas, kidney tubule

Benign tumors can give you trouble by compressing normal structures, making a hormone, or (not very often) turning malignant.

One American in five dies nowadays of cancer. Malignant tumors in the U.S:

The most common cancers:
Males (in descending order): prostate, lung, colorectal
Females (in descending order): breast, lung, colorectal

The most commonly fatal cancers
Males (in descending order): lung, colorectal, prostate
Females (in descending order): lung, breast, colorectal

Worldwide, cancer of the cervix is the great killer of women, especially young women. The other great third-world killer is hepatocellular carcinoma, which is primarily a man's tumor (because of hepatitis B carrier status and iron overload; the third risk factor, aflatoxin exposure, happens to both sexes).

In order to metastasize, cancer cells need only develop the ability to chew through basement membrane (like polys do), and stick someplace else, and start the new stroma growing. There are four routes:

(1) Seeding of serosal surfaces (or, in the case of CNS tumors, up and down the neuraxis in the CSF)

(2) Mechanical transplantation (rare, typically iatrogenic;

(3) Via lymphatics (traditional route for tumors of epithelial origin, i.e., carcinomas)

(4) Via blood vessels (traditional route for tumors of mesenchymal origin, i.e., sarcomas, because the tumor cells are in direct contact with blood vessels from the beginning)

Most tumors prefer certain metastatic sites. The common sites for metastatic spread for many common cancers include lymph nodes, lung, liver, bone, and brain. Most cancers seldom metastasize to the muscles, spleen or gonads. A tumor's stage is how far it seems to have gotten, and is assigned by the clinician. A tumor's grade is how anaplastic its worst area looks, and is assigned by the pathologist.

Both help tell the prognosis and best therapy. Most high-grade tumors present at high-stage, and most low-grade tumors present at low-stage.

Tumor Nomenclature

I. To assign a name to a tumor which you have examined, begin by writing the suffix -oma. Most tumor names end in this way. (Unfortunately, the suffix simply means "swelling", and some non-neoplasms also use the suffix, i.e., granuloma, hematoma, xanthoma, traumatic neuroma).

II. If the tumor is malignant, write the root carcin- ("crab") if the tumor is of epithelial origin, or sarc- ("flesh") if the tumor is of mesenchymal origin, before -oma. If the tumor is benign, do not write anything.

III. Now choose one or more roots to describe the cell of origin.

If the tumor originated in glandular epithelium, use the root adeno-. (It probably makes little glands and/or mucin.)

If the tumor originated in squamous or transitional epithelium, is benign, and protrudes above the epithelial surface, use the root papillo-.

If the tumor originated in non-glandular epithelium and is malignant, name it for the cell of origin.

Basal cell carcinoma (skin)
Renal cell carcinoma (proximal tubule)
Squamous cell carcinoma (squamous epithelium)
Cholangiocarcinoma (bile ducts)

If the tumor originated from a non-epithelial cell, look for a root in the following list. (We do not consider endothelium and mesothelium to be epithelium.)

fibro- fibroblasts
myxo- myxoid tissue (Wharton's jelly, etc.)

chondro- cartilage
osteo- osteoblasts
lipo- fat
chordo- notochord remnants

leiomyo- smooth muscle

rhabdomyo- striated muscle

schwanno- nerve sheath
(neurilemmo-)
(neurofibro-)

hemangio- blood vessels
lymphangio- lymphatics
glomangio- glomus

synovio- synovium
mesothelio- mesothelium
meningio- arachnoid

lympho- lymphocytes

There are a few epithelial roots you will have to learn. For example:

chorio- placenta
pheochromocyto- adrenal medulla

If the neoplastic cell types are mixed, use a compound, for example, fibroadenoma. Some tumors arise in "totipotential cells" and contain a variety of different mature and/or immature tissues from different germ layers, and these are given names with the root terato- ("monster").

IV. If needed, add an adjective to further describe the tumor. Some examples:

papillary well-differentiated
keratinizing moderately well-differentiated
mucin-producing poorly differentiated
follicular pleomorphic
signet-ring cell cystic (cysto-)
scirrhus desmoplastic
medullary comedo-

V. A handful of tumors that are thoroughly malignant have "benign" names. You will just have to learn these.

lymphoma mesothelioma myeloma ("multiple", plasma cell)
astrocytoma carcinoid glioma (micro-, oligodendro-)
ependymoma seminoma hepatoma
melanoma dysgerminoma leukemia

VI. A hamartoma is "not a tumor, but is a developmental anomaly" (?) which contains the same tissues as the organ in which it is found, but in the wrong proportions.

A choristoma is a mass of normal tissue in an abnormal location.

A tumor which ends in blastoma is composed of cells that resemble those seen in a developing organ. Most blastomas are malignant (but it depends on the site).

A few tumors of uncertain histogenesis are named eponymously: Ewing's sarcoma, Hodgkin's disease, Pindborg tumor, Wilms' tumor, Enzinger's sarcoma.

Carcinogenesis: A series of events leading up to expression of full malignant potential. Transformation: this process as applied to cells themselves. The Nowell multi-step clonal evolution model, [first articulated Science 194: 23, 1976,] is one of the most successful theories in modern science (explanatory power, predictive value) and should now be called "Nowell's Law". Mutations accumulate in overgrowing clones. If we're on our way to becoming cancer, non-disjunction creates cells with extra chromosomes (the deprived cells, we may think, die off), and many (but not all) cancers become aneuploid. Tumor progression refers both to the growth and distant spread of cancer, and to the way the front-line cells become more aggressive and more resistant to therapy (i.e., by the emergence, and selection for, nasty subclones; "multiple-steps"). It is wrong to think of cancer just as "cells growing more rapidly than other cells". Rather, they are less subject to normal controls, and are growing faster than they are dying off. "Growth fraction" can be determined using the monoclonal antibody Ki-67, or getting out the tritiated thymidine and finding the "labelling index." A bizarre mitotic figure can perhaps stick around for weeks.

Cancers cells exhibit transplantability: i.e., they grow easily in culture or syngenic hosts or athymic ("nude") mice; immortality: i.e., they don't Hayflick Out after 50 generations, loss of contact inhibition: i.e., cultured cells continue dividing and actually pile up, instead of stopping once they have formed a nice monolayer; loss of serum and anchorage requirements, loss of density-dependent growth inhibition, and so forth.

Every cancer probably has its own chromosomal fingerprint, though no two are exactly alike in all their mutations. Worth knowing:

t(9;22): chronic myelogenous leukemia (Philadelphia chromosome)
t(8,14): Burkitt's lymphoma
del 3p: renal cell and oat cell carcinoma
del 13q: retinoblastoma
del 11p: Wilms tumor
monosomy 22: meningioma

Antigenic changes, studied in cancer, has generated almost nothing of value.

Rules:

1. All tumors evoked by a specific oncogenic retrovirus (in one organ in one species) tend to have the same tumor-specific antigens (Nowell's law; laboratory retroviruses carry extremely potent oncogenes sufficient to transform by themselves).

2. Tumors induced by a specific chemical are all pretty much different antigenically (Nowell's law, the background of other mutations is different in each case).

There is still no known antigen unique to any cancer. This probably accounts for the disappointing results of chemotherapy ("drugs that are more toxic to cancer cells than normal cells") for the most common cancers. "Cancer is not 'other', it is 'us'". "To fully understand cancer, we will need to understand all of life."

Metabolic changes, much studied, with no useful results. The "Warberg hypothesis", still occasionally described, is dead wrong; the "chymotrypsin deficiency / trophoblast theory" was part of a cynical fraud (laetrile).

Chemicals and cancer. The Delaney Clause forbids the presence of any "cancer-producing chemical" in any concentration in U.S. food. Today this is silly. Now is a good time to learn the following associations:

Soot Cancer of the scrotum ("chimney sweep's cancer" -- discovered by Percival Pott)
Cancer chemoRx Acute leukemia (the bad ones include cyclophosphamide, chlorambucil, busulfan, melphalan, others -- the alkylating agents)
Cyclophosphamide Transitional epithelial (mostly bladder) cancers
Other alkylaters Many cancers (remember nitrogen mustard,

	bischloromethyl ether, benzyl chloride)
Polycyclic HC's	Tobacco smoking-related cancers (lung, larynx, mouth, throat, esophagus, pancreas, bladder, kidney -- remember 3-methylcholanthrene, benz(a)anthracene and benzo(a)pyrene).
Azo dyes	Bladder cancer (dye factory workers, ?? red-M&M eaters, etc., etc. -- remember "butter yellow" in margarine, "scarlet red" in maraschino cherries, and beta-naphthylamine)
Aflatoxin	Eaters of moldy grain and peanuts (hepatocellular carcinoma, endemic in Africa; the mold is aspergillus species)
Betel nut	Mouth and throat cancer (addictive substance chewed in India)
Mat,	Uruguayan herbal concoction; with black tobacco, takes blame for Uruguayan epidemic of bladder cancer
Pickled fish	Chinese nasopharyngeal cancer
Pickled vegetables	Chinese esophageal cancer
Safrole	Sassafras (stomach cancer? other cancers?; a free-radical generator
Vinyl chloride	Angiosarcoma of the liver (factory workers)
Chromium, nickel	Lung cancer (factory workers -- scramble chromosomes)
Cadmium	Prostate cancer (battery factory workers)
Asbestos	Lung cancer, mesothelioma (scrambles chromosomes)
Arsenic	Skin cancers (amplifies genes)
PCB's	Polychlorinated biphenyls (pollutants, suspected of causing human cancers)
Saccharin	Bladder cancer (in huge doses given to animals, but epidemiologically not a significant risk to human users)
Cyclamates	Ditto
Human feces	Several known carcinogens, including those derived from bile salts (try and ban that, Senator Delaney!)
Benzene	Leukemias and related problems
Phenacetin	Transitional epithelial (mostly bladder) cancers
Anabolic steroids	Liver cancer (this particular risk is relatively small, but there are many other, worse risks from use of these substances by athletes)
Estrogen	Endometrial hyperplasias and carcinomas
Ferric ion	Liver cancer (hemochromatosis patients);

	perhaps many other cancers ("free radical generator")
Herbicides	Chlorphenoxy- and chlorophenyl herbicides seem to be linked to soft tissue sarcomas; Well, maybe.

Some environmental carcinogens are direct-acting ("activation-independent"), and exert their effect directly. However, the majority (procarcinogens) require metabolic conversion (activation, often by hepatic cytochrome P450) to produce carcinogenic forms (ultimate carcinogens). Famous direct-acting carcinogens include the alkylating agents (cancer chemotherapeutic agents) and a few acylators. The heavy metals actually depolymerize DNA. Probably all chemicals that really induce cancer are mutagens. The non-mutagens are probably promoters, i.e., promote cell division and/or activate protein kinase C in order to allow the malignant cells actually to overgrow. A rule that works most of the time is that the actual carcinogen either damages DNA directly (the alkylating and acylating agents) or is a potent electrophile (the epoxide ultimate carcinogens derived from polycyclic hydrocarbons, vinyl chloride, and aflatoxins; the N-hydroxylated dye metabolites; the alkyldiazonium ions derived from nitrosamines, etc., etc. etc.)

Selective memory ("I've been trying SO HARD to think what could have given Little Johnny his leukemia!") probably explains the ludicrous (to be frank) "statistical studies showing a relationship" between familiar things and cancer (magnetic fields, cellular telephones). Where the link has proved genuine, the relationship has been striking, and it makes sense biologically.

Two terms from classic studies of chemical carcinogenesis: (1) Initiation: The result of exposure of a cell or cells to a carcinogen, which permanently alters its genetic material but not its phenotype (yet). As noted, these are mutagens. (2) Promotion: A substance that causes initiated cells to turn into tumors. Tumors result when the promoter is administered after, but not before, initiation. Promoters tend to be inducers of rapid cell turnover and/or induces of protein kinase C.

A complete carcinogen is a substance that is both initiator and promoter, such as "tobacco smoke" or certain really awful chemicals. The Ames test for mutagenicity (and presumably carcinogenicity) relies on production of mutants in a culture of typhoid bacteria.

Radiation carcinogenesis. Gamma rays (including x-rays) and ultraviolet light cause mutations. The bane of the Curie family, and

many of the other pioneers. Atomic bomb survivors have greatly increased incidences of all the common leukemias (except CLL; the incubation time is a few years), and minor increases in many (but not most) solid tumors (remember thyroid, breast, salivary gland, lung). Chernobyl's children are getting thyroid cancer from radioactive iodine, and other problems. Your lecturer believes the "radon in your home" stuff is a scam. Nobody's shown an increased risk from living near nuclear power plants. Radium paint workers who put their brushes in their mouths developed bone and nose cancers. Uranium miners have a greatly increased incidence of lung cancer, even if they do not smoke. People given high doses of radiation for ankylosing spondylitis (x-rays) or polycythemia vera (radiophosphorus) have greatly increased incidences of all the common leukemias. Newborns treated for mythical "enlarged thymus" developed many thyroid cancers as young adults. Ultraviolet radiation is the principal risk factor in most skin cancers (basal cell, squamous cell, malignant melanoma). Suntanning will not protect you from the wavelengths that cause cancer and elastosis ("aging of the skin").

Viral carcinogenesis: Most cancers are not contagious, period.

Wart virus ("human papilloma virus", HPV) causes warts ("benign tumors") in humans, and certain strains also cause cancer of the uterine cervix, penis, and anal canal in humans. The cancer-producing strains produce products which tie up Rb and p53 antioncogene products.

Epstein-Barr virus ("herpes 4") is necessary (but not sufficient) to cause African Burkitt's lymphoma, and is etiologic in Chinese nasopharyngeal cancer, immunoblastic lymphoma, and Eskimo endemic salivary gland adenocarcinoma.

Hepatitis B virus and hepatitis C virus cause hepatocellular carcinoma by acting as mitogens, encouraging selection of damaged cells.

HTLV-I causes epidemic leukemia in Japanese humans. HTLV-II seems to cause hairy cell "leukemia" (which might simply be an infection).

Before you tell me that "nobody would ask us about particular cancer genes", be advised that they already have. I've chosen the most-testworthy.

Oncogenes were originally discovered in transforming retroviruses ("the RNA tumor viruses"). "Viral oncogenes" turned out to be cancer-producing genes that the viruses had just happened to pick up ("transduced") while growing in established tumors. A proto-oncogene that has acquired the ability to cause cancer (i.e., has become an

oncogene) is said to be activated.

(1) Classic tyrosine kinase proto-oncogenes: signal-transducers, across membranes. src, abl (from the bcr/abl translocation in the Philadelphia translocation in chronic myelogenous leukemia), RET (multiple endocrine neoplasia type II). Usually activate by mutation.

(2) GTP-binding protein proto-oncogenes: tell cells to divide in response to signals (or just divide, period, when they're damaged). Includes the ras family, which takes mutations at certain hot-spot codons (12, 13, 61), which code for the active site.

(3) DNA-binding protein proto-oncogenes: the myc family, whose protein products are intranuclear and bind to DNA itself. myc activation is usually by amplification (excess copies of a gene) and/or translocation rather than by mutation. In Burkitt's lymphoma of B-cells, c-myc (chromosome 8) is moved next to the immunoglobulin gene (chromosome 14), i.e., the cell decides to multiply like crazy every time it is told to make antibodies. myc genes are much amplified in neuroblastomas and oat cell lung carcinomas.

(4) Growth factor protein proto-oncogenes. c-sis codes for the beta chain of platelet-derived growth factor (PDGF), the stuff that tells fibroblasts to divide in wound healing. Probably sis-induced cancers grow by autocrine self-stimulation by PDGF.

(5) Protein growth factor receptor proto-oncogenes. erbB, which codes for a protein homologous to the epidermal growth factor receptor, neu / HER2 and fms, which codes for macrophage colony-stimulating factor. These work by the familiar inositol triphosphate . diacylglycerol second-messenger systems.

(6) Enhancer binding protein proto-oncogenes; erbA codes for the human thyroid hormone receptor. It is linked to a variety of animal cancers.

(7) Master-switches: jun is the factor that initiates transcription of DNA at a particular sequence. fos apparently turns short-term stimulation into long-term differentiation and immortalize.

(8) int-2, the second site where the mouse mammary tumor virus integrates, is the gene for fibroblast growth factor #3; flg is FGF1 and bck is FGF2.

(9) bcl-2, activated in most B-cell lymphomas, and its relative bcl-X, tell the cell not to undergo apoptosis, but to divide if told to do so. Nobody knows how it works.

(10) p16, discovered in 1993 on 9p21, is one of a new family of cyclin-dependent kinase inhibitors; Cyclin D1 itself (11q13, bcl1, the PRAD locus) is another cancer gene.

(11) A subject that will probably soon be important is the activation of genes that enable cancer cells to metastasize.

Anti-oncogenes keep cells benign, even when the oncogenes are activated. To lose their anti-cancer effect, both copies must be altered. (Contrast the proto-oncogenes which exert their effect when a single copy is activated to an oncogene.)

Knudson's Law for anti-oncogenes

One hit: You have a cell with a much increased propensity to turn malignant

Two hits: You have a cancer cell.

If you derive from a mutation-bearing sperm or egg, or were hit at conception, you have one of the autosomal dominant anti-oncogene deletion ("tumor-susceptibility") syndromes. The malignant phenotype requires both copies to be bad, so it is autosomal recessive.

Sporadic examples of cancers seen in these cancer-family syndromes exhibit the same markers, i.e., sporadic (bad-luck) retinoblastomas are homozygous for loss of Rb.

Rb: Deletion syndrome features retinoblastomas in childhood, osteosarcoma and breast cancer in survivors.

p53: Deletion syndrome is LiFraumeni, with increased prevalence of cancer in most organs. The gene tells cells to undergo apoptosis, or at least not to divide, if their genome has been injured. Lose p53, and your clone's genome has become profoundly unstable. Many, if not most, cancers lose p53. Aflatoxin produces a trademark mutation in both p53 and ras.

p16INK4 (no syndrome) is a cell-cycle gene which is very commonly deleted in lots of cancers.

VHL: Deletion syndrome is von Hippel-Lindau, with hemangioblastomas of the cerebellum, eye hemangiomas, and kidney cancers. All renal cell

carcinomas have lost VHL.

WT1 (was WAGR): Deletion is an aniridia syndrome with Wilms' tumor.

NF-1: Deletion syndrome is common Von Recklinghausen's neurofibromatosis. Gene product "neurofibromin" facilitates action of normal ras. Von Recklinghausen's is common (1 person in 3000), variably expressive but very penetrant. Nerve tumors (schwammomas, neurofibromas) anywhere, and pigmented skin lesions ("caf, au lait", i.e., coffee with milk, spots with smooth borders; look around the armpits). The "elephant man's" elephant skin was caused by epidermal and dermal hyperplasia overlying neurofibromas.

NF-2: Deletion syndrome is neurofibromatosis type II, with acoustic neuromas.

APC: Deletion syndrome is familial polyposis of the colon. All colon cancers lose this. Gardner's, with colon and mesenchymal (soft tissue, bone) tumors, is a different allele here.

MEN-I: Deletion syndrome is multiple endocrine neoplasia type I (pituitary adenomas, parathyroid adenomas / hyperplasia, gastrinomas).

RET: Deletion syndrome is multiple endocrine neoplasia type II.

The Lynch genes: Deletion syndrome is non-polyposis colon cancer. Very common. Genes repair DNA mismatches.

> NOTE: Turcot's, with brain tumors and colon cancers, can be at the APC or Lynch loci.

Peutz-Jegher's: Not yet cloned; black freckles on the lips, hamartomas of the intestines.

BRCA-1: Deletion syndrome is familial breast and over cancer, early in life. Made the cover of "Time". Very common.

Dysplastic nevus syndrome: Deletion syndrome causes a variant melanin which generates, rather than quenches, free radicals. Lots of melanomas.

CDKN2 and P16-1NK4: pancreatic cancer and melanoma; Cyclin inhibitors.

Tuberous sclerosis: We'd love to know where the genes are... TS is common (1 in 2000 folks is you look) with lots of hamartomas, and no two cases alike. Notable "tumors" include "adenoma sebaceum"

(misnomer; fibromuscular bumps on the maxillary region, nose, and chin); "candle gutterings" (benign glial nodules on the walls of the cerebral ventricles); "rhabdomyomas" of the heart; "angiomyolipomas" of the kidney; various brain tumors. Many have seizures, most are at least a bit slow mentally. Ash-leaf spots are easiest to see with ultraviolet.

Autosomal recessive cancer family syndromes may involve chromosomal instability; for the first three, heterozygotes are mildly affected.

Ataxia-telangiectasia: immunodeficiency from breaks in the T-cell receptor genes, extra tumor risk and radiosensitivity, chromosomal instability; Purkinje cells tend to die off, rheumatoid arthritis is common.

Fanconi's anemia (pancytopenia, multiple birth defects, white cell tumors, chromosomal instability)

Bloom's syndrome (carcinomas, leukemias; DNA ligase I deficiency)

Xeroderma pigmentosum (skin cancers -- cannot repair DNA; actually a family of 16 different loci)

Werner's syndrome (sarcomas; this is the famous "accelerated aging" syndrome, where 40 year olds look like 80 year olds from a distance)

Cancer problems: There's no need to explain the havoc wrought by cancerous invasion of the brain, destruction of the bone, replacement of the marrow, or necrosis with fistula formation.

Sex hormones can wreck havoc. They're usually from adrenal or gonad.

Low serum sodium from hypersecretion of hADH: oat cell carcinoma, some others.

High serum calcium: Bone metastases, plasma cell myeloma osteoclastic activation, parathormone-like substance produced by squamous cell lung cancer.

Hypoglycemia from insulinomas. Feels bad, makes you fat, kills.

Carcinoid syndrome (paroxysms of flushing, wheezing, and diarrhea) from production of serotonin and kinins by certain apudomas.

Erythrocytosis (excessively high red cell mass): renal cell carcinoma

produces excessive erythropoietin.

Autoimmune hemolytic anemia: think of malignant lymphoma.

Hyperviscosity syndrome results from cancers that elaborate IgM. The very thick blood sludges in the brain and death results.

Brain syndromes are often autoimmune. Anti-Yo disease (cerebellum), Anti-Ri disease (opsoclonus), anti-retina antibody disease (blinded by oat-cell), Anti-Hu disease (protean, oat-cell); Eaton-Lambert syndrome antibody against calcium channel in myoneural junction, seen with oat-cell.

Acanthosis nigricans is an accumulation of black hyperkeratotic papules in the armpits and groin. Think adenocarcinoma somewhere.

Dermatomyositis-polymyositis is often a marker of occult cancer.

Clubbing of the digits ("Hippocratic change"; "hypertrophic osteoarthropathy") commonly results from lung cancer, but is nonspecific (and seen in many non-cancerous diseases, notably those which cause extensive lung damage or right-to-left cardiac shunts).

Venous thrombosis, not just in the legs, is a marker for pancreatic cancer ("Trousseau's other sign")

Disseminated intravascular coagulation is common in advanced cancer, especially when the blood vessels have been invaded

Marantic endocarditis is little fibrin vegetations on the heart valves seen in patients with any wasting disorder. They are prone to embolize.

Myasthenia gravis, immune destruction of normoblasts and suppression of plasma cells are all common in thymomas.

Plugging of the renal tubules by immunoglobulin light chains is common in cancer of the plasma cells.

Glomerular protein leakage ("the nephrotic syndrome") is a troublesome remote effect of various cancers, nobody knows why.

Cancer pain: Invasion of bone with microfractures. Obstruction of a hollow organ. Invasion of nerve plexus. After surgery (post-op analgesia is a joke since surgeons are lawyer-shy.) Psychosocial problems in our screwed-up health-care system range from trouble

getting a job (if you survive) to ridiculous laws that make it hard to give drugs for pain "for fear of causing addiction".

Death from cancer: Pneumonia (neutropenia, airway obstruction, not breathing deeply, too weak to cough, got stuff down the wrong throat). Sepsis leading to shock, the portal of entry being the tumor, the bladder, the constipated gut, or the bedsores. Hemorrhage (brain, gut, elsewhere) from thrombocytopenia. Pulmonary emboli from being hypercoagulable and bedridden. Kidney failure. Paraneoplastic syndrome (above). Iatrogenic disease. Suicide and active euthanasia; before you consider these, remember that almost all cancer pain is controllable if (and only if) the government will let you.

Tumor immunity is a subject of perpetual interest, and I'm sorry to have to tell you that the immune surveillance theory, so popular with quacks, is simply not true. Folks who are immune-crippled only get cancers of cells that tend to be hyperplastic in them (i.e., B-cells) and/or caused by viruses (Epstein-Barr, Kaposi's). Nude mice (no transplant immunity) have no higher rate of spontaneous cancers.

Harvesting lymphocytes from tumors, growing them, and reinjecting them occasionally helps, and there are magic-bullets against those rare cancers (notably melanomas) that express antigens not usually expressed by benign cells.

Cancer epidemiology: It's simply not true that cancer's becoming more common, if you control for the fact that we're not dying of infections and violence as kids. Lung cancer: Becoming more common in populations that are taking up smoking, less common in populations that have been giving it up. Stomach cancer used to be very common, and is now pretty rare. Melanoma is getting more common because of sunbathing.

Geographic differences seem related to environment rather than genes, as shown by immigrant studies. Breast cancer is less common in the poor nations where a woman is usually pregnant or nursing. Colon cancer is highest where there's a high-meat, high-saturated-fat, low-roughage diet. Prostate cancer is very rare in Japan; Afro-Americans have a very high incidence. Esophageal cancer is the scourge of China and central Asia. Stomach cancer is very common in Japan and Chile, possibly from bacteria. Burkitt's lymphoma is epidemic in, and only in, the African virus belt; explanations range from malaria to eating poinsettias. Hepatocellular carcinoma runs with aflatoxin (moldy food), iron overload, and hepatitis B in sub-Saharan Africa. Cancer of the cervix is lifestyle-related, and is a sexually-transmitted disease; if the man is circumcised, he has less chance of transmitting HPV. Choriocarcinoma is common in the Far East because of the high rate of

molar pregnancies. Squamous cell carcinoma of the bladder is caused by schistosome eggs and is a scourge in Egypt. Transitional cell carcinoma of the bladder was a horrible problem in Rumania, where the communists declared barns illegal (ideology at work); the cause may be a toxin or mouse hantavirus in the grain, which folks had to store in their houses.

[The major cancer frauds of the century include laetrile (apricot pits, pseudo-conservatives), krebiozen (creatine in mineral oil), New Age stuff (pseudo-liberals) and macrobiotics (no relation to real Buddhism). There are literally hundreds of others. Using stolen stationery to get your articles published in the refereed scientific literature: JAMA 266: 1471 & 1749, 1991 ("We were told it was often necessary to deceive the unenlightened to advance our guru's plan to save the world.") It's to your credit that you chose scientific medicine instead. While we practice it, our best weapon against cancer quackery is the quack's own: Take time with your patient, be kind and considerate and use common sense, explain things, let the patient make choices within reason, be tactile when it's right, and just generally be nice (even when it's hard).]

I am resisting the temptation to review basic immunology here. If you don't know about the various cytokines, clonal expansion (one stimulated T-cell or B-cell becomes thousands, with the same specificity), please brush up.

Type I immune injury. "Anaphylactic". "Immediate-hypersensitivity". "Reagin-mediated". "Atopy" (strange). IgE on the mast cells / basophils and all that. Starts in moments, ends within a few hours. IgE / mast cells are worm protection.

Allergy freaks make IgE more readily and/or have a more hair-trigger allele for the IgE receptor on the mast cell.

Allergy symptoms are the kinds of things that would expel a worm (itchy-urticaria, sneezing, coughing, vomiting). In each case, histamine from mast cells makes vessels leaky, causes bronchial smooth muscle to constrict, and causes the gastric parietal cells to churn out acid. Mast cells also release "eosinophil chemotactic factor of anaphylaxis" and neutrophil chemotactic stuff. Leukotrienes (C4, D4, E4) are "secondary mediators" synthesized special after the first round of degranulation. Leukotrienes are responsible for some of the allergic wheezing, etc., that does not respond to antihistamines.

Systemic anaphylaxis: Penicillin injections, insect stings, infamous food allergies (eggs, peanuts, shellfish). The whole vascular bed

opens and leaks ("anaphylactic shock"), then bronchospasm occurs.

Type II immune injury. Antibodies attach to antigens on the surfaces of a cell, and then something (complement, hungry phagocyte, special T-cell) injures or destroys the cell.

Transfusion reactions: ABO you should know, usually involves ready-made, complement-fixing IgM. Rh incompatibility usually involves IgG which must be induced. If you are Rh ("D") negative, the second time you encounter the Rh antigen, you may get a little sick when, beginning a few days later, the transfused red cells are slowly destroyed.

Hemolytic disease of the newborn ("erythroblastosis fetalis"), Mom is sensitized to one of the father's red cell antigens which she does not share (probably during the birth of a previous child, with mixing of fetal-maternal blood). If the isoantibody is IgG, it can cross the placenta and wreck havoc on the fetus's red cells, causing anemia, normoblastic ("erythroblastic") hyperplasia, etc. And when the baby is born, there's no placenta to carry all the breakdown products of hemoglobin away, so the child becomes jaundiced.

Autoimmune hemolytic anemia (lupus, lymphoma), autoimmune neutropenia, autoimmune thrombocytopenia. Penicillin-as-a-hapten hemolysis. In paroxysmal cold hemoglobinuria, the antibody against the red cells is an IgM active only in the cold.

Goodpasture's disease: Autoantibody against lung and glomerular basement membrane. Cough up blood; rapidly progressive glomerulonephritis. Treat with plasma exchange daily until recovery supervenes.

Pemphigus: Antibodies against desmosomes. Pemphigoid: Antibodies against hemidesmosomes.

Autoimmune gland problems tend to feature a mix of autoantibodies and angry T-cells, working together to destroy the gland. This includes juvenile-onset diabetes, Hashimoto's / lymphocytic thyroiditis, pernicious anemia, autoimmune adrenalitis, Sjogren's, and a few oddities.

Hyperacute rejection of an organ is mediated by already-present antibodies (type II + type III).

Rheumatic fever features autoantibodies against streptococci which cross-react with other tissues; nobody really understands it. In

Sydenham's chorea, a component of the syndrome, antibodies against streptococci cross-react with basal ganglia.

Anti-neutrophil cytoplasmic antibody diseases includes Wegener's and small-vessel polyarteritis.

The paraneoplastic encephalopathies (the antigen is a cancer, the victim is the normal cell) have been considered above.

Lyme neuropathy: Antibodies against the bug crossreact with the axon.

HIV infection features destruction of uninfected T-cells by anti-HIV antibodies directed against dead viruses, which stick to the surfaces of the unfortunate T-cells.

Type III immune injury. Caused by antigen-antibody complexes precipitating when they're mixed in just the wrong proportions. The "aches and pains of the viral illness" is the most familiar, and least deadly.

Serum sickness: You get an injection of horse serum, against which you already have antibodies. Total-body vasculitis. Arthus reaction: You get an intramuscular injection of something against which you have antibodies already. (Ever get a sore arm after a booster shot?)

Glomerulonephritis includes many variants that are type III immune-mediated, including all the ones that look interesting on electron microscopy.

In Farmer's lung, there's a vasculitis from antibodies precipitating with inhaled bacteria.

In lupus, type III immune injury is a major problem.

n drug reactions, systemic infections, carcinomatosis, etc., etc., hypersensitivity angiitis of small arteries and small veins may be due to drugs allergy, systemic infections, carcinomatosis, or what-have-you.

In AIDS and childhood immune thrombocytopenia, antigen-antibody complexes coat platelets, causing their destruction.

Polyarteritis nodosa is a reaction pattern which in many cases is caused by antigen-antibody complexes with hepatitis B surface antigen.

Rheumatoid factor is IgM antibodies again the Fc portion of IgG. These

tend to precipitate in the walls of vessels, producing a vasculitis.

I'm surprised more folks don't get awful sick from allergy shots.

Classic delayed hypersensitivity (Type IV immune injury variant): Special T-helper cells (TD) programmed to recognize a particular "altered self" antigen with HLA Class II, are stimulated. They in turn coordinate other lymphocytes, macrophages, and other tissue elements. The object is to destroy every cell bearing the "altered self" antigen, i.e., get rid of those pesky viruses, any cells sheltering TB, your transplants, etc. The local macrophages get angry and do most of the dirty-work. The tissue reaction can be very brisk and locally destructive. Antibodies are not involved. Inability to mount this particular response is called anergy.

Cell-mediated cytotoxicity (Type IV immune injury variant): Special T-cell (T-CTL) are programmed to alter a particular altered-self antigen in association with HLA Class I. The T-CTL cell assassinates its target using its perforin, without harm to surrounding tissues. Antibodies may or may not be involved, too.

> NOTE: Some folks call cell-mediated cytotoxicity "Type IV-B" if (and only if) it is antibody-dependent. Other call it "Type V"; still others put it under "Type II". Yeah, these are artificial.

The tuberculin skin test is the prototype of classic delayed cytotoxicity. Hepatitis B (antibody-independent) and the autoimmune endocrinopathies (antibody-dependent) are prototypes of cell-mediated cytotoxicity.

You've also known these processes if you've ever had poison ivy, allergy to jewelry, or neomycin rash. It's also the basis of cell damage in hepatitis B and the viral skin rashes.

Type V immune injury (as I number them) is said to be present when antibodies bind to cells and cause them to malfunction instead of being destroyed.

Circulating anticoagulants are antibodies against a coagulation factor (usually VIII or prothrombin activator).

Classic pernicious anemia is due to an auto-antibody which binds to intrinsic factor, rendering it unable to carry vitamin B12 through the ileal mucosa.

A few cases of insulin-resistant diabetes mellitus are caused by

autoantibodies that tie up insulin receptors.

Antibodies against animal insulin were the bane of diabetics in past years.

Graves' disease: Stimulatory autoantibodies against the TSH receptor.

Celiac sprue / dermatitis herpetiformis features antibodies against reticulin, induced by exposure to gluten in wheat.

Stiff-man syndrome: autoantibody against glutamic acid decarboxylase, which synthesizes the neurotransmitter gamma-amino butyric acid. There are LOTS more type V's known.

Hyperacute transplant rejection happens when the patient gets a allograft and already has antibodies against it (oops!). There is a pattern of type II + type III immune injury. Nasty.

Acute rejection is mediated by T-cells and is basically done by cell-mediated immunity, mostly T-CTL. Can happen suddenly, years after the transplant. Look for onion-skinning (i.e., subacute vasculitis).

Chronic rejection is still rather mysterious, and is usual in old allografts. Mostly you will see fibrosis of the organ and dense fibrous narrowing of the arterial lumens.

Graft vs. host disease: Marrow or other T-cell-bearing material given to an immune-disabled host attack the "foreign" recipient. Skin (dermatitis), intestine (diarrhea, malabsorption), and liver (biliary epithelium -- jaundice, elevated serum alkaline phosphatase, portal fibrosis) in the acute disease. Chronic graft-vs.-host is more widespread and looks like scleroderma.

Mechanisms of autoimmunity: Still mysterious. Molecular mimicry: Well-established in rheumatic fever (antibodies against M-protein in streptococcus cross-reacts with heart and brain). Lyme spirochetes mimic axons, thymoma mimics myoneural junction, oat cell carcinoma mimics various neural antigens. Less clear: Coxsackie-B virus and heart (Barney Clark), measles and T-cells (measles anergy), Klebsiella and HLA-B27, Yersinia and the TSH-receptor, Escherichia and primary biliary cirrhosis antigen, cow's milk and type I diabetes autoantigen, Epstein-Barr virus and myelin. Autoimmune diseases exacerbate and remit since the immune system is feedback-loops within feedback-loops, both positive and negative. Autoimmune diseases tend to occur together in the same person. You'll learn the familiar combinations later. In the autoimmune endocrinopathies, the process seems to involve

expression, inappropriately, of HLA-II antigens on the surfaces of attacked cells.

Women have a stronger immune system than men. [That's not politics; it's the truth.] Which gender gets more of a particular disease (if both genders can get that disease)? If a disease is autoimmune, women get it more often than men. If a disease is not autoimmune, men get it more than women. This almost always works. Exceptions: Men get more of the HLA-B linked diseases (i.e., the ankylosing spondylitis family), women get more osteoporosis, and autoimmune diabetes is sexes-equal.

Systemic lupus: Autoantibodies against ubiquitous little antigens; usually anti-double stranded DNA. rim pattern on fluorescent ANA. Anti-Sm, if present, is diagnostic. LE-cell is a phagocyte that's eaten a stripped, homogenized nucleus. A "hematoxylin body" is a stripped, homogenized nucleus. Butterfly rash. Discoid rash (different, may occur alone). Non-mutilating arthritis (synovitis). Insanity (anti-ribosomal antibody). Autoimmune hemolysis. "Lupus anticoagulant" (anti-phospholipid antibody) makes blood hypercoagulable (sic.), produces abortions, makes a false-positive syphilis screening test; it's common enough in non-lupus patients. Immune-complex glomerulonephritis. Libman-Sacks endocarditis features sterile vegetations on all heart surfaces. Vasculitis with type III immune injury. "Lupus band test" shows immune complexes in the dermal-epidermal junction, as granules. Aphthae in the mouth are infarcts ("canker sores"). Serositis (pleuritis, peritonitis). Neonatal lupus: anti-Ro crosses the placenta and causes a rash and heart block. Single-organ autoimmune disease (endocrinopathy, myasthenia) doesn't usually appear in lupus. Lupus patients feel terrible, look healthy.

Drug-induced lupus: Anti-histone, homogeneous pattern on ANA. Hydralazine, procainamide, less often isoniazid. Are you a slow-acetylator?

Sjogren's: Autoimmune destruction of the salivary and lacrimal glands. Common. Most have anti-Ro and anti-La. B-cell lymphomas tend to arise here.

Scleroderma: Fibrous thickening of selected body parts (always the fingers, often the rest of the dermis). Fibrous proliferation (onion-skinning) of little arteries causes the Raynaud's that always precedes scleroderma. Esophagus (garden hose, trouble swallowing), skin (linoleum), lungs (pulmonary fibrosis, deadly), gut (malabsorption), renal vessels (hypertensive crisis). Anti-topoisomerase (anti-Scl70) is common. Anti-nucleolar antibodies; nucleolar pattern on ANA.

CREST: calcification of the fingerpads, Raynaud's, esophageal fibrosis, sclerodactyly (linoleum fingers), telangiectasias (dilated vessels from scars contracting). Defined by antibodies against centromeres.

Morphea: Localized scleroderma. Saber-cut scleroderma, etc. Eosinophilic fasciitis, a scleroderma variant with eosinophils, is idiopathic, and resembles the horrible eosinophilia-myalgia syndrome from tainted "health food" tryptophan.

Polymyositis-dermatomyositis: Polymyositis features T-cells attacking skeletal muscle, especially hips and shoulders, with pain and weakness. Many patients have anti-Jo, antibodies against transfer-RNA synthetase, and so forth. "Dermatomyositis" is polymyositis plus a distinctive rash, with purple ("heliotrope") eyelids, purple bumps on the knuckles, and so forth. Work these folks up for underlying cancer.

Mixed connective tissue disease: Antibodies against U1-ribonucleoprotein (U1-RNP). Speckled pattern on ANA. Raynaud's, arthritis, maybe more.

Polyarteritis nodosa: All-three-layer vasculitis with lots of little aneurysms, i.e., the process is a vicious cycle locally. A great imitator, and easy to miss, with fatal results. Small-vessel polyarteritis is anti-myeloperoxidase disease (anti-neutrophil cytoplasmic antibody with peripheral staining, p-ANCA disease). Gets any body-part except lung; thrombosis in the little aneurysms is devastating. Cyclophosphamide is the mainstay of treatment. Other patients have type III immune injury with hepatitis B surface antigen and antibody. Kawasaki disease features the histopathology of polyarteritis, with a rash (face, palm, soles), sore throat, big lymph nodes, and maybe coronary vasculitis; often in kids of Japanese ancestry after any of several viruses. Henoch-Schonlein purpura: Polyarteritis-like disease, without the aneurysms, and with lots of IgA in the vessels; IgA glomerulopathy, arthritis, GI-bleed, skin rash; kids get better by themselves.

Wegener's granulomatosis: Another great imitator, caused by c-ANCA (anti-proteinase 3), with features of type III and classic type IV activity, i.e., polyarteritis plus granulomas. Ears-eyes-nose-throat involvement ("saddle nose"), lung-involvement, and/or necrotizing glomerulonephritis. Fatal if untreated; cyclophosphamide is the mainstay of therapy. Nobody knows how ANCA really cause disease; probably we're expressing the antigens on the surfaces of other cells, too.

Know your amyloids:

Amyloid A (AA) Serum amyloid-associated protein; those with longstanding chronic inflammation (lepers, familial mediterranean fever, osteomyelitis, TB, rheumatoid arthritis); roughest on the kidneys

Amyloid B (AL) Immunoglobulin light chains; plasma cell myeloma or other clonal overgrowths of B-cells; roughest on the heart

Amyloid C (AF) Transthyretin; hereditary substituted forms are the most amyloidogenic; peripheral neuropathy with chronic pain

Amyloid H HLA light chains ("beta-2 microglobulin"); hemodialysis patients, since the kidney normally clears these chains; worst on the joints and carpal tunnels

Amyloid E Protein hormones, in the stroma of endocrine tumors and the islands of some type II diabetics (in the latter, it's beta-pleated amylin)

Amyloid beta / A4 Alzheimer's.

Kuru plaques Prions. This is the basis of the "mad cow" flap in England; at present, I believe the index series is a selection artifact.

There are others. Amyloid's effects... Heart: heart block, restrictive cardiomyopathy (stiff heart). Vessels: brittle. Gut: Stiff, malabsorption, diarrhea, constipation. Liver: Huge but normally functioning, do not biopsy it. Wrist: Carpal tunnel syndrome. Kidney: nephrotic syndrome progressing to uremia. Sago spleen: amyloid in the white pulp (like the granules in tapioca). Lard spleen: amyloid in the red pulp (like lard, with little air pockets). Make the diagnosis on biopsy.

Immunodeficiency: Hereditary, retroviral, iatrogenic (cancer chemotherapy, transplants), or secondary (Cushingism, alcoholism, malnutrition, uremia, diabetes). B-cell problems / complement problems / neutrophil problems: Infections with the common bacteria. T-cell problems: candida, later pneumocystis and the intracellular, non-bacterial pathogens.

Bruton's X-linked hypogammaglobulinemia: Lack of a tyrosine kinase

essential to B-cell multiplication. Treat with gamma globulin injections.

Isolated IgA deficiency: Not much of a problem, unless you get allergic to IgA in a blood transfusion, then get another transfusion.

DiGeorge's thymic dysembryogenesis: No thymus, other midline defects; often no parathyroids either.

Severe combined immunodeficiency: Lack of B-cells and T-cells. Most familiar is adenosine deaminase deficiency (dATP builds up and is toxic to lymphocytes), the first disease cured by gene therapy. In one X-linked SCID, the interleukin 2 receptor is absent; another form affected "David the Bubble Boy". There are others.

Wiscott-Aldrich syndrome: Lack of CD43, on the X-chromosome. Boys have eczema, scanty platelets, poorly-understood immune deficiency.

There's another, poorly-understood X-linked immunodeficiency called sex-linked lymphoproliferative syndrome in which affected boys develop lethal lymphomas when they meet the Epstein-Barr virus.

T-cell membrane defects: For example, lack of a CD3 subunit.

Common variable immunodeficiency: Poorly-understood syndromes that appear later in life, perhaps from clonal overgrowth; problems making enough of the right kinds of antibodies.

Complement component deficiencies will confuse you. Remember that C2 deficiency presents an ANA-negative lupus picture, while the higher-numbered deficiencies have problems with meningococcemia.

HIV disease: Retroviral immunodeficiency. HIV-1 (East Africa) is probably a chimp zoonosis that's become established among humans; HIV-2 (West Africa) is probably a sooty mangabee zoonosis. Don't even ask me about Duesberg; you should be able to see through his stuff yourself.

HIV infection wipes out T-helper cells (T4, CD4; counts and function); there's a major dip during the acute infection (a mononucleosis-like syndrome), then counts return to near-normal, then wane over the following years until the opportunistic infections appear; T-cells are lost/inactivated because of viral lysis, coating of the CD4 receptor by gp120; B-cell hyperplasia creates a compensatory hypergammaglobulinemia which handles most bacterial infections okay. Note that gp120 also binds to, and HIV infects, the less-study-able dendritic macrophage system. You know the opportunistic infections, which include "Kaposi's

sarcoma" (herpes 8 infection), "lymphoma" (Epstein-Barr infections), pneumocystosis (lung), CMV (retina or anywhere else), TB, atypical mycobacteria, histoplasmosis, coccidioidomycosis, giardiasis, candidiasis, rochalimaea, herpes simplex, herpes zoster, toxoplasmosis, cryptosporidiosis, campylobacter, herpes 6 ("roseola bug"), progressive multifocal leukoencephalopathy (JC papovavirus), skin fungi (dandruff, jock itch, more), etc., etc., etc..

HIV is neurotoxic; look for neuronal dropout, granuloma-style giant cells in the brain (microglia eating each other because of the gp120 on their surfaces; HIV "giant cell encephalitis").

Other problems: Thrombocytopenia from platelets getting coated with antigen-antibody complexes. Cachexia: nobody knows why, maybe muscle cell apoptosis. AIDS nephropathy is severe foot-process disease.

Good to know: HIV probably can't infect a white cell that isn't already upset about something. The virus is passed cell-to-cell, avoiding antibodies. The most efficient route of transfer is receptive anal intercourse; there's lots of good recipient cells here. A man having unprotected regular intercourse with his wife has maybe a 20% chance of transmitting the infection over 70 years; a hygienic, lesion-free man is very unlikely to catch it from a woman during regular intercourse. Childbirth places the baby at risk, and so does breast-feeding. HIV in babies usually progresses faster than in adults. Oral sex isn't very efficient for HIV transmission, and kissing and necking are safe. Missionaries in HIV-infested parts of the world (mosquitoes, etc.) just aren't getting infected. Needle-sticks with HIV-positive blood have about a 0.3% chance of transmitting the infection. Sharing dirty needles is riskier. A blood transfusion with HIV-positive blood is 90% likely to infect you. The ELISA is a good screening test; the Western blot is definitive. AZT works by inhibiting reverse transcriptase. Non-progressive HIV: About 5% of cases. Some are defective viruses, some are mysterious. This is THE topic in AIDS work right now. [I prefer understanding to rhetoric, and science to ideology and prejudice; my saddest AIDS story is a gym acquaintance who told me, in early 1996, "There was only one man, I didn't like how it felt, but I did it because I wanted a friend."]

["A hungry man is not a free man."
-- Adlai E. Stevenson

"It is better to know some of the questions than all of the answers."
-- James Thurber

Each day, 50,000 people die directly or indirectly from undernutrition. Most of the suffering is borne by children, and survivors are often brain-damaged. Yet the world currently produces more than enough food. Right now, all hunger is political. The problems are complex; my prescription, like Virchow's, is democracy.]

Marasmus ("wasting"): Total-calorie malnutrition. Wasting, ravenous appetite.

Kwashiorkor (African term): Protein malnutrition, as when the child is displaced at the breast by a younger sibling. Hypoalbuminemia, fatty liver, edema, sluggish mind, depigmentation ("flag sign" in the hair), pellagra-like paint-chip rash.

Vitamin deficiencies: Hard to find nowadays in their pure forms, except vitamin A deficiency. Usually seen as features of mixed malnutrition. Folic acid is relatively deficient in the U.S. "twinkies and diet pepsi" diet; iron less so. I am not aware of any good study confirming the popular claim of "widespread subclinical vitamin deficiencies". Fat-soluble vitamins (A, D, E, K) may get depleted in those with fat malabsorption (steatorrhea, or any generalized malabsorption).

Vitamin A deficiency: Major world health problem. Metaplasia of columnar epithelium into stratified squamous epithelium; over-keratinization of existing stratified squamous epithelium (xerophthalmia, Bitot's spots, acne). Bad respiratory infections (no cilia), measles is likely to be fatal. Loss of visual pigments (rods first, night-blindness). Several million people are blinded yearly from vitamin A deficiency; the problem is worst in General Khadaffi's Libya.

Vitamin A excess: Vitamin faddists, polar-bear liver eaters; you can't do it with carrots) get increased intracranial pressure ("pseudotumor cerebri") with headache and nausea-vomiting, a special kind of fatty liver (vitamin A clogging the "Ito cells"), and desquamation of the skin (as seen in those taking Accutane, but worse). Remember retinoids, but not carotenoids, are teratogens.

Vitamin D deficiency: Rare in the developed nations unless you "tea-and-toast" for all your meals. "Rickets" in kids, "osteomalacia" in adults; problem is failure of the bone to mineralize. "Rickets" features Harrison's groove, the "rachitic rosary", bow-legs, "craniotabes", "frontal bossing", "pigeon breast", "square head", pelvic deformities (die in childbirth).

Vitamin D excess: Vitamin faddists get hypercalcemia and kidney stones.

Vitamin E deficiency: Malabsorption or total-parental-nutrition. Ceroid in the gut, damaged sensory pathways in the cord. Animals get hyposexuality and infertility. Vitamin E therapy helps preemies with their eye problems and hemolytic anemia.

Vitamin K deficiency: Vitamin K is the cofactor required to add a gamma-carboxyl group to clotting factors II, VII, IX, X, S, Z, and C. Required for clotting; your gut bacteria may or may not give you enough vitamin K. Deficiencies, usually in preemies, are preventable with an injection of vitamin K; you may want to inject your cirrhotic patients too.

Vitamin B1 deficiency (thiamine): Polished rice eaters (historical), alcoholics, women with hyperemesis of pregnancy. Beriberi may be dry (neuropathy) or wet (congestive heart failure; heart is flabby, yet vessels are dilated for "high-output failure"). Wernicke's (ataxia, eye movement problems, damaged mammillary bodies; why you give drunkards a shot of thiamine before starting the glucose) and Korsakoff's (can't tell real from imagined memories, damaged dorsomedian nucleus of thalamus).

Vitamin B2 deficiency (riboflavin): FAD precursor. I doubt its existence as a distinct disease; the books describe "cheilitis" (cracked angles of mouth), seborrheic-type dermatitis on the nose, cheeks, and hands ("glove dermatitis"), and purple tongue.

Vitamin B3 deficiency (niacin, nicotinic acid): NAD precursor. Deficiency is pellagra, with dermatitis (paint-flakes, especially on the shins and wherever the sun shines), dementia (schizophrenia-like), diarrhea, and death (the "D"'s). Maize-eaters (lack of tryptophan, a niacin precursor, and something that binds niacin).

Vitamin B6 deficiency (pyridoxine): Amino group shuttle. Best way to get "deficient" is to poison your pathways with isoniazid. Neuropathy.

Folic acid deficiency (Vitamin P): In vegetables. Methyl-group shuttle. Deficient in many alcoholics, pregnant women, folks with malabsorption (especially disease of the terminal ileum), bacterial overgrowth of the gut (including "tropical sprue", vicious cycle) folks taking phenytoin "Dilantin". Macrocytic anemia, mental changes, neural tube defects in babies.

Vitamin B12 deficiency (cobalamin, cyanocobalamin): In all foods of animal origin. Deficiencies in the strictest vegetarians, those with fish tapeworm, those with resected ileum or Crohn's disease here, or

antibodies again / lack of intrinsic factor ("pernicious anemia"). Macrocytic anemia, demyelinized posterior columns ("subacute combined degeneration of the cord"), later brain dysfunction.

Biotin deficiency: Remember that "avidin" in raw eggs is very effective at blocking absorption of biotin ("Rocky Balboa" take note).

Vitamin C deficiency (ascorbic acid): Redox cofactor, required for making and maintaining collagen and for other stuff. Deficiency is "scurvy". In kids, osteoid is deficient, mimicking rickets. Regardless of age, capillaries weaken, with bleeds and general misery (the worst is bleeds under the periosteum), old wounds reopen, bleeding gums.

Vitamin C megadosing: Surprisingly safe; uremics die of oxalic acid poisoning, normals get increased iron absorption and false-negative blood and glucose tests in urine. The Linus Pauling story, if you care to learn it, is sad.

Iron deficiency: From diet ("twinkies and diet pepsi", milk-only), disease of duodenum (where it's absorbed), kooky diets ("macrobiotics"), rapidly-growing youngsters, heavy blood loss (heavy periods, GI bleeders notably those with ulcers, cancer, or hookworm; hematuria, overzealous blood donors), starch-eaters. Rampant in our world. Anemia (hypochromic, microcytic) appears late. The story about "esophageal webs" just isn't true -- these are problem-drinkers with scars from ripping their esophagus during the dry-heaves. Serum ferritin tells your iron stores ("zero" in symptomatic deficiency); other techniques include looking at zinc protoporphyrin (porphyrin molecules building up waiting in line for iron) and transferring saturation (Fe/TIBC).

Zinc deficiency: Malabsorption, breast-milk-only, etc. "Acrodermatitis enteropathica" and loss of senses of smell and taste.

Copper deficiency: Preemies, starvation. Copper oxidizes iron, cross-links lysine side-chains, oxidizes melanin.

Selenium deficiency: "Keshan disease", a deadly heart-failure syndrome in Red China (a bureaucrat forget to add selenium to the fertilizer). You need selenium for glutathione reduction.

Iodine deficiency: A world scandal. Hypothyroidism, goiter (extra TSH), several million kids permanently brain-damaged each year.

Manganese poisoning: Simulates Parkinsonism.

Fat: In the U.S., even the beggars ("Will work for food") are often fat. Those who are genuinely hungry are mostly the children of substance abusers. Yet our women, on the average, are leaner and far more physically fit than women, on the average, in many of the poor nations. Your bodyfat is calories-in (food, alcohol) vs. calories-out (malabsorption, work of living, work of carrying-your-body-weight, exercise, heat given off from your skin, vomiting, tumor burden, uncoupled mitochondria). Hunger ("I'm hungry") vs. appetite ("Mmmm, that looks good!"). Appetite uppers: Hypothalamus (brain injury, Froehlich's, peptides), anabolic steroids, marijuana. The Ob gene product (discovered 1995), leptin, suppresses appetite in the presence of adequate or excess bodyfat. [The "ideal weight charts" are subscience at it stupidest (the whole track team is "underweight", the steroid-free weightlifters are "obese"); your best weight is what looks and feels right for you, and which enables you to be athletic. Despite all the sub-scientific chatter, I am not aware of any reason to believe that a man needs any measurable bodyfat; women do best with a few pounds, helps with the estrogen. "Measuring bodyfat" by dipping you in water is also bunk (a bit of gas in your intestines will....)]

Obesity: Causes problems, but how serious? Think: (1) un-aesthetic, (2) bad back; (3) sore knees; (4) sore hips; (5) exacerbates hypertension maybe; (6) exacerbates type II diabetes somehow; (7) helps form gallstones somehow; (8) makes surgeon's job harder; (9) airway problems during sleep; (10) uterus cancer by making extra estrogens; (11) slight fatty change in the liver but nothing serious; (12) slight elevation of uric acid; (13) hard to keep your skinfold area clean (crotchrot, etc.), (14) varicose veins.... Beyond this, it's probably not an independent risk factor for anything. Are you thinking what I'm thinking, i.e., that obesity is over-rated as a health problem? Fun to know: fat cells divide if you're overfed before age 1; they only hypertrophy afterwards.

Malnutrition in America: malabsorption, don't feel like eating, child abuse. Alcoholics: folate and thiamine deficiency, protein-calorie malnutrition, later scurvy.

Tobacco: "The American Indian's Revenge". More physically addictive than heroin, cocaine, or alcohol. (1) Lung cancer; (2) Emphysema; (3) atherosclerosis; (4) mouth cancer; (5) esophageal cancer; (6) larynx cancer; (7) bladder cancer; (8) kidney cancer; (9) pancreatic cancer; (10) gastric ulcers; (11) Buerger's; (12) brain-damage to the fetus (stay tuned, this is probably true); (13) household fires; (14) gum disease; (15) stained teeth; (16) bad breath; (17) earlier wrinkling of the skin. Quitting is always good. Emphysema is irreversible, but the

risk of cancer drops to baseline after some years, i.e., away from smoke, there's selection against the bad clones.

Pneumoconiosis: Dust-disease of the lung. Particles 1-3 microns are most likely to get deposited, and they'll be most abundant in the respiratory bronchioles, where the wind speed drops.

Black lung: Coal miners. A mix of anthracosis (coal dust, nonfibrogenic, mild, "coal macules" made of carbon-laden macrophages can be washed out), silicosis (fibrogenic, nasty), TB, damage from pollution, and/or tobacco effect. Weird immune responses to coal occur in a few percent of coal workers (Caplan's is rheumatoid nodules in the lung with lupus, rheumatoid arthritis, scleroderma, and/or polymyositis-dermatomyositis; progressive massive fibrosis is a gruesome, tumor-like mass).

Silicosis: Rock dust, sandblasters. Fibrogenic (when eaten by macrophages, they produce interleukin 1). Nodules grow concentrically around respiratory bronchioles, never stopping. Eggshell calcifications. Increased TB risk, sometimes Caplan's.

Asbestosis: Fibrous silicate forms needles which move around in the lung. Coated with iron ("ferruginous bodies"). Shipyard workers, insulation workers, asbestos-abatement workers. Greatly increase your risk for lung cancer if you smoke (trick question: the most common asbestos-related cancer is common bronchogenic carcinoma). You need asbestos to get mesothelioma, i.e. cancer of the pleura. Pulmonary interstitial fibrosis, pleural fibrosis.

Berylliosis: Rocket workers (formerly), fluorescent bulbs (formerly); Rocky Flats plant. Some folks have their T-helper cells excited by beryllium, and these people get an exuberant growth of non-caseating granulomas. Zirconium can do the same thing; it was big in deodorants in past years ("armpit sarcoid").

Organic pneumoconioses: Spores from bacteria and/or mold. Farmers, dirty air-conditioners. Type I, III, and/or IV immune injury. Bagassosis: mold in sugarcane. Byssinosis: sensitized to cotton dust; a dubious entity.

[Violence is the antithesis of creativity and wholeness. It destroys community and makes brotherhood impossible.

-- Martin Luther King 1967

Go not in and out at the courts of law, that thy name

may not stink.
-- Egyptian papyrus, c. 900 B.C.

Confucius said, "In hearing litigation, I am no different from any other judge. But if you insist on a difference, it is, perhaps, that I try to get the parties not to resort to litigation in the first place."
-- Analects XII.13.

I have no easy solution to the world's violence. You already know the right-wing and left-wing crackpot solutions; these would be funny if only.... As before, my best prescription is Dr. Virchow's: reduce the hurting and confusion through real democracy, honest science, reasonable security of person and property, and access to education and rewarding work.]

[Whose body is it? Distraught relatives are notoriously unreliable. Time of death: Not an exact science. Filling out a death certificate... The cause of death is your best opinion, as a physician, with or without an autopsy. You list this on the death certificate.

CAUSE OF DEATH: Thromboembolus in right main pulmonary artery (circa 1 minute)
SECONDARY TO: Thrombophlebitis of leg vein (circa 5 days)
SECONDARY TO: Adenocarcinoma of the pancreas (circa 6 months)

Please don't write "cardiopulmonary arrest" as the cause of death. We already knew that....]

The mechanism of death is your story. "The Trousseau pulmonary embolus strained the right ventricle and a rhythm disturbance developed." Once again, this is your best opinion.

The manner of death is for the lawyers: natural, accidental, suicide, homicide, undetermined. This generates much weirdness.

All drugs are poisons, and all poisons are drugs.

Predictable toxicities:

Bleomycin	Pulmonary fibrosis (high doses)
Cyclophosphamide	Bladder inflammation
Adriamycin	Cardiomyopathy, soft tissue necrosis

Vincristine	Dysautonomia, painful neuropathy
Reserpine	Sadness
Phenytoin	Gum hyperplasia, teratogen
Cyclophosphamide	Teratogen, kidney poison, gum hyperplasia
Coumadin	Teratogen
Accutane (isotretinoin)	Teratogen
Aspirin	Rough on stomach and platelets
Benzodiazepines	Amnesia
Scopolamine	Amnesia
Caffeine	Mild withdrawal syndrome (headache, crabby)
Amphotericin B	acute renal tubular necrosis
Opiates	constipation, impotence
Methyldopa	impotence
Serotonin happy pills	delayed ejaculation
Thioridazine	retrograde ejaculation
Anabolic steroids	cholestasis, weird man stuff
Penicillin, high dose	non-immune hemolysis
Methotrexate	cirrhosis (be careful with doses)

"The perfect crime". I bet I'd still catch you if you poisoned someone with digitalis, succinylcholine, sodium fluoride, or insulin.

Unpredictable drug effects: The dose doesn't much matter

Penicillin	anaphylaxis, rash
Quinidine class	sudden death
Clozapine	agranulocytosis
Phenylbutazone	agranulocytosis
Gold	nephrotic syndrome
Penicillamine	nephrotic syndrome
Nitrofurantoin	ARDS
Cyclophosphamide	ARDS
Bleomycin	ARDS
Busulfan	ARDS
Azathioprine	ARDS
Amiodarone	ARDS, hepatitis
Griseofulvin	hepatitis
Isoniazid	hepatitis, lupus
NSAIDS	renal shutdown
halothane	liver necrosis
hydralazine	lupus
procainamide	lupus
methysergide	retroperitoneal fibrosis
anti-malarials	retinitis and blindness
anything	rash

Cocaine: Major evil presence. Ischemic necrosis of nasal septum. Cardiac muscle cell necrosis, vasospasm, sensitization to epinephrine. Crack babies.

Opiates: The dangers of addiction itself have been greatly overrated; it's constipating and bad for your sex drive, an overdose can kill you (brain depression and/or pulmonary edema), and you'll make undesirable friends. The bad health effects are from unhygienic practices.

[Cannabis (marijuana, pot, grass, hashish, etc.; "I did not inhale"): Extremely political, but not really good for you. Probably makes you lazy and stupid. Marijuana's been suggested as helpful for glaucoma, AIDS wasting, and toxicity of chemotherapy; in the current political climate, this isn't going to get acted-on.

The "war on drugs" needs no description. If our politicians (liberal, conservative) actually WANTED to do something effective about our godawful drug problem (rather than just making political capital off it), we'd have humane detoxification available on demand. We could, and we don't.]

Elemental mercury: Work exposure, toxic encephalopathy, behavior problems ("mad hatter"), clumsiness, sometimes ALS-like syndrome. Inorganic mercury: Kidney tubule poison. Organic mercury: Environmental contamination, particularly in high-on-the-food-chain fishes. Minimata disease was a dread neurologic syndrome among Japanese who ate fish caught near a mercury dump site.

Lead ("plumbism"): industrial exposure, moonshine, and children who eat the sweet lead paint chips in slum housing. Stays in bone. Hypochromic-microcytic anemia (inhibits delta-ALA synthetase and ferrochelatase); also binds sulfhydryls. Basophilic stippling of red cells. Renal Fanconi syndrome (proximal tubular dysfunction) with acid-fast eosinophilic i intranuclear inclusions. "Lead line" in dirty mouths. Encephalopathy, peripheral neuropathy (wrist drop).

Arsenic: Crime-fiction and crime-fact. (The guy in St. Louis who kept his wife sick with arsenic "wanted quality time with her".) Disrupts oxidative phosphorylation. Vomiting, blood diarrhea acutely, maybe brain necrosis. Chronic cases (1) hyperkeratosis of the skin, particularly the palms; these may turn into squamous cell carcinomas; (2) "Mee's lines", white lines in the fingernails, where arsenic is bound to keratin.

Paraquat: Drink it, and you'll die in a few weeks of ARDS.

Chlorinated hydrocarbon insecticides (DDT, dieldrin, others): neurotoxins.

Organophosphate insecticides (malathion, parathion): Acute, or from breakdown of bodyfat. Acetylcholinesterase inhibitors, i.e., first you'll twitch, then go limp (why?).

Polychlorinated biphenyls ("PCB's"): Politicized; innumerable claims that mostly can't be true. They do stay around in the environment forever.

Dioxins: Agent orange, etc. Politicized, much bunk, but there's reason to worry. A few weeks after heavy exposure, a human's sebaceous gland basal cells undergo metaplasia into keratinocytes, pushing sebum out of the follicle in huge horny blobs ("chloracne"). This gets better in a few months or years.

Toadstools: Amanita phalloides, the "death angel" produces aminitin, which inhibits RNA polymerase. Death results from hepatic necrosis. Amanita muscaria produces muscarin(e), prototype of the parasympathomimetic drugs. ("SLUD" strikes again.) Expect to survive.

["When I put my arms around you and kiss you on your mouth,
Then I am happy even without beer!"
-- Ancient Egyptian love song]

Alcohol: Your lecturer thinks he's being fair when he says that the harm caused by alcohol exceeds, by an order of magnitude, the harm from the illegal drugs. Yet most people who drink alcohol sensibly appear to take no harm and perhaps even derive some healthy pleasure. Noah needed a drink when... and made an "ass" of himself, the "butt" of his son's joke. Proof: Double the percentage of ethanol. Nobody knows the chemistry of drunkenness. The liver metabolizes alcohol first to acetaldehyde (via alcohol dehydrogenase), then to acetic acid, and ultimately to carbon dioxide and water. Problem drinkers lose their dendritic spines; "each drink kills x-number of brain cells" is rubbish. Each beer or shot raises a normal-size dude's blood alcohol level by 20 mg/dL; "legally drunk" is maybe 100 mg/dL but you're impaired below this. You metabolize alcohol at a rate of 15 mg/dL/hr, using basically zero-order kinetics; faster if you're a practiced drunkards.

Health problems of heavy drinkers: (1) alcoholic hepatitis and hepatic cirrhosis; (2) brain damage (loss of dendritic spines, Wernicke, Korsakoff, cerebellar atrophy); (3) pancreatitis (acute and the painful

chronic form); (4) cancer of esophagus, throat, and larynx; (5) GI bleeding from ulcers, varices, gastritis; (6) fetal alcohol syndrome (variable; look for flat philtrum, epicanthic folds, growth and mental retardation); (7) neuropathy (numb fingers); (8) cardiomyopathy (rare); (9) rhabdomyolysis (seldom dramatic, but probably contributes to long-term wasting); (10) hangover, tremulousness, seizures, delirium tremens on withdrawal ("pink elephants on parade", etc.); (11) losing job, family, friends; (12) oh, and by the way, it probably has a slight favorable effect on HDL and coronary atherosclerosis. Gee whiz.

["I've been asked if I ever get the
DT's. I don't know. It's hard to tell
where Hollywood ends and the DT's begin."

-- W.C. Fields]

Methanol ("meth", "wood alcohol", "blind, vomiting, and drunk") is metabolized to formaldehyde and thence to formic acid (which gives the famous high anion gap acidosis). The retina toxicity is infamous ("like stepping into a snowstorm") and can be persistent. Part of the treatment involves saturating alcohol dehydrogenase with ethanol.

Isopropanol ("rubbing alcohol", users are "rubby-dubs", etc.) is about twice as potent an intoxicant as ethanol, but really nasty to the gastric mucosa. Metabolized to acetone via alcohol dehydrogenase, and produces an modest anion gap acidosis.

Ethylene glycol (anti-freeze) is metabolized to glycolaldehyde, glyoxylic acid, and oxalic acid. Big anion gap acidosis, and little crystals that carve up renal tubules, meninges, etc. Not a nice way to die.

I'm resisting the temptation to talk about guns.

Abrasions: Epidermis scraped off, dermis not much damaged, heal with no scar. Lacerations: Splits and tears of skin and/or soft tissue, due to stretching-shearing or crushing, on the body surface or deep inside. Flail-chest: Broken ribs go in and out, making breathing relatively ineffective. Tension pneumothorax: A rip in the pleural admits air to the pleural cavity on inspiration, but does not allow it to exit; this will push the mediastinal contents to the other side, obstructing venous return.

Stab wounds (i.e., the track is deeper than the width of the skin wound); incised wounds (cuts, i.e., the track is less deep than the width of the skin wound); chop wounds (incised wounds plus an

underlying bone fracture or groove, made by heavy instruments). Sharp trauma gives clean margins and no bridging in the depths. Blunt trauma (i.e., lacerations) give bridging in the depths of the wound, frayed and bruised margins.

Suffocation: Failure of oxygen to reach the uppermost airway. Too little oxygen to breathe, and the hemoglobin refuses to bind it any more. Smothering: suffocation by something pressing on the face. Choking: Obstruction within the air passages. When "natural", the cause is epiglottitis. Accidents include the cafe-coronary, popcorn, vomit (Jimi Hendrix). Homicides: (1) stuffing a baby's mouth with toilet paper to stop its crying, or (2) using a rag in the mouth in conjunction with a gag. Mechanical asphyxia: Pressure outside the body; large snakes, human piles, cars falling on mechanics. Each time you breathe out, your chest is further constricted. When you try to breathe back in, you cannot. At autopsy, you'll see bruises, petechiae all over the conjunctiva and sclera, and impressive congestion of the head. An important variation is positional asphyxia. Someone slips into a confined space, and each exhalation causes the person to slip deeper. Suffocating gases: Gases may displace oxygen in the atmosphere. Methane ("How's that canary doing?") and carbon dioxide.

Strangulation: Occlusion of the blood flow and air passages in the neck by external compression. Look for petechiae on the conjunctiva. Hanging: Compression of neck structures secondary to a noose tightened by body weight. (Humans are "hanged", inanimate objects are "hung"; a man saying he's "hung" is bragging.) Death is due to a fractured spine in a properly-done judicial hanging; more often, it's due to arterial or venous compression. Ligature strangulation: Compression of neck structures is secondary to a noose tightened by something other than body weight. Manual strangulation: Compression of neck structures by someone else's body part.

Chemical asphyxia. Cyanide: Blocks the cytochrome system. Painful, and by no means instantaneous. At autopsy, look for (1) bright red blood (i.e., cyanide prevents utilization of oxygen) (2) the "bitter almonds" smell (around 1 person in 3 cannot smell it); (3) thiocyanate in the blood (normal folks, especially smokers, will have some of this on board already.) Carbon monoxide: Acts by tying up hemoglobin. Its affinity for hemoglobin is 200 times that of oxygen. Smokers are likely to have 10% saturation of hemoglobin. Saturation from 20-30% will make you sick (it's at this point that cherry-red lividity may appear). Saturation of 60% or more will probably kill you. In acute toxicity, there is headache, drowsiness, and ultimately confusion and coma. Necrosis of the basal ganglia, early or late, is common. Whole family has a headache? How's that home heater working?

Surface burns.....

First-degree: The outer epidermis is damaged. The dermal vessels probably dilate, but there are no blisters.
Second-degree: Living cells are killed in the epidermis. There will be a blister.
Third-degree: No more epidermis.
Fourth-degree: Charred through.

Complications of burns include:

-- hyperkalemia, from disruption of red cells and other cells by the heat;
-- shock and hemoconcentration, from the tremendous amount of fluid lost in the inflammatory exudate (this is the most serious problem in the emergency department);
-- acute renal tubular necrosis;
-- disseminated intravascular coagulation, due to damaged vessel walls and bad stuff getting into the bloodstream (distant endothelium really is damaged);
-- Curling's ulcers of the gastric mucosa, with GI bleeding.
-- infection of the burn (pseudomonas, candida); this is the most serious problem in today's burn unit.

["What was the last thing the judge said to Ted Bundy? More power to you!"
-- Anonymous

"What was Ted Bundy's last job? Conductor!"
-- Anonymous]

High-voltage alternating current (i.e., 7680 volts, from the generator plant) kills by generating heat.

Low-voltage alternating current (i.e., 110 volt household current) kills by inducing ventricular fibrillation; or if the amperage is high, the heart simply cannot re-polarize.

High-voltage direct current: Lightning; arborescent patterns.

Effect of current:

1 milliamp tingle, "let-go" current
10 milliamps "can't-let-go" current

30 milliamps respiratory paralysis
75-250 milliamps ventricular fibrillation is likely
4 amps asystole

Heat problems: Babies, the elderly, and those taking anticholinergic agents and phenothiazine drugs are especially vulnerable to these problems; so are those on cocaine, those doing forced labor in hot quarters, and those training in the heat. Heat exhaustion, a person over-exerts in a hot environment. Electrolyte problems, lactic acidosis, maybe rhabdomyolysis. Heat stroke: Body gets so hot that its thermoregulatory controls no longer work. Vicious cycle to death.

Cold: Below 31øC / 86øF, our enzymes don't work well. As a person dies of hypothermia, the skin blanches (vasoconstriction, why?), then reddens (loss of vasomotor control, with resultant rapid loss of heat.) The latter effect probably explains why many people who are freezing to death remove their clothes. Death probably results from brain and/or heart dysfunction. Chilblains: Purple spots on the shins in cold exposure; nobody understands it.

Ionizing radiation: Cells that normally divide a lot (i.e., epidermis and its adnexa, GI mucosa, bronchi) are more vulnerable to radiation than most other organs. Germ cells and lymphocytes also carry the instruction: "If you're hurt, then die, don't divide." (Why might that be?) Bone, muscle, cartilage, and nerve are highly radioresistant. Except as noted above, the susceptibility of a cancer to radiation has little to do with the susceptibility of its parent cell. Pathologists look for hyaline vascular sclerosis and big, hyperchromatic nuclei.

Radiation sickness

200- 500 rads Hemopoietic syndrome. Early nausea and vomiting on the first day. Afterwards, blood cells disappear from the body (lymphocytes first, since they are the most vulnerable; afterwards, short-lived neutrophils and platelets; ultimately, survivors become anemic.) Victims receiving 200 rads will probably survive; those receiving 500 rads will probably die.

500-1000 rads Gastrointestinal syndrome. Severe nausea and vomiting occur within a few hours, and are only the most prominent symptom in a body in which many cells have died in many places. Most victims will die in a few days.

>5000 rads Cerebral syndrome. Brain necrosis and edema will produce drowsiness, coma, and death in an hour or two.

Lead me from death to life, from falsehood to truth.
Lead me from despair to hope, from fear to trust.
Lead me from hate to love, from war to peace.
Let peace fill our heart, our world, our universe.
-- Brihadaranyaka Upanishad
(Hindu scripture)

I think that people want peace so much that one of these days governments had better get out of the way and let them have it.
-- Dwight D. Eisenhower, 8/31/1959

Embryo: An unborn child / product of conception with child parts for the first eight weeks after the moment of conception. Fetus: An unborn child / product of conception with child-parts (rather than just placenta), between eight weeks after conception and the moment of live birth ("all-the-way-out with a beating heart" for our lawyer friends). Neonate: A child in the first four weeks of life after birth. Infant: A child in the first year of life after birth. Infant mortality: For a population, how many of its people per 1000 live births die before their first birthday.

Pre-term: Born before 37-38 weeks. Born at 22 weeks: Will almost surely die in first six months. Born at 23 weeks: Will probably never be healthy. Born at 25 weeks: 50% chance of not having gross brain damage. Post-term: Both after 42 weeks. Small for gestational age ("small for dates"): Below 10th percentile on the charts. The child did not grow properly in the uterus, and the organs will have extra problems once the child is born.... Why SGA?

- Problems with the unborn child itself
  - Chromosomal problems
  - Congenital infections ("torch")
    - Toxoplasmosis
    - Other (syphilis, etc.)
    - Rubella
    - Cytomegalovirus
    - Herpes (usually not an intra-uterine infection)
  - Other congenital anomalies
- Problems with the placenta or uterus
  - Infarcts
  - Tumors
  - Etc., etc.

- Problems with Mother
  - Cocaine ("crack babies")
  - Tobacco
  - Opiate abuse
  - Alcoholism
  - Toxemia and other hypertension

Large for gestational age: Above 90th percentile on the charts. Think of maternal diabetes. Low birth weight: As it sounds; a mix of "small for gestational age" and "preterm". By definition, <2500 gm. Very low birth weight: <1500 gm.

Uterine constraint: begins around our 35th week of intrauterine life. Worse with twins, oligohydramnios (no kidneys / leaky sac), fibroids, bicornuate uterus. Deformation (as opposed to a "malformation"): molded out of shape by uterine constraint. Two percent of kids get a significant deformation. Most famous is oligohydramnios sequence, with squashed ("Potter's") face and badly bent limbs.

Malformations result from chromosomal problems, genes of large effect, deletions of chunks of a chromosome, polygenic problems, or "just happen". Range from hypospadias to anencephaly.... Around 3% of kids have a malformation that's at least of serious cosmetic importance (i.e., "a major malformation").

Neonatal asphyxia is an important cause of death and brain damage in babies.

- Causes:
  - Placental problems
    - Placenta previa (i.e., a low-slung placenta overlying the os)
    - Abruption (i.e., a big bleed between placenta and uterine wall)
  - Cord problems
    - Compression (around neck, breech delivery, etc., etc.)
  - Other (poorly-understood)
    - Toxemia
    - Prolonged rupture of the membranes
    - Chorioamnionitis
    - Etc.

Birth injuries: Remember intracerebral hemorrhages from dural sinuses or brain substance. The most important birth injury, devastating. Upper extremity injuries: Fractured clavicle, brachial plexus injury (Erb's palsy, etc., etc.), fractured humerus. Facial nerve injury:

Often from forceps (Silvester Stallone's syndrome).

Galactosemia: Two autosomal-recessive inborn errors. The not-so-bad kind of galactosemia: lack of galactokinase. Galactolol cataracts. The bad kind of galactosemia is caused by galactose-1-phosphate uridyl transferase deficiency. Nobody really understands the pathophysiology. Liver swelling, brain damage. You must eliminate milk from the diet.

Phenylketonuria should be familiar to you; inability to metabolize phenylalanine properly results in brain damage, and a restricted diet helps prevent this. Kids are typically fair-complected (not much tyrosine to make melanin from).

Cystic fibrosis: homozygous lack of a membrane component (CFTR) essential to proper chloride transport across membranes of the mucus-producing exocrine glands and eccrine sweat glands in response to cAMP. Name comes from the pancreatic and salivary gland changes resulting from gooey plugs. Pancreatic insufficiency, causing malabsorption, is easily corrected by supplementing enzymes. Sweat ducts fail to resorb salt (hence "salty skin", positive sweat test). Goo fills the bronchi, leading to bronchiectasis and repeated lung infections (staph, pseudomonas). Good in the meconium causes meconium ileus. Males are infertile (poor spermatogenesis, often the vas is lacking). Diabetes and cirrhosis are rare; these kids usually die nowadays in young adult life from lung problems.

"God is great, God is good,
Get me through my childhood!"
-- Bart Simpson

"Ed tells it like it is." SIDS (the leading killer of normally-formed kids age one month to one year) is far less mysterious than you've been led to believe. Known causes include (1) falling asleep face-down and smothering on the mattress; (2) parent falling asleep (passing out from alcohol or drugs, etc.) on top of the baby; (3) negligence on the part of caretakers; (4) murder by smothering. Rule out (4) epilepsy; (5) obstructive sleep apnea; (6) botulism from raw honey; (7) ectodermal dysplasia with no sweat glands; (8) anomalous coronary arteries; (8) carbon monoxide; (9) kinks in fatty acid metabolism. To be fair, some cases probably are (10) "mysterious". To clinch what most pathologists have known since the "SIDS mystery" nonsense began... Waneta E. Hoyte, the mother whose "tragic story" led to the paper (Ped. 50, 646, 1972) that spawned the apnea monitor racket confessed in 1994 to having smothered her five children. ("Their screaming made her feel useless": Ped. 93: 944, 1994). This is now common-knowledge, and the writers of the USMLE surely know it; it would make a great test question.

[Children do not vote, and when politicians get involved (even to "protect our children"), kids are almost always the big losers. Tonight in the U.S., 100,000 kids will be sleeping on the streets; almost all of them have run away / been discarded from intolerable home situations. However, in the current political climate, you'd better not even try to be a real friend to the neglected, mistreated kids in your own community. If you don't know this now, you will soon.]

[Old people like to give good advice, as solace for no longer being able to provide bad examples.
-- de la Rochefoucauld

Not so much to add years to life, as to add life to years.
-- Geriatrician's motto]

Our bodies are programmed to wear out. [The Darwinian advantage is surely that this makes way for our children, who combine our genes with those of others to make their long-term survival more likely.] The Hayflick phenomenon results in the non-replication of baby's cells in tissue culture after 50 divisions; it's unlikely that this has to do with human aging, since there's no reason to think it applies to stem cells, and the cells that bear the brunt of aging (i.e., brain) are post-mitotic. Loss of telomeres with each cell cycle, and their re-synthesis in germ cells, is interesting, but doesn't even account for the Hayflick phenomenon, since a Hayflicked-out nucleus suppresses division in a baby's nucleus. Stochastic theories ("wear and tear") simply don't explain the stereotyped changes in aging, though "wear and tear" does account for some of the degenerative changes. Attempts to use free-radical acceptors to slow aging have been a total flop, though they seem to control some wear-and-tear diseases.

Older folks have (1) more lipofuscin in their cells; (2) slower rates of cell turnover; (3) greater vulnerability of mitochondria to hypoxia; (4) extra cross-linking of connective-tissue molecules (why I'm stiff); (5) non-enzymatic glycosylation of proteins (why diabetics' vessels "age faster"); (6) more lymphoid tissue but less ability to make antibodies appropriately, though this is mild; (7) more autoantibodies, but less autoimmune disease (contrary to some texts); (8) less ability to the T-cells to proliferate; (9) thinning of the dermis and epidermis, and loss of some connective tissues (reversible with growth hormone); (10) less sex hormone (we men will be getting replacement when we get old, trust me); (11) some loss of neurons in brain and ganglia, nobody knows why; (12) some loss of hearing, both conductive and nerve; (13) some thickening of the intima of arteries, even without atherosclerosis; (14) some decrease in glucose tolerance; (15)

substantially diminished nitric oxide synthesis in endothelium; (16) loss of androgen receptors on erectile tissue, guys; (17) mild loss of elasticity in the lungs and skin; the lungs get it much worse if you smoke; (18) some loss of bone matrix (osteoporosis); (19) diminished sense of smell, but not taste); (20) little bumps of various sorts on your skin; (21) hair turns gray; (22) lens of the eye stiffens ("presbyopia"), get those reading glasses.

You will surely die at, or soon after, age 100, even if you have no diseases at all; and this hasn't changed since reliable record-keeping became the norm. Every other vertebrate species has a maximum age, too; it varies some among inbred strains.

Syndromes of accelerated aging aren't. Classic progeria, autosomal recessive, features kids born looking old, with peachfuzz instead of hair; this doesn't progress. Werner's features people that look older than they are, and Werner's cells Hayflick-out at about 20-30 divisions instead of 50. Both feature increased "degenerative diseases" as in old folks,

> ["Anything you can turn your hand to, do with whatever power you have; for there will be no work, nor reason, nor knowledge, nor wisdom in the grave where you are going."
> -- Ecclesiastes 9:10]

Symbiont: The organism and its host have a mutually advantageous arrangement (mitochondria producing ATP, E. coli producing vitamin K, in exchange for room & board). Commensal: The organism does the host no good and no harm (worthless bugs in the gut, hepatitis B carrier). Parasite: The organism thrives by harming the host (i.e., the pathogenic micro-organisms). Saprophyte: The organism lives off dead stuff (i.e., fungi that thrive only in the hair, nails, or dead keratin layer of the skin). Infection: The parasite or saprophyte is making somebody sick. Infestation: A commensal, parasite, or saprophyte has been detected, other than what most people carry, whether or not somebody is sick. Superinfection: An infection which results because tissues are made vulnerable by another infection. Hyperinfection: Orders of magnitude more infectious agents than you "should" have, because of a fundamental change in your relationship with your parasite. (The prime example is strongyloidiasis, where the worm changes its life cycle in the immunosuppressed). Vector: A multicellular animal (usually an arthropod) which transmits an infectious micro-organism. Fomites: Inanimate objects which carry infectious organisms. Carrier: A clinically healthy person who is shedding an infectious organism, and can make others sick. Nosocomial infection: A hospital-acquired infection. Hospital pathogens are the

result of decades of selection for antibiotic-resistance and the ability to infect the very-sick.... Epidemic: An outbreak of infectious disease. Endemic: A never-ending epidemic. Pandemic: An epidemic involving the whole world. Zoonosis: A disease contracted from animals (ZOE-uh-NO-sis). Epizo”tic: An epidemic among animals (EP-uh-zoe-OTT-ick). You already know Koch's postulates. Today, the final "fifth postulate", which establishes the micro-organism as agent of the disease, is the demonstration of a virulence gene.

Viruses:

- Double-stranded DNA viruses
  - Adenovirus family
  - Hepadnavirus family
    - Hepatitis B
  - Herpes viruses
    - Cytomegalovirus
    - Epstein-Barr
    - Herpes simplex I
    - Herpes simplex II
    - Human herpes virus 6
    - Herpes zoster / chickenpox
  - Papovavirus family
    - Human papillomavirus
    - JC virus (PML, brain disease)
  - Poxvirus family
    - Molluscum contagiosum
    - Smallpox
    - Smallpox vaccine ("vaccinia")

- RNA viruses
  - Reovirus family
    - Rotavirus (sporadic viral gastroenteritis)
  - Coronavirus family
  - Orthomyxovirus family
    - Influenza group
  - Picornavirus family
    - Calcivirus subfamily
      - Hepatitis E
      - Winter vomiting disease virus
    - Enterovirus subfamily
      - Coxsackie virus
      - Echovirus
      - Poliovirus
      - Many others
    - Hepatitis A

- Hoof & mouth disease (animals, see above)
- Rhinovirus subfamily
- Paramyxovirus family
  - Hepatitis G (?)
  - Measles
  - Mumps
  - Parainfluenza
  - Respiratory syncytial virus
- Retrovirus family
  - HIV-1 & 2 and their kin
  - HTLV I & II
  - Animal tumor viruses (many)
- Togavirus family
  - Rubella
  - Hepatitis C (a flavivirus?)
- "Arboviruses" (toga-, flavi-, arena-, bunya-, reo-, filo-)
  - Arbovirus encephalitis viruses
  - Colorado tick fever
  - Dengue family
  - Regional hemorrhagic fevers
  - Yellow fever
  - Hantavirus ("Navajo pneumonia", others)
- Other
  - Norwalk agent (epidemic viral gastroenteritis)
  - Parvovirus
  - Rabies virus

Viral inclusions are aggregates of virus proteins, visible by light microscopy. These assist greatly with the histologic diagnosis of viral disease. Worth remembering:

- Intranuclear ("Cowdry A" and "Cowdry B"; don't worry about the distinction)
  - Adenovirus ("smudge cells")
  - Cytomegalovirus (one large, clearly-defined)
  - Herpes simplex I & II (1 large, clear, + multinucleate)
  - Herpes zoster (same as simplex)
  - Measles (in Warthin-Finkeldey cells, and SSPE)

- Intracytoplasmic
  - Cytomegalovirus (many small)
  - Rabies ("Negri bodies" in neurons)
  - Molluscum contagiosum ("molluscum bodies" in skin)
  - Smallpox ("Guarnieri bodies" in skin)
  - Chlamydia (not really viruses....)

The common cold: Rhinovirus, coronavirus; bad ones are adenovirus. Adenovirus produces the famous "smudge cells" in pneumonitis. "Viral" chest colds may be mycoplasma.

> ["Dost thou pray to thy god that thy
> nose may not run? Nay, foolish one!
> Thou blowest thy nose on the sleeve of
> thy toga!"
> -- Epictetus]

Influenza A: Pandemic influenza. Influenza B: Epidemics; children badly affected. Influenza C: Sporadic, upper respiratory infections. Influenza in the lungs tends to get superinfected with staph. Parainfluenza: Like influenza, causes "croup".

Coxsackie A: blisters on the back of the throat ("herpangina"), a misnomer, and/or hand-foot-and-mouth disease. Coxsackie B: pleuritis, myocarditis. Respiratory syncytial virus: Bronchiolitis in kids, fused epithelial cells; now known to be common in debilitated adults.

Mumps: Salivary glands inflamed in kids, sometimes pancreas; orchitis in grown men, if severe and bilateral, may sterilize but never demasculinize; the cause is edema and ischemia because of the tight capsule. Despite immunization, the virus is still around.

The GI 'flu: rotavirus (winter vomiting in kids), calicivirus (winter vomiting), Norwalk agent (vomiting and diarrhea anytime), adenoviruses, echoviruses; most sporadic "GI 'flu" is food poisoning.

HPV-2: The common wart. HPV 16 & 18: genital warts that tend to turn into cancer. ("Genital warts" used to be called "condyloma acuminatum").

Measles: Droplets. Incubation period 2 weeks. Koplik's spots are blister-ulcers next to Stetson's duct. Rash, photophobia, anergy. Dread complications include pneumonitis ("measles giant-cell pneumonia", Warthin-Finkeldey epithelial giant cells), and/or autoimmune brain damage. Slow-virus measles produces subacute sclerosing panencephalitis. Measles is a morbillivirus, the other one being the Australian horse-trainer-killer virus of 1995 fame.

Rubella: German measles, three-day measles. Arthritis, mild rash, and teratogenicity (high IgM in cord, blindness, deafness, heart defects, thrombocytopenia, big liver and spleen, skeletal deformities).

Smallpox: Do you think every rogue-nation has discarded its supply? I

doubt it, so someday we'll probably see it again. Droplet infection, blisters on the skin, damage throughout the body of course.

Parvovirus 19: erythema infectiosum / "fifth disease", is now known to be responsible for aplastic crisis in sicklers and spherocytosis folks.

Herpes 6: exanthem subitem / roseola, an AIDS opportunist which probably speeds progression; lives in B-cells. Herpes 8 (KSHV): The Kaposi's virus. Kaposi's "sarcoma" clearly is not, and never was, cancer. It's epidemic in Africa (HIV or no HIV), arises multifocally, usually shows no anaplasia, and gives a good therapeutic response to antiviral agents.

Herpes simplex 1: fever blisters, from getting kissed as a baby perhaps. Hides in the gasserian ganglion. Can be a major problem for folks with eczema; "Kaposi's varicelliform eruption" is herpes simplex pretending to be chickenpox in the immunosuppressed. Dendritic corneal ulcers. Esophageal herpes is painful in the immunosuppressed, and the presence of herpes is a risk for mouth, throat, and esophageal cancer (synergistic with alcohol and tobacco). Sudden necrosis of the temporal lobes ("herpes encephalitis") is a nightmare disease. Herpes simplex 2: genital herpes, needs no description; don't let a mother give vaginal birth while her lesions are active, or baby will get very sick. Herpes zoster: chickenpox and recurrent one-dermatome "shingles", the latter often with a pain syndrome. All blistering herpes diseases are intraepithelial necrosis. Spot any of these with a Tzanck smear, i.e., look for the herpes large epithelial cells with swollen nuclei and maybe a prominent single intranuclear inclusion.

Cytomegalovirus: Another herpes virus. Met in the second trimester of intrauterine life, this can produce a devastating infection (small for gestational age, jaundiced, hemolytic anemia, thrombocytopenia, "blueberry muffin" purpura, blind, deaf, retarded, and/or epileptic; brain necrosis with calcifications around the ventricles is common). Most intrauterine CMV produces none of this. Meet it in childhood, nothing happens. Most of us meet it when we start kissing on dates. CMV is a lung, gut, and/or retina opportunist in the very immunosuppressed.

Epstein-Barr virus: Herpes 4. The acute infection immortalizes B-cells and, in older folks, produces EBV infectious mononucleosis (blood is full of big T-cells, called "atypical lymphocytes" or "virocytes", pursuing the virus, which is hiding in B-cells). (Other mononucleosis syndromes result from meeting CMV, toxoplasmosis, and HIV). In EBV infectious mono, there's often cold agglutinins, mild thrombocytopenia, or a rash (if you take ampicillin); you're already familiar with the

fever, malaise, and big nodes and spleen. For the lab diagnosis of EBV, ask a microbiologist. Other EBV diseases: (1) Burkitt's lymphoma (EBV scrambles chromosomes and probably promotes); (2) multiple sclerosis (stay tuned); (3) Chinese nasopharyngeal cancer; (4) Eskimo salivary gland cancer; (4) other cancers in the immunosuppressed, including lymphomas and sarcomas.

Yellow fever: Apoptosis of hepatocytes, especially midzonally. Reservoir is monkeys, vector is Aedes mosquito.

Dengue: Epidemic right now in Mexico. Painful, self-limited mosquito-borne fever. DENGG-ee is the preferred pronunciation. Regional hemorrhagic fevers are carried by ticks, or by mouse droppings. They produce a platelet poison somehow. The worst is Lassa fever; the closest we have is Colorado tick fever.

Marburg virus: hemorrhagic fever in people exposed to monkey blood; explodes endothelium. Ebola virus, from Africa, is a severe, moderately contagious hemorrhagic fever. It got into the U.S. in 1990 among some monkeys, but didn't stay. Hantaviruses, the cause of Korean hemorrhagic fever and the agent now established as the cause of the outbreak of fatal disease in the U.S. southwest in 1993, were once popular candidates for biologic warfare agents.

Chronic fatigue syndrome is real and probably represents widespread immune overactivation from any of a number of viruses.

Chlamydia: Little incomplete bacteria adapted for intracellular life. Psittacosis ("parrot fever") is a chlamydia pneumonia. Trachoma is low-virulence chlamydia in the eye in poor nations, especially with vitamin A deficiency already there; we know it better in its even-more-benign form as inclusion body conjunctivitis, one of the reasons we chlorinate swimming pools. The same bug that produces swimming-pool conjunctivitis gives genital chlamydia, giving a man a drop, and a woman cervicitis/salpingitis, like gonorrhea but not quite so impressive. Lymphogranuloma venereum is caused by aggressive chlamydia, and is a festering, deep chlamydial infection of the perineum ("watering-can bottom", etc.) TWAR chlamydia cause pneumonia, especially in old folks.

Rickettsia: Little gram-negative bacteria that have adapted to live inside endothelium, which they damage as they grow; they also release noxious stuff into the bloodstream. Rocky mountain spotted fever (R. rickettsii): tick-borne (the big spits into you), most common in Appalachia (uh-huh), petechiae all over including the palms and soles. Ehrlichiosis: Rocky Mountain Spotless Fever. Typhus (R. prowazekii) is

louse-born (the creature defecates while dining), less often flying squirrel fleas; the bug hides between epidemics and re-emerges as sporadic Brill-Zinsser disease, which can infect another louse. Murine typhus (R. typhi) is rat-borne and mild. Scrub typhus (R. tsutsugamushi), is a scourge of the Asian tropics. Q-fever (Coxiella burnetti) is a pneumonia transmitted by ticks or sneezes, from humans or animals. Bartonella (Rochalimaea) quintana is a rickettsia-like creature that causes bacillary angiomatosis in AIDS and other immune-compromised folks. Rochalimaea (formerly "Afipia felis") causes cat-scratch fever.

Rash on the palms and soles: secondary syphilis, toxic shock, Rocky mountain spotted fever, Kawasaki, and don't ever forget meningococcemia.

Mycoplasma are more little incomplete bacteria. Mycoplasma pneumonia (M. pneumoniae) is a common winter chest cold; most of these folks respond to antibiotics and so forth. Other mycoplasma can cause urethritis. There are rumors of a mycoplasma as the cause of Desert Storm syndrome.

[Few "issues" are more one-sided than immunization; the fact that people don't understand "odds" and "risk-benefit" keeps Las Vegas in business. The extraordinary success and surprising safety of today's vaccines has not stopped people (pseudo-liberals, pseudo-conservatives) from making political capital by telling folks not to get immunized. The 1980's saw devastating epidemics of rubella, measles, and whooping-cough among the children of people who should have known better.]

Bacterial infections used to strike down people in their primes, and still provide the pathway out of life for the sick and disabled. Some bugs are very virulent (i.e., pneumonic plague), but most require some weak spot for entry. If the weak spot is some already-existing disease, the bacteria can produce a superinfection. The surface of a foreign body is a great place for bacteria to grow, since neutrophils cannot gobble them up.

Exactly how bacteria make us sick is still largely mysterious. The ideas about depriving normally-perfused tissue of its buffers and nutrients is ludicrous. Exotoxins (soluble molecules made by living bugs) are rare; notable are the products of certain clostridia (botulism, tetanus, perfringens) and other food-poisoners. Broken-down walls may contain endotoxin. Phagocytes chasing bacteria will predictably harm the body, at least to some extent.

Bacteremia: Bacteria in the blood, as after tooth-brushing. Sepsis /

septicemia / septic shock is currently getting sorted out and the nomenclature standardized, but it means the bacteria have a foothold in your bloodstream; your grandma called it "blood poisoning".

Staphylococci include the vicious "coagulase positive" / "aureas"=gold strain, famous cause of hair-infections (big ones are "furuncles", bigger ones are "carbuncles"); growing on magnesium-rich tampons, some produced toxic-shock syndromes, and there are related skin-toxin syndromes ("scalded skin"; epidermolytic toxin) too. Impetigo is staph-strep infection of the upper-epidermis-only. Virulence factors are coagulase, hemolysin, protein A (binds Fc of Ig), catalase (neutralizes H2O2); food poisoning is from enterotoxin B (the warm-milkshake and donut-creme-filling bug). Gold-staph's gimmick is coagulase, which makes a fibrin cocoon to protect it from phagocytes, hence the localized infections. Methicillin-resistant staph, a fad problem, is best controlled by handwashing. White staph ("epidermidis", coagulase-negative) are likely to infect heart valve prostheses.

Strep A: Strep pyogenes, strep throat, rheumatic fever, skin infections (impetigo), soft tissue infections (cellulitis, phlegmon, erysipelas, lymphangitis streaks), post-streptococcal glomerulonephritis. Virulence factors include the capsular polysaccharides, the M-proteins, streptokinase, streptodornase (DNA wrecker), and streptolysin A. Strep's gimmick is to dissolve ground substance and spread faster than the polys can chase it. Strep throat needs no description; quinsy is peritonsillar abscess, Ludwig's angina is cellulitis of the floor of the mouth which can compromise the lower airway. Scarlet fever follows strep throat when the bug contains the phage to produce erythrogenic toxin. Puerperal sepsis: childbed fever, uterine infection post-partum, was iatrogenic until handwashing was introduced. The flesh-eater produces necrotizing soft-tissue infections and/or pneumonia; its virulence factors are pyrogenic exotoxin A (activates huge numbers of T-cells, which is unwholesome), and pyrogenic exotoxin B (cysteine protease that actually dissolves tissue).

Strep B: New baby infections. Strep D: Enterococcus, now a drug-resistance champion; others. Untyped: Green viridans strep which grow on already-damaged heart valves; pneumococci; the latter are the familiar encapsulated gram-positive diplococci so familiar from lobar pneumonia; pneumococcal sepsis is a problem for those lacking a spleen (surgery, sicklers), and pneumococci thrive in the ascites fluid of cirrhotics and nephrotics.

Neisseria, the familiar gram-negative bean-shaped diplococci, include the meningococcus, a nasal bug that from time to time mutates and

produces epidemics of meningitis and/or sepsis-DIC. Waterhouse-Friderichsen syndrome is adrenal-cortex hemorrhage and necrosis in meningococcemia or other sepsis. The gonococcus produces the familiar urethritis, cervicitis, salpingitis, pharyngitis, proctitis, and conjunctivitis problems; around the liver capsule, it's "Fitz-Hugh-Curtis". Branhamella is similar to neisseria, and causes pneumonia in older folks.

Escherichia coli is the most familiar of the enterics, most famous for producing bladder infections when, for any reason, urine flow is stagnant. Enteropathic E. coli actually sits and does a kind of dance on the surface of an enterocyte, causing it to secrete fluid ("Montezuma's revenge"); there are other strains that actually produce a toxin which works like cholera toxin (toxigenic E. coli, more "Montezuma's revenge"). Enteroinvasive E. coli flourish in America's southwest, and invade like shigella, producing a bloody diarrhea (dysentery) rich in neutrophils. Klebsiella pneumoniae ("Friedlander's", relationship to your lecturer unknown) is a gooey-encapsulated bug that causes its victims (usually drinkers) to cough up red slime. Proteus gets its energy from splitting urea into ammonia and carbon dioxide, hence its ability to lay down magnesium ammonium phosphate crystals in kidney and bladder. Pseudomonas is the bane of the burn unit, the cystic fibrosis unit, and anywhere in which antibiotics get used a lot, since it's resistant; the bug smells like grapes. "Ecthyma gangrenosum" is severe pseudomonas tissue infection.

Legionella are gram-negative rods that produce a vicious pneumonia ("Legionnaire's disease") in smoker-drinkers and the unlucky; use the Deiterle silver stain; Pontiac fever is the mild form.

Anaerobic infections are usually mixed, and the bugs are generally not super-strict anaerobes, but the more familiar bacteroides, fusobacteria, peptostreptococci, and so forth. They evoke lots of pus, and worse smells.

Hemophilus influenza affects younger children, especially those under 5 who do not make the antibody well and tend to get meningitis. Older kids get pink eye, croup (epiglottitis); the mean version is type "B". Hemophilus ducreyi causes chancroid, a sexually-transmitted disease that mostly affects the unwashed. Bordetella pertussis causes whooping cough by binding to the epithelium of the large airways; it is still around.

Diphtheria is caused by a gram-positive corynebacterium rod with a toxin-producing phage. The toxin produces surface necrosis and pseudomembrane formation, then ties up carnitine, causing the heart to

fail.

Salmonella typhi produces typhoid, which grows first in the Peyers' patches and then spread. Bugs will grow from the blood, but seldom from stool, and patients tend to be constipated. Rose spots, erythrophagocytosis, spiking fevers; monocyte-macrophage response rather than neutrophils. Carriers have gallstones. Other salmonella cause mild food poisoning (vomiting, diarrhea), or osteomyelitis/arthritis in sickle cell patients. Stomach acid protects you from salmonella, which are ubiquitous (they teem over uncooked chicken; they caused the ban in pet turtles).

Shigella produces dysentery, and only a few ingested bugs is enough to make you very sick. Cholera needs no description, and the action of its toxin via cyclic AMP is well-known. Helicobacter thrives on cleaving urea in the acid milieu of the upper gut, and causing ulcers and gastritis; the link to gastric cancer is more tenuous. Yersinia enterocolitica causes mesenteric adenitis or dysentery. Bacillus cereus is the fried-rice food-poisoning bug. Staph and clostridial food poisoning require ingestion of pre-formed toxin.

Tetanus is the result of tetanus clostridia germinating in the anaerobic milieu of a deep, devitalized wound, especially with foreign crud (rust from a nail is great). The toxin binds to the inhibitory internuncials of the cord. Lockjaw, opisthotonos. Botulism requires the ingestion of pre-formed toxin, usually from poorly-canned food, and this is extremely powerful; this time, the result is paralysis, first of the eyes. Gas gangrene is caused by aggressive clostridia that dissolve tissue faster than the body can respond; lecithinase (alpha-toxin) hemolyzes. Pseudomembranous enterocolitis results from antibiotic administration which allows overgrowth of the relatively resistant "C. difficile".

The zoonoses: Anthrax is a gram-positive zoonosis from sheep; its produces dry necrosis ("eschar", "black spot") where it enters; inhaled spores produce the lethal "woolsorter's disease". Listeriosis is a zoonosis among the immunosuppressed. Erysipeloid (Erysipelothrix rhusipathiae) is fish-handler's disease, a soft-tissue infection. Plague results from Yersinia pestis, carried by fleas from the dead rats; the "buboes" are suppurating lymph nodes, and later the disease may mutate into an aggressive form transmissible by coughing. Tularemia is why you're not advised to catch the slow bunnies. Brucellosis is a major cause of chronic ill-health, a smoldering infection among slaughterhouse workers and farmers. Glanders (Pseudomonas mallei) affects donkeys and horses in the poor nations; melioidosis (Pseudomonas pseudomallei) infests southeast Asia and can

linger in Vietnam vets ("the bacterial time bomb"); it produces hard-to-treat infections. Leptospirosis produces hemolysis and/or jaundice ("Weil's disease"), or just a mild meningitis. Relapsing fever (Borrelia recurritens) mutates every week or so to produce a new episode.

Actinomyces are filamentous bacteria ("ray fungi", a misnomer) that grow in dense masses ("sulfur granules"), rendering them impervious to phagocytosis. These infections begin on rotten teeth ("lumpy jaw") or intrauterine contraceptive devices. The Whipple bacillus has not been grown yet, but seems to be a relative. Nocardia is a weakly acid-fast filamentous rod that causes jungle-foot infections and opportunistic pneumonia, both hard to treat.

Syphilis: Treponema pallidum, "the American Indians' other revenge" against Columbus, whose men were the first European victims. In spite of what you've been told, the actual derivation of the name is unrepeatable here. Primary syphilis is the familiar painless, firm, ulcer (chancre) at the site of inoculation. Secondary syphilis is a variable rash, weeks or months later; condyloma latum is the oozy form seen in moist places. Both stages teem with spirochetes. The histopathology of each stage is a vasculitis with lots of plasma cells. Tertiary syphilis: (1) narrowed vasa vasora weaken the aorta, which balloons where the pressure is highest, i.e., its ascending portion; stretch-marks produce "tree-barking", and eventually the aneurysm bursts; (2) gummas are granulomas of syphilis; under the periosteum, they account for chronic severe pain, while necrosis caused the familiar saddle-nose; (3) general paresis kills cells in the cerebral ("windswept") cortex and makes victims crazy; (4) meningovascular syphilis is an awful headache; (5) tabes dorsalis merely looks like demyelinated posterior columns, but can hurt bad; eventually there's loss of proprioception.

Congenital syphilis: Acquired during the second trimester; (1) "saber shins" and other bony deformities; (2) "mulberry molars", "Hutchinson's teeth", "screwdriver incisors", i.e., dental deformities; (3) gummas destroying the bridge of the nose and/or the hard palate; (4) pulmonary consolidation ("pneumonia alba", white pneumonia); (5) "hepar lobatum", enlargement and severe distortion of liver architecture due to gummas, and related splenomegaly; (6) rash resembling bad secondary syphilis, often with sloughing of skin on palms and soles; (7) mental retardation, nerve deafness, blindness, etc., etc.; (8) necrotizing inflammation of the umbilical cord ("necrotizing funisitis"); (9) and/or any other sign of secondary or tertiary syphilis. These babies teem with spirochetes at birth.

Other spirochetes: "Trench mouth" (necrotizing gingivitis) is synergy among mouth organisms; the most severe cases cause necrosis of the face (noma). Yaws, bajel, and pinta are other spirochete diseases in the syphilis family.

Lyme disease is caught from ixodes ticks that drank from infected deer mice. Primary Lyme disease, which may not even be visible, occurs around tick bite as the spirochetes spread outward in circles ("erythema chronicum migrans"). The subsequent immune havoc (and maybe other problems) produce "arthritis", cranial nerve palsies (Lyme "flagellin" mimics an axon protein); non-suppurative meningitis; demyelinating disease, and goodness-knows-what-else. "When in doubt, treat for Lyme disease".

Granuloma inguinale: Calymmatobacterium donovani, a nasty mix of pus and granulomas on the genitals.

Tuberculosis is enjoying a resurgence. The acid-fast mycobacterium enters the lungs, where it gets notice by T-cells, induces a powerful over-reaction by the body, with eventual caseous necrosis. The bug wants this, since it is transmitted by riding coughed-up bits of the powder. Initial exposure to the bug results in the infectious site being walled off in a calcified granuloma (a "Ghon focus"; if some bugs have made it to the lymph nodes, "Ghon complex"). The midlung is the favorite site for a Ghon focus. TB may go on to wipe out your lungs; contrary to what you've read, primary progressive tuberculosis (the bugs were never walled-off successfully) is probably more common than secondary-reactivation tuberculosis. (I never knew why we taught the other....) Risk factors include poverty, alcoholism, crowding, immunosuppression (especially AIDS), silicosis, and glucocorticoid administration. Miliary TB spreads like millet-seed (as millions, or at least thousands, of little granulomas) through the oxygen-rich areas of the body, and TB in the lung prefers the oxygen-rich apices, where necrosis leads to cavity formation (the insides are coughed up). Meningeal TB favors the high-oxygen areas around the circle of Willis. Pott's disease is vertebral TB. Bovine TB abounds in cow's milk, especially in the poor nations; it enters the body via the duodenal lymphoid tissue.

Other mycobacteria include "intracellulare" and "avium", opportunists which you must hope you do not catch; the scrofula bug (neck nodes), and the leprosy bacillus. Immune-competent (paucibacillary, tuberculoid) leprosy features neuropathy, granulomas, depigmentation, and a positive lepromin test. Immune-poor (multibacullary, lepromatous) leprosy features the leonine facies, globi (macrophages packed with bacilli), and hideous mutilation.

Candida: Ubiquitous fungus, with pseudohyphae. Look like balloon animals in smears and tissue. Most familiar as "thrush" in the mouth and esophagus, or "yeast infections" in the vagina or groin (spot the latter by its satellite lesions). The fungus thrives on parenteral nutrition catheters (good stuff to eat) and anywhere in a diabetic (lots of glucose); it's an early opportunist in anybody losing T-cell function. "The Yeast Connection"; imaginary candidiasis was a fad diagnosis some years back.

Mucormycosis: bread mold spores germinating in the body at low pH, i.e., in ketoacidosis, or wherever there's a major break in defenses. The favorite site is the deep faces, around the nasal sinuses. Once they're germinated, you're in trouble. They invade vessels infarct tissues. Wide-angle branching, no septa.

Aspergillosis: the familiar fruiting-body fungus. Likes to invade vessels, and make its home in cavities in the lung ("fungus balls"); or it can colonize the airway surfaces, or produce type I, type III, and/or type IV injury. Narrow-angle branching, septa.

Cryptococcus: Pigeon-dropping bug, an encapsulated yeast that grows in the lungs and/or spinal fluid of the immune-compromised. India-ink test; single narrow-based bud. Fatal cases of meningeal cryptococcus involve invasion of the Virchow-Robin spaces producing swiss-cheese brain.

Blastomycosis: Midwest riverbank fungus. Yeast with a single broad-based bud. Skin and/or lung infections, a mix of granulomas and pus, hard to treat.

South-American blastomycosis (paracoccidioidomycosis): Amazon jungle fungus, a devastating mouth or generalized disease. Yeast with multiple buds ("mariner's wheel").

There's a popular tale that both variants of "blastomycosis", even on the skin or in the mouth, always got there by way of the lungs; after having investigated this claim, I found no reason to think it's true.

Coccidioidomycosis: San Joaquin valley fever, a large spherical yeast full of endospores. Inhaling the spores may produce anything from a mild chest-cold to a fatal systemic infection.

Histoplasmosis: A tiny (two micron) yeast, ubiquitous in the Midwest, especially starling and bat guano. The pathology matches that of TB.

Sporotrichosis: Rose thorn or bayberry thorn prick; follows the lymphatics up the arm.

The protozoans:

- Luminal protozoa
  - Amebiasis
  - Amebic meningoencephalitis
  - Balantidium infestation
  - Cryptosporidiosis
  - Isosporidiosis
  - Sarcocystosis
  - Giardiasis
  - Trichomoniasis
  - Pneumocystosis
- Blood and tissue protozoa
  - Malaria
  - Babesiasis
  - African trypanosomiasis
- Intracellular protozoa
  - Chagas's disease
  - Leishmaniasis
  - Toxoplasmosis

Amebiasis: Entamoeba histolytica produces flask-shaped ulcers (the bottoms lie along the muscularis mucosae; the bug uses perforins to wreck havoc), where it engulfs and digests red cells (marker for virulence). The bugs look like round Remington shavers. Bad cases spread to the liver ("anchovy paste" abscesses, a misnomer since there are few or no polys). Fecal-oral; ubiquitous in the poor nations, and was (in the 1970's) very common among non-monogamous gay guys.

Acanthamoeba is the contact-lens amoeba, while Naegleria is the reason not to swim in stagnant farm ponds (meningitis and worse).

Giardia: A sulfide-producing luminal parasite famous for producing malabsorption, upset tummy, and mercaptans ("phew!" "purple burps"). Drink from a nice mountain stream in Colorado, and you'll probably get giardiasis; it's easy to catch from the drinking water where the politics is especially bad, most famously in Leningrad.

Cryptosporidiosis ("Milwaukee diarrhea"): a protozoan that lives in the brush-border. Once considered a "non-pathogen", then a "zoonosis", then "only causes disease in the immune-compromised", we now know that cryptosporidiosis is one of the most common causes of diarrhea worldwide, as the city of Milwaukee found out recently when its water

supply was contaminated. The bugs are acid-fast and easy enough to spot in the stool.

Trichomonas: A sexually-transmitted disease which typically hides out in his prostate (slight or no discomfort) and creates a frothy, malodorous "strawberry vaginitis" in her. On wet mounts (which you'll do), these loathsome creatures look like pears doing the hoochie-koochie dance.

Pneumocystis: Once known as the cause of "plasma cell pneumonia" in preemies, this is now familiar as a lung infestation (lower lobes, "ground glass opacities") in the T-cell deficient (AIDS, chemotherapy patients). The organisms pack exudate-filled alveoli, typically (in immunosuppression) with no sign of an inflammatory response, creating a foamy-like appearance.

Malaria: An extremely severe health problem worldwide. "Falciparum" is worst, probably because of the type III immune injury superimposed on the episodes of hemolysis. Worth remembering about malaria: (1) large spleen; (2) hemoglobin can shut down kidneys (blackwater fever).

Toxoplasmosis: From eating undercooked beef, or from emptying kitty-litter that's sat too long; the protozoan can only complete its life cycle if you're devoured by a cat, lion, tiger, leopard, saber-tooth, etc. Mild or no disease if you're healthy; brain damage (maybe) if you're a second-trimester fetus; retinitis if you're unlucky; massive necrosis of the brain if you have AIDS or are otherwise T-cell compromised.

Babesiosis: "Nantucket fever", with tiny malaria-like parasites in the red cells. Mostly a problem if you lack your spleen.

African trypanosomiasis: Tsetse flies carry these dread organisms; population pressures have forced people back into these once-shunned territories. No one knows how they effect their neurotoxicity, but "sleeping sickness" is a grisly disease.

American trypanosomiasis: Chagas' disease, acquired from the disgusting reduvid bug ("kissing bug") in the Latin American mountains. Paralysis of the esophagus (dysphagia, cancer risk), less often the colon; dilated cardiomyopathy.

Leishmaniasis: "Baghdad boil", "Kala-azar", etc., etc. Acquired from phlebotomus sandflies; these protozoans are about 2 microns across and live inside phagocytes.

Ascariasis: Fecal-oral transmission. A large worm burden can kill you by obstructing or perforating the bowel.

Whipworm (trichuris): Fecal-oral. Harmless unless the infestation is massive.

Pinworm (enterobius): This charming parasite lays her eggs on the anoderm, hoping you'll scratch and then put your fingers in somebody else's mouth or food. Judging by the success of the creature, this happens a lot. Scotch-tape test.

Hookworm (necator, ancylostoma): Acquired from walking barefoot on larva-infested soil, the worms pass through the lungs, get swallowed, settle in the duodenum, and tear at the mucosa with their fangs in order to get blood to drink. Each hookworm costs you a teaspoon of blood each day, and iron deficiency soon supervenes.

Strongyloides: Appalachia and elsewhere. Acquired from the soil, like hookworm; in the immune-compromised, these worms can carry out their life cycle without needing to leave your body ("hyperinfection", bad news).

Dracunculosis: Guinea worm, acquired from wading in water bearing infected cyclopses (little marine critters). The worm encysts under the skin, then erupts when mature; the cure is still to wrap the critter, day by day, around a stick (origin of the caduceus, most likely; one snake is medicine, two snakes is commerce, diplomacy, and thievery.)

Trichinosis: Undercooked pork. Worms coil and encyst in busy muscle, preferring those of the eye and the diaphragm. Eosinophilia, sick as heck, but usually self-limited.

Filariasis: Mosquito-borne worms plug lymphatics.

Onchocerciasis ("river blindness"): Worms spread by river-flies invade the eyes. A grim West African disease.

Cysticercosis: Stray larvae of a pork tapeworm find their way to the brain. The most common cause of seizures in many poor nations.

Echinococcus: A tapeworm that cycles between canines and herbivores (wolves and caribou, sheepdogs and sheep, others) finds its way to a human, typically via dog feces (a doggie puts its nose in another doggie's behind, then licks your mouth). "Hydatid cysts" are full of dozens of little worms, like masses of grapes, they can be several

centimeters across. Don't bust the cyst, anaphylaxis can result. Call a surgeon with special tools.

Schistosomes: Blood flukes with a life cycle between humans and snails. Ma and Pa schistosome live and love in the veins of the abdomen and/or pelvis, laying their eggs and letting the razor-sharp spines cut their way through the vital organs to the lumens of bowel and bladder.

Mansoni	Big lateral spine
Hematobium	Big terminal spine
Japonicum	Small lateral spine

Other flukes worth remembering include the Chinese liver fluke, memorable as a cause of biliary tree cancer, and paragonimiasis, a lung fluke which causes tremendous suffering in Asia.

"Test all things; hold fast to what is good."
-- Paul (I Th 5:12)

Blood gases:

In caring for sick patients in whom you suspect cardiac or pulmonary disease, you will frequently order blood gas determination. Arterial blood is collected in a special syringe and sent to the laboratory on ice for immediate analysis. Within a few minutes, you know the patient's arterial pH, pO2, and pCO2, and from these the lab calculates the arterial HCO3-, hemoglobin % saturation, and base excess. (Instruments that determine "electrolytes" on venous blood report the "total CO2". Because the pKa of H2CO3 is 6.1, "total CO2" closely approximates the venous or arterial HCO3- at any pH compatible with life. However, when you send arterial blood for arterial blood gases, you get the actual arterial HCO3-, calculated using the Henderson-Hasselbalch equation.)

Interpreting these numbers is tricky and depends on an understanding of basic physiology. Normals:

Arterial pH = 7.35-7.45
Arterial pO2 = 80-110 mm Hg
Arterial pCO2 = 32-48 mm Hg
Arterial calculated HCO3- = 18-23 mEq/L
Venous total CO2 = 22-26 mEq/L

Carbon dioxide: Most of the "carbon dioxide" in the blood is tied up as HCO3-, which is in equilibrium with H2CO3 and CO2 in the blood. No matter how sick a person gets, the alveolar walls remain permeable

to carbon dioxide. Therefore, the entire "bicarbonate buffer system" is in equilibrium with the alveolar carbon dioxide content. Alveolar carbon dioxide content in turn depends on adequacy of pulmonary ventilation. ("How effectively is the lung getting rid of CO2 that isn't required for buffering the blood?")

If pulmonary ventilation is decreased (decreased respiratory drive from drugs or in CNS disease or COPD, muscle weakness, restrictive lung disease, obstructed airways, or fluid in alveoli), there will be increased alveolar carbon dioxide content and thus increased arterial pCO2. Respiratory acidosis results. (Another cause of increased alveolar carbon dioxide content is increased carbon dioxide content of inspired air, i.e., rebreathing air using a paper bag. Respiratory compensation of metabolic alkalosis will also decrease pulmonary ventilation.)

If pulmonary ventilation is increased (anxiety, hypoxia, fever), there will be decreased alveolar carbon dioxide content and thus decreased arterial pCO2. Respiratory alkalosis results. (Respiratory compensation of metabolic acidosis will also increase pulmonary ventilation.)

In pH disturbances of respiratory origin, arterial HCO3- (as calculated in the blood gas report) and venous HCO3- (as approximated by the "total CO2" measured in the electrolyte panel) will be altered in the same direction as arterial pCO2, especially if metabolic (renal) compensation has occurred. The magnitude of this change, however, is never very great. Venous total CO2 less than 19 mEq/L generally indicates metabolic acidosis, and venous total CO2 greater than 30 generally indicates metabolic alkalosis.

As you know, venous pCO2 is only about 6 mm Hg higher than arterial pCO2, and a right-to-left shunt through the lung will produce a negligible increase in arterial pCO2.

Oxygen: Because of the shape of the hemoglobin-oxygen dissociation curve, normal hemoglobin is almost fully saturated when pO2 is above 80 mm Hg. (Remember arterial pO2 is the measure of the small amount of oxygen in solution in the plasma, not the oxygen bound to hemoglobin. Increasing arterial pO2 above the range 80-100 is not going to significantly improve overall oxygenation of the blood. Conversely, a drop in pO2 below 60 mm Hg is bad.)

Unlike carbon dioxide, arterial pO2 depends on several factors. ("Are the alveoli being ventilated adequately and evenly, is all the right-sided cardiac output getting to the alveoli, and can oxygen

diffuse through the alveolar-capillary membrane?") Decreased ventilation of alveoli results in decreased alveolar oxygen content. There may be decreased ventilation of all alveoli (drugs, CNS or muscle disease, restrictive lung disease, asthma, ARDS, pulmonary edema), or uneven ventilation (atelectasis, pneumonia, COPD, airways obstructed by secretions or tumor).

Because venous pO2 is only a fraction of arterial pO2 (especially in sickness, where tissue oxygen requirements may be increased and cardiac output may be low), shunting of venous blood through poorly-ventilated alveoli will result in a great decrease in arterial pO2. (Perfusion without ventilation also results from right-to-left intracardiac or intrapulmonary shunts.) Remember that, in health, increasing alveolar ventilation does not greatly increase alveolar oxygen content. (Because inspired air is about 20% oxygen, alveolar oxygen content is increased about 1 mm Hg for every 5 mm Hg that alveolar carbon dioxide content is decreased. To increase alveolar oxygen content, have the patient breathe supplemental oxygen.) Even fairly mild thickening of the alveolar walls (pulmonary edema, ARDS, interstitial fibrosis, lymphangitic carcinomatosis) renders them relatively impermeable to oxygen ("diffusion barrier").

Dead space is the volume of ventilation that does not exchange with the blood. It includes anatomic dead space (large airways) and functional dead space (due to ventilation-perfusion mismatching, some of which is inevitable due to gravity.) Increased dead space is usually due to pulmonary embolus or decreased right-sided cardiac output (shock, pulmonary hypertension.)

* The clinical dead-space equation:

$$\frac{\text{Dead space ventilation}}{\text{Total ventilation}} = \frac{\text{pCO2 (arterial)} - \text{pCO2 (expired air)}}{\text{pCO2 (arterial)}}$$

Shunt fraction is the fraction of cardiac output that does not exchange with alveolar gas. Because there is uneven distribution of ventilation in almost all lung disease, there is always an increase in shunt fraction. Formulas to calculate the shunt fraction exist.

Base excess is a measure of the metabolic (i.e., nonrespiratory) component of a pH disturbance. A positive base excess indicates the degree of metabolic alkalosis. A negative base excess indicates the degree of metabolic acidosis. Base excess is calculated from the blood gases by a complicated formula (i.e., using a nomogram or calculator.)

Electrolytes :The principal extracellular cation is sodium; the principal extracellular anions are bicarbonate, chloride, and proteins. The principal intracellular cation is potassium; the principal intracellular anions are phosphates and proteins. Most of the body's calcium is extracellular; most of the body's magnesium is intracellular.

Of course, all the above are electrolytes. But when you "order electrolytes on a patient", you are asking for serum concentrations of of sodium, potassium, chloride, and bicarbonate ("total CO2"). Remember that electrolytes are generally measured as milliequivalents per liter (meq/L). Remember also that an "equivalent" is a mole of charge. Thus, a milliequivalent of univalent ions (sodium, potassium, chloride, bicarbonate) is a millimole of these ions. And a millie-quivalent of divalent ions (calcium, magnesium) is half a millimole of these ions. And since, around physiologic pH, phosphate anion is a mixture of H2PO4-1 and HPO4-2, it is very inconvenient to talk about milliequivalents of phosphate anion. That value would even be different at different pH values. As a result, only the univalent ions are generally reported in meq/L.

Very generally, here is what an "electrolyte panel" tells you:

> Sodium tells you if the patient is dehydrated or overhydrated.
>
> Potassium tells you the patient's serum potassium status. (This must be kept as close to normal as possible.)
>
> Bicarbonate tells you if the patient has metabolic acidosis or alkalosis.
>
> Chloride is provided so that you can calculate whether the patient has an abnormally high anion gap.

Indications for ordering serum electrolytes are very broad. All fluid therapy on seriously ill patients is guided by monitoring serum electrolytes. (You will learn a great deal about this during your rotations.) Patients on digitalis and/or diuretics, with renal failure, or with extensive tissue injury especially need to have their potassium levels watched. Patients who are post-surgical, febrile, dehydrated, unconscious, having seizures, and many others all need to have "electrolytes" checked.

NORMAL RANGES

Sodium = 136-145 meq/L
Potassium = 3.5-5.0 meq/L
Chloride = 96-106 meq/L
Bicarbonate = 24-30 meq/L ("total carbon dioxide content")
Anion gap = 8-16 meq/L

Before we look more closely at sodium and potassium, here is a formula for the bedside calculation of serum osmolality.

$$\text{Serum osmolality} = (2 \times \text{sodium}) + \frac{\text{glucose}}{20} + \frac{\text{urea nitrogen}}{3}$$

(Variations on this formula exist; this version is fine.)

Serum osmolality is one of the most tightly regulated physiologic parameters. Normal range is 275-295, lower in babies. The lab can measure it directly by freezing point depression, though the above formula is good so long as the serum is not loaded with ethanol, mannitol, ketoacids, etc. Serum osmolality is a better measure of water depletion or water overload than serum sodium. See below.

Increased serum sodium is, for practical purposes, due only to dehydration. (A possible exception would be a psychotic or child abuse victim with table salt intoxication.) Inability to replace water loss due to burns, sweating, drainage; inability to replace respiratory, urinary, and fecal losses (babies, the severely disabled.) Diabetes insipidus (posterior pituitary disease, renal collecting tubule disease). Osmotic diuresis due to hyperglycemia (leading to hyperosmolar nonketotic diabetic coma), ketoacidosis, mannitol administration, some patients with "the diuretic phase" of renal failure. Rarely, hyperaldosteronism can cause actual hypernatremia. Usually there is a corresponding increase in plasma volume, however.

Decreased serum sodium: This is a very common problem in clinical medicine. The danger is that decreased serum osmolality will result in cerebral edema. Respiratory arrest and/or brain damage can and do occur. Before you decide to treat a low serum sodium, be sure it is not just the result of dilution by some other osmotically active substance. Check the urea ("BUN") and glucose (these values come with many "electrolyte profiles") and calculate the approximate osmolality using the formula. Remember ethanol, M-proteins, mannitol, and triglycerides (the last is important if the level is above 2000 mg/dL, normal is a tenth that) can also depress the sodium level while osmolality remains normal. If in doubt, have the lab check the serum osmolality.

"Genuine" low sodium (synonymous, in practice, with low serum osmolality) will be found to be due to renal sodium wasting, extra-renal sodium wasting, water overload, inappropriate hADH, or cachexia. In most cases, it is helpful to check the urine sodium to decide which mechanism is operating. Remember that, in health, urinary sodium output corresponds to dietary intake.

Renal sodium wasting: diuretic therapy (and diuretic abuse, currently popular), Addison's disease, some renal interstitial disease. Urine sodium is usually above 20 meq/L in these disorders.

Extra-renal sodium wasting: losses because of vomiting, diarrhea, suction, surgical drains, burns, or heavy sweating. In each case, hyponatremia develops when water replacement occurs! Urine sodium is usually below 10 meq/L in these disorders.

Water overload is seen in psychogenic water drinking, overzealous IV therapy with "D5/W" or the like, and in generalized edema and ascites (congestive heart failure, cirrhosis, nephrotic syndrome.) In generalized edema, the effective circulating blood volume is low. The kidneys are unable to dispose of all the water the patient drinks. There may also be increased hADH, or the patient may have been receiving a sodium-wasting diuretic. These factors override the effects of secondary aldosteronism, and result in a low serum sodium. Urine sodium is usually below 10 meq/L in these disorders.

Syndrome of inappropriate hADH: a special cause of water overload. It may be due to oat cell carcinoma of the lung, CNS disease, chlorpropamide, bad TB, porphyria, or other causes. Urine sodium is usually above 20 meq/L in "SIADH." Criteria exist for the diagnosis of this problem; unfortunately, hADH assays are not readily available. Essential features are:

-- low serum sodium, with urine more concentrated than serum

-- adequate hydration (though these patients are not edematous)

-- failure of serum sodium to respond as expected to administration of sodium chloride

-- return of serum sodium to more normal values upon restriction of water intake (making the "inappropriate" hADH level "appropriate.")

Cachexia results in serum sodium levels that are often somewhat

low and which cannot be corrected by fluid restriction or sodium chloride administration. Probably this results from the loss of intracellular protein anions, so that intracellular osmolality (which must equal extracellular osmolality) becomes low. This is also called the "reset osmostat syndrome" or the "tired cell syndrome."

BEWARE: Correct lower serum sodium slowly, or risk central pontine myelinolysis!

Increased serum potassium (1) Renal failure is by far the commonest cause of increased serum potassium; (2) iatrogenic over-administration of potassium supplements; (3) dehydration (potassium follows water out of cells); (4) lack of mineralocorticoid (Addison's disease, spironolactone, inadequate renin response); (5) massive hemolysis, GI bleeding, or tissue necrosis (rare, seen most often in chemotherapy of certain white cell neoplasms); (6) Artifact: Unfortunately very common! tourniquet and fist-pumping (up to 2.0 meq/L); specimen hemolysis (serum will be pink when potassium is 0.1 meq/L too high; lysis of 1% of red cells raises potassium 1.0 meq/L); thrombocytosis (over 500,000 platelets/cu mm releases more potassium than the normal value takes into account); refrigeration (enzymes that keep potassium inside red cells are inhibited in the cold); marked leukocytosis (leukemia with WBC over 100,000)

Decreased serum potassium: (1) Diuretics (thiazide, furosemide, etc.); (2) Aldosteronism (Conn's syndrome, cirrhosis); (3) Diarrhea (especially with longstanding, as in chronic laxative abuse or villous adenoma of the colon); (4) Iatrogenic (forgetting to administer supplemental potassium when needed, especially when treating diabetic ketoacidosis as potassium follows glucose into the cells); (5) metabolic alkalosis both causes and result from hypokalemia, as sodium is exchanged for both protons and potassium in the kidney and elsewhere. There are other, rare causes.

Metabolic acidosis: (1) Loss of fixed base, or (2) presence of a non-volatile acid.

Loss of fixed base: renal tubular acidosis (inability of the proximal tubule to reabsorb bicarbonate normally), drainage of pancreatic fluid (rich in bicarbonate), diarrhea (rich in bicarbonate), Addison's disease (failure to reabsorb sodium in the distal tubule, thus retaining protons instead). Each of these will result in hyperchloremic acidosis. (Why?)

Learn the types of renal tubular acidosis:

RTA type 1 ("Distal"): distal tubule has trouble excreting protons, or protons leak back in the collecting ducts. There is secondary hypercalciuria, with rickets, osteomalacia, kidney stones.

RTA type 2 ("Proximal"): proximal tubule has trouble reabsorbing bicarbonate;

RTA type 3: combination of 1 & 2, very rare

RTA type 4: the kidney fails to produce renin (and therefore aldosterone) when it is required. This is very common in patients with renal microvascular disease (diabetes, hypertension). The acidosis is worst in hyperkalemia, since potassium suppresses the production of ammonia.

Abnormal presence of a nonvolatile acid: lactic acidosis, diabetic ketoacidosis (acetoacetic acid, beta-hydroxybutyric acid), uremia (sulfuric acid, phosphoric acid, others), aspirin poisoning (salicylic acid), ethylene glycol poisoning (oxalic acid), methanol poisoning (formic acid.) Each of these will result in an increased anion gap.

The anion gap, as usually defined, is sodium minus chloride minus bicarbonate. The normal value is 8-16 meq/L. (Why?) Always calculate the anion gap when you encounter metabolic acidosis!

Metabolic alkalosis: (1) Loss of fixed acid: vomiting, nasogastric suction, hyperaldosteronism (excess reabsorption of sodium in the distal tubule, thus losing protons instead -- Conn's syndrome, Cushing's syndrome, licorice toxicity). (2) Addition of fixed base: bicarbonate administration, milk-alkali syndrome. NOTE: Neither of these mechanisms results in a metabolic alkalosis which can be reversed by saline administration, i.e., they produce "chloride non-responsive metabolic alkalosis." (3) Water lack requiring renal bicarbonate retention: dehydration from most causes (invalidism, diarrhea, laxative abuse, diuretics, suction), often with hypokalemia (lack of potassium to exchange for reabsorbed sodium in the nephron forces loss of protons.) The kidney is forced, in severe dehydration, to retain sodium bicarbonate in order to retain water. This type of metabolic alkalosis can often be reversed by saline administration, i.e., it is "chloride responsive metabolic alkalosis."

Appendix
Reference Ranges for Common Lab Tests

NOTE: These are commonly-cited ranges. "Normal" depends on the technique, the lab, and the population.

WHITE CELL COUNT 4.8-10.8 x 103

RED CELL COUNT Men 4.7-6.1 x 106
Women 4.2-5.4 x 106

HEMOGLOBIN Men 14-18 gm/dL
Women 12-16 gm/dL

MEAN CORPUSCULAR VOLUME Men 80-94 fL
Women 81-99 fL

NOTE: Pay less attention to hematocrit, MCH, and MCHC; these are derived values.

RED CELL SIZE DISTRIBUTION WIDTH 11.5-14.5

PLATELET COUNT 130-400 x 103

MEAN PLATELET VOLUME 7.4-10.4 fL

ABSOLUTE LYMPHOCYTE COUNT 1.2-3.4 x 103

ABSOLUTE MONOCYTE COUNT 0.11-0.59 x 103

ABSOLUTE GRANULOCYTE COUNT 1.4-6.5 x 103

Almost always, almost all of these are neutrophils. The large majority of these should be mature forms, not bands.

ABSOLUTE EOSINOPHIL COUNT < 400

SODIUM 136-145 meq/L

POTASSIUM 3.5-5.0 meq/L

CHLORIDE 96-106 meq/L

BICARBONATE ("total CO2 content") 24-30 meq/L

ANION GAP 8-16 meq/L

SERUM GLUCOSE 70-110 mg/dL fasting

SERUM UREA NITROGEN (BUN) 5-25 mg/dL

SERUM CREATININE 0.5-1.4 mg/dL

SERUM CALCIUM 8.7-10.7 mg/dL

Pitfall: Ionized calcium is what's regulated; low-albumin means less un-ionized calcium, so less total calcium without a calcium problem.

SERUM MAGNESIUM 1.6-2.4 mg/dL

SERUM PHOSPHORUS 2.6-4.9 mg/dL

SERUM URIC ACID 2.5-9.2 mg/dL

SERUM CHOLESTEROL Decision Level 200 mg/dL

SERUM TRIGLYCERIDES 30-200 mg/dL fasting (a dubious "normal range")

TOTAL PROTEIN 6.1-8.0 gm/dL

ALBUMIN 3.5-4.9 gm/dL

TOTAL BILIRUBIN 0.0-1.2 mg/dL

ALKALINE PHOSPHATASE 37-107 U/L

CREATINE KINASE (CK, CPK) 61-224 U/L

CPK isoenzymes to remember...
MM = CK3: Think skeletal muscle
MB = CK2: Think cardiac muscle
BB = CK1: "Brain enzyme", but you'll seldom see it

LACTATE DEHYDROGENASE (LD, LDH) 94-172 U/L

LDH isoenzymes to remember...
1: Heart, kidney, red cells
5: Skeletal muscle, liver

GLUTAMATE OXALOACETIC TRANSAMINASE (GOT, SGOT, AST) 12-45 U/L

GLUTAMATE PYRUVATE TRANSAMINASE

(GPT, SGPT, ALT)	7-40 U/L
RETICULOCYTE COUNT	0.5-1.5%
DIRECT COOMBS TEST	NEGATIVE
FLUORESCENT ANA	< 1:20

CLASSICAL ROOTS

annulus	little ring
anser	goose
acanth	spine, prickle
aceto	vinegar
acou	hear
acro	extremity, tip, sharp
actin	ray, beam
acu	sharp, abrupt, sudden
adeno	gland
adipo	fat
aero	air
(a)esth	perception
agogue	leader
agon	contest, struggle
ala	wing
alb	white
algo	pain
alien	stranger, strange
allelo	one another, mutual
amauros	blind
am(o)eb	constantly changing
ambi/amph	both sides
ambly	dim, faint
amnio	amnion, "bowl"
amylo	starch
andro	male
angio	vessel (blood, bile)
ankyl	bent, crooked; a joint locked in one position
anthem	flower
anthrac	black
anthro	man / human
aort	aorta
aphro	froth, sexual love
aqu	water
arachn	spider, spiderweb
archo	ancient, beginning

argy	silver, shiny
artero	artery (as opposed to vein)
arthro	joint
artic	little joint
asthm	panting, short breaths
athero	gruel
atri	entry chamber
axilla	armpit
axo	center, axis
aud	hear
aur	hear
aus	hear
auto	self
aux	make grow
azo	nitrogen
bac(t)	rod
ball	throw
balano	acorn, glans
blast	sprout
blenno	snot
bleph	eyelid
bol	throw
brachi	arm
brady	slow
branch	gill
bronch	bronchus
bucc	cheek (inside)
burs	bursa, purse
caes	cut deep
c(h)ord	notochord
c(o)ele	rupture
carpo	wrist
calci	limestone
calco	heel, spur
calyc	cup
campy	bend
canc	crab
capo	head, expanded part
centr	center
carbo	charcoal, carbon
carcin	crab
carcinoma	cancer from epithelium
card	heart, heart-shape
carot	great neck arteries
carpo	wrist
caus	burn

centesis	puncture
centr	center
cep(h)	head, expanded part
cephal	head
cept	seize, take
cereb(r)	brain
cervic	neck
ch(e)ir	hand
chemo	chemistry
chlor	light green
chol(e)	bile
chondr	cartilage; grain
chorea	dance
chori	chorionic membrane
chrom	color
chron	time, long time
chyle	digested food juice
cide	killing, "falling"
cise	cut deep
cili	eyelash
cion	uvula
clast	break
claustr	barrier
cleido	collarbone, key
clino	bed
clivus	slope
coagul	coagulate, clot
coccus	berry
coccyx	cuckoo, cuckoo bill
collic	hill
collo	glue
collus	neck
conios	dust
cond	hard knob
core	dolly, pupil (of eye)
cori	leather
corn	horn
cox(a)	hip
corp	physical body
cre(s)c	grow
cribi	sieve
crine	secretion ("separation")
cubit	elbow
cubo	lay down
cule	little
culpo	vagina

cuneo	wedge
cutis	skin
cyan	dark blue
cycl	circle, wheel
cysto	urinary bladder
cyto	cell
dacr	tear (from the eye)
dacty	finger
demos	people
dens	tooth
dent	tooth
derm	skin
desm	harden, bind together
desis	binding
desmo	hard
dextro	right-sided
diadocho	succeed, take over
didym	twin
digi(t)	finger, toe
diphth	leathery membrane
docho	cup, container
drepan	sickle
dromo	running a race; course
duc, duct	lead, guide
dynia	pain
echin	spiny
echo	echo
ectasia	dilatation
edem(a)	excess tissue fluid
embol	bottle stopper
embryo	embryo, fetus
em(ia)	blood
enceph	brain
enchyme	filling, installation
entero	intestine
ergo	work
erythro	red
esthesia	perception
f(a)eco	feces, refuse
fac	make, build, do, perform
facie	face, countenance, looks
fasc	bundle, fascia
fec	make, build, do, perform
fer	carrying, bearing
fibr	fibrous
fic	make, build, do, perform

fis, fid	split, cleave, divide
flagel	whip
flav	yellow
flat	blow
flect	bend
flex	bend
fora/foro	make a hole
fornic	arch
fract	break into pieces
frag	break into pieces
fring	break into pieces
fuge	flee
fun	melt, pour
fus	melt, pour
gala(k)	milk
gam(y)	marry
gangl	knot
gangr	gangrene, gnawing sore
galact	milk
gastr	stomach, belly
gemin	twin
gen	become, beget, produce
genesis	origin
genu	knee
ger	old age
gest	bring forth, produce
glans	acorn
gleno	shoulder
gli(o)	glial cells, literally "glue"
glob	sphere, ball, round body
glomer	tuft
gloss	tongue
glute	buttocks
gnatho	jaw
gnosis	know
gogue	lead
gono	offspring, product, seed, semen
gonio	angle
gracile	slender
gram	record
gran	grain
graph	writing, scratching
gryph	claw
gynec	female
(h)(a)em	blood
habeo	to hold, habit, general state of

halluc	big toe
helic	spiral
helm	worm
hemraphro	male and female in one body
hepat	liver
hernia	rupture, hernia
hidr	sweat
hippo	horse
histo	tissue, web, cloth
hy(a)l	glass, primitive material
hydatid	water drop
hydro	water
hypno	sleep
hystero	uterus
iatric	healing
iatro	physician
ichth	fish
idio	self, personal, private
inguin	part of body from groin to hip
insul	island
irid	rainbow, bright-color circle
ischi	hip joint
islet	island
ject	throw, hurl
jejun	hungry
junc	join together
jug	join together
jux	join together
kera	horny
kerato	skin surface, cornea, horn
kine	set in motion
kyn	dog
lachry	tear (from the eye)
labio	lip
lacto	milk
lal	babble, talk
latero	side
lecith	egg yolk
leiomyo	smooth muscle
lein	spleen
lens	lentil
lepros	rough and rotting off
lepto	thin, fine, slender
leuco	white
levo	left-sided
liga(t)	bind together, bandage

ling	tongue
lith	stone
lumbo	lower back, loin
lumbri	earthworm
lumen	the tube down a hollow organ
lymph	"clear fresh water"
lysis	breaking down
malar	cheek (outside)
mal(i)	abnormal, bad
malacia	soft
malako	soft
medi	middle portion
medulla	soft inner part
meli	sweet
melleo	hammer
mere	part
manu	hand
mara	wither
mast(i)	whip, flog, beat
mast(o)	breast
mea	passage
meatus	external opening
meios	lessening
melano	black
melia	limb
mening	meninges
men(i)s	moon, month
ment	mind, chin
meter	measure
metro	uterus
mito	thread
mnem	memory
mnes	memory
mob	move
morb	sick
morph	shapes, dreams
mot	move
mur(al)	wall
musc	mouse, muscle
myc(o)	fungus
myelo	soft, pith
myi	fly (insect)
myo	muscle
myxo/muco	slime
narco	sleep
naso	nose

necro	dead
nephelo	cloud
nephr	kidney
nerv	nerve
neuro	nerve
nos, nox	nasty, sickening
nous	mind, spirit
nyct	night
occiput	back of the head
ocul	eye
(h)odo	way, path, road
odon	tooth
odyn	pain
olfact	smell
oma	tumor/lump
omen(t)	omentum
omphalo	belly button
on(e/t)	to be
onco	tumor, mass
onycho	nail (finger/toe)
o”	egg
o”phor	ovary
op	eye, see, etc.
ophth	eye
opio	poppy juice
opsi	late
opson	relish, meat seasoning
orbi	wheel
orch	testis
org	work
oro	mouth
ortho	straight
os	bone, mouth
osm	smell
ost(eo)	bone
ot(o)	ear
ovin	sheep
oxy	oxygen, acid
p(a)ed	child
palpebr	eyelid
pap	nipple
par(i)t	have a baby
parietal	wall
partheno	virgin
partum	birth
patho	disease, misery

pect	chest
pelvis	basin
pes/ped	foot
phage	eat
phakos	lentil, lens of the eye
pharmako	sorcery, poison, drug
phase	phase
pheo	ugly, dusky
phero	carry, bear
philo	like, love
phlebo	vein
phleg	flame
phoco	seal (the animal)
phoro	carry, bear
phos/phot	light
phragm	divide into two, wall off
phren	mind, breath
phth	waste away, wither
phyllo	leaf-like
physio	nature
phyte	a plant
pineo	pine cone
pinna	feather
pino	drink
pisi	pea
pituit	snot
placent	cake, placenta
plak	cake
plantar	sole of the foot
plasm	molded
plast	molded
platy	flat
plegia	stroke, paralysis
pleur	pleura ("side of ribs")
plex	braid, wind together
plexy	stroke
plic	braid, wind together
pn(e)	breath
pod(o)	foot
poie(sis)	making
polio	gray; gray matter of the nervous system
pollic	thumb
pomp	precede, parade
porph	purple
porta	door
posthe	foreskin

prac	done
prag	done
prax	done
pre/pro	before
procto	rectum
pron(o)	prone, face down
proto	first
pseud	false
psyche	spirit, mind
psychr	cold, frigid
pter	wing
pto	droop
pty(alo)	spit
pulmo	lung
punct	prick, little spot
pupa	doll, miniature figure
purp	purple
pyelo	vat, basin, pelvis
pykno	shrivelled
pyo	pus
p(u/y)ri	pear
pyr(o)	fever (cognate to "fire")
radi	rod
r(h)ach	backbone
re(i)n	kidney
ret(ic)	net
rhabdo	striated muscle
rhaph	sew together
rheo	flow
rheum	runny stuff
rhino	nose
riso	smile
rrha(g)	discharge from a burst vessel
rub(r)	red
sacc	sack
sacch(ar)	sugar
salpinx	trumpet, oviduct
sang(ui)	blood
sapro	dead
sarc(o)	flesh
sarcoma	cancer from connective tissue or muscle
scato	feces, filth
scapho	boat
schi(s/z)	split
sclero	hard
scope	examine carefully

sebo	hard fat, skin grease, suet
sec/seg	cut
sella	saddle
seps/sept	make rotten
septo	fence, partition
sero	whey, wet protein
sial	saliva
sinus	hollow or pocket
skel	dried up, skeleton
soma/somy	body
spasmo	a drawing tight
spondylo	spine
sphinct	bind tight, squeeze shut
sphygno	heartbeat
spir	breathing
splanchn	innards
staphyl	bunch of grapes
stasis	standing up, being stable
stat	stop
statio	standing up, being stable
staxis	drip, drop
stem	standing up, being stable
steato	fat
sterco	feces
sthen	strength
stigm	spot
stole	to pull, to draw
stom(a)	mouth
stomy	mouth
strepto	wavy
stylo	stylus
sudo	sweat
sulco	plowed furrow
syring	pipe, tube, reed
tachy	fast, swift
tact	touch
tainia	band, tapeworm
talo	ankle
tasis	stretch
tarso	flat plate
taxo	arrangement, put in order
telo	the tip, the end
temporal	temple
ten(d)o	stretch, tendon
terato	monster
theca	box (sheath, covering)

thel	breast, covering layer
thenar	palm, sole
thym	mind, spirit, mood
thym	warty mass, thymus gland
thyro	oblong shield
toco	have a baby
tom(e)	cut
tono	stretch
topo	place
tort	twist
tox(o)	bow, arrow, poisoned arrow
trema	hole
tricho	hair
trophy	grow/food
tryps	break into many pieces, crush
tuber	bump, potato(e)
typho	smoky, delirious fever
typhl	cecum
unguis	nail (finger, toe)
uro	urine
uvo	grape
vacc	cow
vago	wanderer
valgus	turned outward
varus	turned inward
vaso	blood vessel
velo	veil, curtain, cover
vener	sexual acts, lusty
veno	vein (as opposed to artery)
vert	turn
vesico	bladder
viscero	innards
volv	turn around, twist around
xantho	yellow
xeno	stranger
xero	dry
z(a)o	to live
zo”	animals
zema	boiled
zygo	yoke
zyme	ferment

a(d)-	towards
a(n)-	without
ab-	from
ab(s)-	away from

ad-	towards
allo-	other, another
ambi-	both
amphi-	on both sides, around
ana-	up to, back, again, movement from
aniso-	different, unequal
ante-	before, forwards
anti-	against, opposite
ap-, apo-	from, back, again
bi(s)-	twice, double
bio-	life
brachy-	short
cata-	down
circum-	around
con-	together
contra-	against
cyte-	cell
de-	from, away from, down from
deca-	ten
di(s)-	two
dia-	through, complete
di(a)s	separation
diplo-	double
dolicho-	long
dur-	hard, firm
dys-	bad, abnormal
e-, ec-	out, from out of
ecto-	outside, external
ek-	out
em-	in
en-	into
endo-	into
ent-	within
epi-	on, up, against, high
eso-	I will carry
eu-	well, abundant, prosperous
eury-	broad, wide
ex-, exo-	out, from out of
extra-	outside, beyond, in addition
haplo-	single
hapto-	bind to
hemi-	half
hept-	seven
hetero-	different
hex-	six
homo-	same

hyper-	above, excessive
hypo-	below, deficient
im-, in-	not
in-	into, to
infra-	below, underneath
inter-	among, between
intra-	within, inside, during
intro-	inward, during
iso-	equal,same
juxta-	adjacent to
kata-	down, down from
macro-	large
magno-	large
medi-	middle
mega-	large
megalo-	very large
meso-	middle
meta-	beyond, between
micro-	small
neo-	new
non-	not
ob-	before, against
octa-	eight
octo-	eight
oligo-	few
pachy-	thick
pan-	all
para-	beside, to the side of, wrong
pent-	five
per-	by, through, throughout
peri-	around, round-about
pleo-	more than usual
poly	many
post-	behind, after
pre-	before, in front, very
pros-	besides
prox-	besides
pseudo-	false, fake
quar(t)-	four
re, red-	back, again
retro-	backwards, behind
semi-	half
sex-	six
sept-	seven
sub-	under, beneath
super-	above, in addition, over

supra-	above, on the upper side
syn-	together, with
sys-	together, with
tetra-	four
thio-	sulfur
trans-	across, beyond
tri-	three
uni-	one
ultra-	beyond, besides, over

-ase	fermenter
-ate	do
-cide	killer
-c(o)ele	cavity, hollow
-ectomy	removal of, cut out
-form	shaped like
-ia	got
-iasis	full of
-ile	little version
-illa	little version
-illus	little version
-in	stuff
-ism	theory, characteristic of
-itis	inflammation
-ity	makes a noun of quality
-ium	thing
-ize	do
-logy	study of, reasoning about
-megaly	large
-noid	mind, spirit
-oid	resembling, image of
-ogen	precursor
-ol(e)	alcohol
-ole	little version
-oma	tumor (usually)
-osis	full of
-ostomy	"mouth-cut"
-pathy	disease of, suffering
-penia	lack
-pexy	fix in place
-plasty	re-shaping
-philia	affection for
-rhage	burst out
-rhea	discharge, flowing out
-rhexis	shredding
-pagus	Siamese twins

-sis idea (makes a noun, typically abstract)
-thrix hair
-tomy cut
-ule little version
-um thing (makes a noun, typically concrete)

* * *

[NOT FOR THE TEST, BUT FOR LIFE.... When you talk about disease, people frequently mention non-scientific ideas. You need to learn to deal with these. Sub-science: Trying to make predictions about things of great importance when it's really hard to do controlled studies. Much popular "health advice", and most of psychology, education, and sociology, are sub-science. Pseudoscience: Using the language and authority of science without using its methods. Pseudoscientists thrive by telling people what they want to hear. Medical quackery is pseudoscience, and there are other pseudosciences. A charlatan is a quack who knows it's bunk; most quacks are sincere and are fooling themselves. Politics: people working with and against each other to decide who gets what limited resources. Politics and especially politicians have always been the world's foremost health problem. This is literally and really true. Ethics today attempts to influence politics by the application of moral indignation, often selective; but the content is important, and never far from the subject matter of pathology.]

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ED'S PATHOLOGY MELTDOWN
Part II -- Systemic Pathology

http://www.pathguy.com/boildown.txt