

GOLJAN PATHOLOGY LECTURE NOTES
(125 PAGES)

Day 1

Audio file 1: Cellular Injury 1

CHAPTER 1: CELLULAR REACTION TO INJURY

Key issues – hypoxia, cyanide poisoning, free radicals, apoptosis, growth alternations (i.e. hypertrophy, atrophy, hyperplasia, etc…)

I. Hypoxia = inadequate oxygenation of tissue (same definition of as shock). Need O_2 for oxidation phosphorylation pathway – where you get ATP from inner Mito membrane (electron transport system, called oxidative phosphorylation). The last rxn is O_2 to receive the electrons. Protons are being kicked off, go back into the membrane, and form ATP, and ATP in formed in the mitochondria

A. Terms:

1. Oxygen content = Hb x O_2 satn + partial pressure of arterial oxygen
(these are the 3 main things that carry O_2 in our blood)

In Hb, the O_2 attaches to heme group (O_2 sat'n)
Partial pressure of arterial O_2 is O_2 dissolved in plasma

In RBC, four heme groups (Fe must be +2; if Fe+ is +3, it cannot carry O_2)
Therefore, when all four heme groups have an O_2 on it, the O_2 sat'n is 100%.

2. O_2 sat'n is the O_2 IN the RBC is attached TO the heme group = (measured by a pulse oximeter)

3. Partial pressure of O_2 is O_2 dissolved in PLASMA

O_2 flow: from alveoli through the interphase, then dissolves in plasma, and increases the partial pressure of O_2, diffuses through the RBC membrane and attaches to the heme groups on the RBC on the Hb, which is the O_2 sat'n

Therefore – if partial pressure of O_2 is decreased, O_2 sat'n HAS to be decreased (B/c O_2 came from amount that was dissolved in plasma)

B. Causes of tissue hypoxia:

1. Ischemia (decrease in ARTERIAL blood flow ……NOT venous)

MCC Ischemia is thrombus in muscular artery (b/c this is the mcc death in USA = MI, therefore MI is good example of ischemia b/c thrombus is blocking arterial blood flow, producing tissue hypoxia)

Other causes of tissue ischemia: decrease in Cardiac Output (leads to hypovolemia and cardiogenic shock) b/c there is a decrease in arterial blood flow.

2. 2nd MCC of tissue hypoxia = hypoxemia

Hypoxia = 'big' term
Hypoxemia = cause of hypoxia (they are not the same); deals with the partial pressure of arterial O_2 (O_2 dissolved in arterial plasma, therefore, when the particle pressure of O_2 is decreased, this is called hypoxemia).

Here are 4 causes of hypoxemia:

a. Resp acidosis (in terms of hypoxemia) – in terms of Dalton's law, the sum of the partial pressure of gas must = 760 at atmospheric pressure (have O_2, CO_2, and nitrogen; nitrogen remains constant – therefore, when you retain CO_2, this is resp acidosis; when CO_2 goes up, pO_2 HAS to go down b/c must have to equal 760;
Therefore, every time you have resp acidosis, from ANY cause, you have hypoxemia b/c low arterial pO_2; increase CO_2= decrease pO_2, and vice versa in resp alkalosis).

b. Ventilation defects – best example is resp distress syndrome (aka hyaline membrane dz in children). In adults, this is called Adult RDS, and has a ventilation defect. Lost ventilation to the alveoli, but still have perfusion; therefore have created an intrapulmonary shunt. Exam question: pt with hypoxemia, given 100% of O_2 for 20 minutes, and pO_2 did not increase, therefore indicates a SHUNT, massive ventilation defect.

c. Perfusion defects – knock off blood flow
MCC perfusion defect = pulmonary embolus, especially in prolonged flights, with sitting down and not getting up. Stasis in veins of the deep veins, leads to propagation of a clot and 3-5 days later an embolus develops and embolizes. In this case, you have ventilation, but no perfusion; therefore there is an increase in dead space. If you give 100% O_2 for a perfusion defect, pO_2 will go UP (way to distinguish vent from perfusion defect), b/c not every single vessel in the lung is not perfused.
Therefore, perfusion defects because an increase in dead space, while ventilation defects cause intrapulmonary shunts. To tell the difference, give 100% O_2 and see whether the pO_2 stays the same, ie does not go up (shunt) or increases (increase in dead space).

d. Diffusion defect – something in the interphase that O_2 cannot get through…ie fibrosis. Best example–Sarcoidosis (a restrictive lung disease); O_2 already have trouble getting through the membrane; with fibrosis it is worse. Another example–Pulmonary edema; O_2 cannot cross; therefore there is a diffusion defect. Another example is plain old fluid from heart failure leads to dyspnea, b/c activated the J reflex is initiated (innervated by CN10); activation of CN10, leads to dyspnea (can't take a full breath) b/c fluid in interstium of the lung, and the J receptor is irritated.
These are the four things that cause hypoxemia (resp acidosis, ventilation defects, perfusion defects, and diffusion defects).

3. Hemoglobin related hypoxia

In the case of anemia, the classic misconception is a hypoxemia (decrease in pO_2). There is NO hypoxemia in anemia, there is normal gas exchange (normal respiration), therefore normal pO_2 and O_2 saturation, but there is a decrease in Hb. That is what anemia is: decrease in Hb. If you have 5 gm of Hb, there is not a whole lot of O_2 that gets to tissue, therefore get tissue hypoxia and the patient has exertional dyspnea with anemia, exercise intolerance.

a. Carbon monoxide (CO): classic – heater in winter; in a closed space with a heater (heater have many combustable materials; automobile exhaust and house fire. In the house fire scenario, two things cause tissue hypoxia: 1) CO poisoning and 2) Cyanide poisoning b/c upholstery is made of polyurethrane products. When theres heat, cyanide gas is given off; therefore pts from house fires commonly have CO and cyanide poisoning.

CO is very diffusible and has a high affinity for Hb, therefore the O_2 SAT'N will be decreased b/c its sitting on the heme group, instead of O_2 (remember that CO has a 200X affinity for Hb).

(Hb is normal – its NOT anemia, pO_2 (O_2 dissolved in plasma) is normal, too); when O_2 diffuses into the RBC, CO already sitting there, and CO has a higher affinity for heme. To treat, give 100% O_2. Decrease of O_2 sat'n = clinical evidence is cyanosis
Not seen in CO poisoning b/c cherry red pigment MASKS it, therefore makes the diagnosis hard to make. MC symptom of CO poisoning = headache

b. Methemoglobin:
Methemoglobin is Fe3+ on heme group, therefore O_2 CANNOT bind. Therefore, in methemoglobin poisoning, the only thing screwed up is O_2 saturation (b/c the iron is +3, instead of +2). Example: pt that has drawn blood, which is chocolate colored b/c there is no O_2 on heme groups (normal pO_2, Hb concentration is normal, but the O_2 saturation is not normal); "seat is empty, but cannot sit in it, b/c it's +3". RBC's have a methemoglobin reductase system in glycolytic cycle (reduction can reduce +3 to +2).

Example: Pt from rocky mountains was cyanotic; they gave him 100% O_2, and he was still cyanotic (was drinking water in mtns – water has nitrites and nitrates, which are oxidizing agents that oxidize Hb so the iron become +3 instead of +2). Clue was that O_2 did not correct the cyanosis. Rx: IV methaline blue (DOC); ancillary Rx = vitamin C (a reducing agent). Most recent drug, Dapsone (used to Rx leprosy) is a sulfa and nitryl drug. Therefore does two things: 1) produce methemoglobin and 2) have potential in producing hemolytic anemia in glucose 6 phosphate dehydrogenase deficiencies. Therefore, hemolysis in G6PD def is referring to oxidizing agents, causing an increase in peroxide, which destroys the RBC; the same drugs that produce hemolysis in G6PD def are sulfa and nitryl drugs. These drugs also produce methemoglobin. Therefore, exposure to dapsone, primaquine, and TMP-SMX, or nitryl drugs (nitroglycerin/nitroprusside), there can be a combo of hemolytic anemia, G6PD def, and methemoglobinemia b/c they are oxidizing agents. Common to see methemoglobinemia in HIV b/c pt is on TMP-SMX for Rx of PCP. Therefore, potential complication of that therapy is methemoglobinemia.

c. Curves: left and right shifts
Want a right shifted curve – want Hb with a decreased affinity for O_2, so it can release O_2 to tissues. Causes: 2,3 bisphosphoglycerate (BPG), fever, low pH (acidosis), high altitude (have a resp alkalosis, therefore have to hyperventilate b/c you will decrease the CO_2, leading to an increase in pO_2, leading to a right shift b/c there is an increase in synthesis of 2,3 BPG).

Left shift – CO, methemoglobin, HbF (fetal Hb), decrease in 2,3-BPG, alkalosis
Therefore, with CO, there is a decrease in O_2 sat'n (hypoxia) and left shift.

4. Problems related to problems related to oxidative pathway

a. Most imp: cytochrome oxidase (last enzyme before it transfers the electrons to O_2. Remember the 3 C's – cytochrome oxidase, cyanide, CO all inhibit cytochrome oxidase. Therefore 3 things for CO – (1) decrease in O_2 sat (hypoxia), (2) left shifts (so, what little you carry, you can't release), and (3) if you were able to release it, it blocks cytochrome oxidase, so the entire system shuts down

b. Uncoupling – ability for inner mito membrane to synthesize ATP. Inner mito membrane is permeable to protons. You only want protons to go through a certain pore, where ATP synthase is the base, leading to production of ATP; you don't want random influx of protons – and that is what uncoupling agents do. Examples: dinitrylphenol (chemical for preserving wood), alcohol, salicylates. Uncoupling agents causes protons to go right through the membrane; therefore you are draining all the protons, and very little ATP being made. B/c our body is in total equilibrium with each other, rxns that produce protons increase (rxns that make NADH and FADH, these were the protons that were delivered to the electron transport system). Therefore any rxn that makes NADH and FADH that leads to proton production will rev up

rxns making NADH and FADH to make more protons. With increased rate of rxns, leads to an increase in temperature; therefore, will also see HYPERTHERMIA. Complication of salicylate toxic = hyperthermia (b/c it is an uncoupling agent). Another example: alcoholic on hot day will lead to heat stroke b/c already have uncoupling of oxidative phosphorylation (b/c mito are already messed up).

These are all the causes of tissue hypoxia (ischemia, Hb related, cyto oxidase block, uncoupling agents). Absolute key things!

5. What happens when there is:

a. resp acidosis – Hb stays same, O_2 sat'n decreased, partial pressure of O_2 decreased (O_2 sat decreased b/c pO_2 is decreased)
b. anemia – only Hb is affected (normal O_2 sat'n and pO_2)
c. CO/methemoglobin – Hb normal, O_2 sat'n decreased, pO_2 normal
Rx CO – 100% O_2; methemo – IV methaline blue (DOC) or vit C (ascorbic acid)

C. Decreased of ATP (as a result of tissue hypoxia)

1. Most imp: have to go into anaerobic glycolysis; end product is lactic acid (pyruvate is converted to lactate b/c of increased NADH); need to make NAD, so that the NAD can feedback into the glycolytic cycle to make 2 more ATP. Why do we have to use anaerobic glycolysis with tissue hypoxia? Mitochondria are the one that makes ATP; however, with anaerobic glycolysis, you make 2 ATP without going into the mitochondria. Every cell (including RBC's) in the body is capable of performing anaerobic glycolysis, therefore surviving on 2 ATP per glucose if you have tissue hypoxia. Mitochondrial system is totally shut down (no O_2 at the end of the electron transport system – can only get 2 ATP with anaerobic glycolysis).

Good news – get 2 ATP
Bad news – build up of lactic acid in the cell and outside the cell (increased anion-gap metabolic acidosis with tissue hypoxia) due to lactic acidosis from anaerobic glycolysis.

However, causes havoc inside the cell b/c increase of acid within a cell will denature proteins (with structural proteins messed up, the configuration will be altered); enzymes will be denatured, too. As a result, cells cannot autodigest anymore b/c enzymes are destroyed b/c buildup of acid. Tissue hypoxia will therefore lead to COAGULATION necrosis (aka infarction). Therefore, buildup of lactic acid within the cell will lead to Coagulation necrosis.

2. 2nd problem of lacking ATP: all ATP pumps are screwed up b/c they run on ATP. ATP is the power, used by muscles, the pump, anything that needs energy needs ATP. **Na/K pump** – blocked by digitalis to allow Na to go into cardiac muscle, so Ca channels open to increase force of contraction (therefore, sometimes you want the pump blocked), and sometimes you want to enhance it.

With no ATP, Na into the cell and it brings H20, which leads to cellular swelling (which is reversible). Therefore, with tissue hypoxia there will be swelling of the cell due to decreased ATP (therefore will get O_2 back, and will pump it out – therefore it is REVERSABLE).

In true RBC, anaerobic glycolysis is the main energy source b/c they do not have mitochondria; not normal in other tissues (want to utilize FA's, TCA, etc).

3. Cell without O_2 leads to irreversible changes.

Ca changes with irreversible damage – Ca/ATPase pump. With decrease in ATP, Ca has easy access into the cell. Within the cell, it activates many enzymes (ie phospholipases in the cell membranes, enzymes in the nucleus, leading to nuclear pyknosis (so the chromatin disappears), into goes into the mito and destroys it).

Ca activates enzymes; hypercalcemia leads to acute pancreatitis b/c enzymes in the pancreas have been activated. Therefore, with irreversible changes, Ca has a major role. Of the two that get damaged (mito and cell membrane), cell membrane is damaged a lot worse, resulting in bad things from the outside to get into the cell. However, to add insult to injury, knock off mitochondria (energy producing factory), it is a very bad situation (cell dies)…CK-MB for MI, transaminases for hepatitis (SGOT and AST/ALT), amylase in pancreatitis.

II. Free Radicals

Liver with brownish pigment – lipofuscin (seen on gross pic; can also be hemosiderin, bilirubin, etc; therefore need to have a case with the gross pic); end products of free radical damage are lipofuscin b/c certain things are not digestible (include lipids).

A. Definition of free radical – compound with unpaired electron that is out of orbit, therefore it's very unstable and it will damage things.

B. Types of Free Radicals:

1. Oxygen: We are breathing O_2, and O_2 can give free radicals. If give a person 50% O_2 for a period of time, will get superoxide free radicals, which lead to reperfusion injury, esp after giving tPA when trying to rid a damaged thrombus. Oxygentated blood goes back into the damaged cardiac muscle=reperfusion injury. Kids with resp distress syndrome can get free radical injury and go blind b/c they destroy the retina – called retinopathy prematurity; also leads to bronchopulmonary dysplasia, which leads to damage in the lungs and a crippling lung disease.

2. Water in tissues converted to hydroxyl free radicals, leading to mutations in tissues. Complication of radiation therapy is CANCER (MC cancer from radiation is leukemia, due to hydroxyl free radicals). Fe2+ produces hydroxyl free radicals b/c of the fenton rxn. This is what makes Fe overload diseases so dangerous, b/c wherever Fe is overloaded, leads to hydroxyl free radicals which will damage that tissue (therefore, in liver leads to cirrhosis, in heart leads to restrictive cardiomyopathy, in pancreas leads to failure, and malabsorption, along with diabetes).

Audio file 2: Cell Injury 2

3. Tylenol (aka acetaminophen):
MCC drug induced fulminant hepatitis b/c free radicals (esp targets the liver, but also targets the kidneys). Cytochrome P450 in liver metabolizes drugs, and can change drugs into free radicals. Drugs are often changed in the liver to the active metabolite – ie phenytoin. Where in the liver does acetaminophen toxicity manifest itself? – right around central vein. Treatment: n-acetylcysteine; how? Well, the free radicals can be neutralized. Superoxide free radicals can be neutralized with supraoxide dismutase (SOD). Glutathione is the end product of the hexose/pentose phosphate shunt and this shunt also generates NADPH. Main function is to neutralize free radicals (esp drug free radicals, and free radicals derived from peroxide). Glutathione gets used up in neutralizing the acetaminophen free radicals. Therefore, when give n-acetylcysteine (aka mucamist); you are replenishing glutathione, therefore giving substrate to make more glutathione, so you can keep up with neutralizing acetaminophen free radicals. (like methotrexate, and leukoverin rescue – using up too much folate, leukoverin supplies the substrate to make DNA, folate reductase).

4. Carbon tetrachloride: CCl4 can be converted to a free radical in the liver (CCl3) in the liver, and a free radical can be formed out of that (seen in dry cleaning industry).

5. Aspirin + Tylenol = very bad for kidney (takes a long time for damage to be seen). Free radicals from acetaminophen are destroying the renal medulla *only receives 10% of the blood supply-relatively hypoxic) and renal tubules. Aspirin is knocking off the vasodilator PGE2, which is made in the afferent arteriole. Therefore AG II (a vasoconstrictor) is left in charge of renal blood flow at the efferent arteriole. Either sloughing of medulla or destroyed ability to concentrate/dilute your urine, which is called analgesic nephropathy (due mainly to acetaminophen).

III. Apoptosis

Programmed cell death. Apoptotic genes – "programmed to die" (theory). Normal functions: (1) embryo – small bowel got lumens from apoptosis. (2) King of the body – Y c'some (for men); MIF very imp b/c all mullarian structures (uterus, cervix, upper 1/3 of vagina) are gone, therefore, no mullarian structures. MIF is a signal working with apoptosis, via caspasases. They destroy everything, then wrap everything in apoptotic bodies to be destroyed, and lipofuscin is left over. (3) For woman – X c'some; only have one functioning one b/c the other is a barr body. Absence of y c'some caused germinal ridge to go the ovarian route, therefore apoptosis knocked off the wolfian structures (epididymis, seminal vesicles, and vas deferens). (4) Thymus in anterior mediastinum – large in kids; if absent, it is DiGeorge syndrome (absent thymic shadow), and would also have tetany; cause of thymus to involute is apoptosis. (5) Apoptosis is the major cancer killing mechanism. (6) Process of atrophy and reduced cell or tissue mass is due to apoptosis. Ex. Hepatitis – councilman body (looks like eosinophilic cell without apoptosis) of apoptosis (individual cell death with inflammation around it). Just needs a signal (hormone or chemical) which activate the caspases, and no inflammation is around it. Apoptosis of neurons – loss brain mass and brain atrophy, and leads to ischemia. Red cytoplasm, and pynotic nucleas. Atherosclerotic plaque. Therefore, apoptosis is involved in embryo, pathology, and knocking off cancer cells.

IV. Types of necrosis – manifestations of tissue damage.

A. Coagulation Necrosis: Results often from a sudden cutoff of blood supply to an organ i.e. Ischemia (definition of ischemia = decrease in arterial blood flow). In ischemia, there is no oxygen therefore lactic acid builds up, and leads to coagulation necrosis. Gross manifestation of coagulation necrosis is infarction. Under microscope, looks like cardiac muscle but there are no striations, no nuclei, bright red, no inflammatory infiltrate, all due to lactic acid that has denatured and destroyed all the enzymes (cannot be broken down – neutrophils need to come in from the outside to breakdown). Therefore, vague outlines = coagulation necrosis (see color change in heart).

1. Pale vs hemorrhagic infarctions: look at consistency of tissue.

(a) Good consistency = grossly look pale: infarct: heart, kidney, spleen, liver (rarest of the organ to infarct b/c dual blood supply); ie coagulation necrosis. Example of a pale infarction of the spleen, most likely due to emboli from left side of heart; causes of emboli: vegetations (rarely embolize in acute rheumatic endocarditis); infective endocarditis; mitral stenosis (heart is repeatedly attacked by group A beta hemolytic streptococcus); and clots/thrombi. The worst arrhythmia associated with embolization in the systemic circulation is atrial fib b/c there is stasis in the atria, clot formation, then it vibrates (lil pieces of clot embolize).

Gangrenous Necrosis: dry and wet gangrene: Picture of a dry gangrene – not wet gangrene b/c there's no pus. Occurs in diabetic's with atherosclerosis of popliteal artery and possible thrombosis; (dry gangrene related to coagulation necrosis related with ischemia (definition of ischemia = decrease in arterial blood flow), which is due to atherosclerosis of the popliteal artery. Pathogenesis of MI: coronary thrombosis overlying the atheromatous plaque, leading to ischemia, and lumen is blocked due to thrombosis. MCC nontraumatic amputation = diabetes b/c enhanced atherosclerosis (popliteal artery = dangerous artery). Coronary is also dangerous b/c small lumen. In wet gangrene, it's complicated by infective heterolysis and consequent liquefactive necrosis.

(b) Loose consistency of tissue= hemorrhagic infarct: bowel, testes (torsion of the testes), especially the lungs b/c is has a loose consistency and when the blood vessels rupture, the RBC's will trickle out, leading to a hemorrhagic appearance.

Example: hemorrhagic infarction of small bowel due to indirect hernia. 2nd MCC of bowel infarction is getting a piece of small bowel trapped in indirect hernial sac. MCC of bowel infarction is adhesions from previous surgery.

Example: In the Lung – hemorrhagic infarction, wedge shaped, went to pleural surface, therefore have effusion and exudates; neutrophils in it; have pleuritic chest pain (knife-like pain on inspiration). Pulmonary embolus leads to hemorrhagic infarction.

B. Liquefactive Necrosis:

Exception to rule of Coagulation necrosis seen with infarctions: brain.
MC site of infarction from carotid artery – why we listen for a bruit (hearing for a noise that is going thru a vessel that has a narrow lumen – place with thrombus develops over atherosclerotic plaque and leads to stroke); leads to transient ischemic attacks is little atherosclerotic plaques going to little vessels of the brain, producing motor and sensory abnormalities, that go away in 24 hrs. Brain with 'meshwork' – in brain, astrocytes is analogous to the fibroblasts b/c of protoplasmic processes. Therefore, acting like fibroblast (can't make collagen), but its protoplasmic processes gives some structure to the brain. Therefore, infarction of the brain basically liquefies it (has no struct), and you see a cyst space – **liquefactive necrosis**. Therefore, exception to the rule of infarctions not being coagulative necrosis is the brain and it undergoes liquefactive necrosis (no struc, therefore leaves a hole). Cerebral abscess and old atherosclerotic stroke -both are liquefactive necrosis.

Liquefactive – liquefies; think neutrophil, b/c their job is to phagocytosis with their enzymes (to 'liquefy'); liquefactive necrosis relates to an infection with neutrophils involved (usually acute infection – producing an abscess or an inflammatory condition, which liquefies tissue). Therefore, liquefactive necrosis usually applies to acute inflammation, related to neutrophils damaging the tissue. Exception to the rule: liquefactive necrosis related to infarct (not an inflammatory condition, it just liquefies) (slide shows liquefactive necrosis due to infection in the brain). So, if you infarct the brain, or have an infection, or have an abscess it is the same process – liquefactive necrosis.

Example: Abscess – gram "+" cocci in clusters. Why are they in clusters? Coagulase, which leads to abscesses with staph aur. Coagulase converts fibrinogen into fibrin, so it localizes the infection, fibrin strands get out, resulting in an abscess. Strep: releases hyaluronidase, which breaks down GAG's in tissue, and infection spreads through the tissue (cellulitis). From point of view of necrosis, neutrophils are involved, therefore it is liquefactive necrosis.
Example: ABSCESS: Lung – yellowish areas, high fever and productive cough; gram stain showed gram "+" diplococcus, which is strep pneumoniae. (MCC of bronchopneumonia.). Not hemorrhagic b/c its pale, and wedged shaped necrosis at the periphery, which leads to pleuritic chest pain.

Example: pt with fever, night sweats, wt loss – M tb, which has granulomatous (caseous) necrosis. Pathogenesis of granuloma (involves IL-12 and subset of helper T cells and "+" PPD).

C. Caseous (cheesy consistency) Necrosis: – either have mycobacterial infection (any infections, including atypicals, or systemic fungal infection); these are the ONLY things that will produce caseation in a granuloma. It is the lipid in the cell wall of the organism's leads to cheesy appearance.

Sarcoidosis – get granulomas, but they are not caseous b/c they are not mybacterium or systemic fungi (hence 'noncaseating' granulomas)
Crohn's dz – get granulomas, but not caseous b/c not related to mycobacterium or systemic fungi.

D. Fat Necrosis:

1. Enzymatic Fat Necrosis: unique to pancreas
Example: pt with epigastric distress with pain radiating to the back – pancreatitis (cannot be Peptic Ulcer Dz b/c pancreas is retroperitoneal), therefore just have epigastric pain radiating to the back. A type of enzymatic FAT necrosis (therefore necrosis related to enzymes). Enzymatic fat necrosis is unique to the pancreas b/c enzymes are breaking down fats into FA's, which combine with Ca salts, forming chalky white areas of enzymatic fat necrosis (chalky white areas due to calcium bound to FA's – saponification (soap/like salt formation)); these can be seen on xrays b/c have calcium in them. Example: A pt with pain constently penetrating into the back, show x-ray of RUQ. Dx is pancreatitis and esp seen in alcoholics. Histo slide on enzymatic fat necrosis – bluish discoloration, which is calcification (a type of dystrophic calcification-calcification of damaged tissue). What enzyme would be elevated? Amylase and lipase (lipase is more specific b/c amylase is also in the parotid gland, small bowel, and fallopian tubes). What type of necrosis? Another example: Enzymatic fat necrosis. Underlying cause? Alcohol produces a thick secretion that will lead to activation of enzymes; which leads to pancreatitis. Therefore, whenever you see blue discoloration and atherosclerotic plaque in a pancreas, it will be calcium.

2. Traumatic Fat Necrosis: Example: woman with damage to breasts is TRAUMATIC FAT necrosis (not enzymatic); it can calcify, can look like cancer on mammogram. Diff btwn that and calcification in breast cancer is that it is painFUL. (cancer = painless). Traumatic fat tissue usually occurs in breast tissue or other adipose tissue

E. Fibrinoid necrosis: (the -oid means: looks like, but isn't)
Therefore, looks like fibrin, but is not fibrin….it is the necrosis of immunologic dz:
Examples of immunologic dz:
Palpable purpura = small vessel vasculitis (immune complex type III).

Fibrinoid necrosis has immune complex deposition of small vessel.
Pathogenesis of immune complex: damage of type III HPY (an immune complex is an Ag-Ab circulating in the circulation; it deposits wherever circulation takes it – ie glomerulus, small vessel, wherever). It activates the complement system (the alt system), which produces C5a, which is chemotactic to neutrophils. Therefore, damage done as a result of type III HPY is done by neutrophils. And they are there b/c the immune complex activated the alternative complement system. The complex has little to do with the damage, it's the neutrophils do eventual damage)

Henoch-Scholein purpura – feel person's legs, and see palpable purpura (due to type III HPY). Rhematic fever (vegetations off the mitral valve) – have fibrin like (fibrinoid necrosis) materials (necrosis of immunologic dz). Morning stiffness = rheumatoid arthritis, see fibrnoid necrosis b/c immunologic damage. Therefore, fibrinoid necrosis is necrosis of immunologic damage (in vessel it's a vasculitis, in kidney it's a glomerulonephritis, and in lupus glomerulonephritis involving immune complexes).

F. Liver: Triad area: portal vein, hepatic artery, bile duct. Liver is unique b/c it has dual blood supply and so hepatic artery and and portal vein will dump blood into sinusoids. Other examples of sinusoid organs are BM and spleen. Characteristic of sinusoids: gaps between endothelial cells, with nothing there so things can fit through (things like RBC's and inflammatory cells). GBM is fenestrated, have little tiny pores within the cells, for filtration. Sinusoids have gaps so large cells can get through them (not true with GBM b/c it is intact, and lil pores allow filtration). Portal vein blood and hepatic artery blood go through sinusoids, and eventually taken up by central vein, which becomes the hepatic vein. The hepatic vein dumps into the inf vena cava, which goes to the right side of the heart. Therefore, there is a communication between right heart and liver. Right HF (blood fills behind failed heart), therefore the liver becomes congested with blood, leading to nutmeg liver (aka congestive hepatomegaly). If you block the portal vein, nothing happens to the liver, b/c it is BEFORE the liver. Blockage of hepatic vein leads to budd chiari and liver becomes congested. Which part of liver is most susceptible to injury normally? Around central vein, b/c it gets first dibbies on O_2 coming out of the sinusoids (zone 1). Zone 2 is where yellow fever will hit (midzone necrosis) due to ides egypti. Zone 3, around portal vein, which will have least O_2 (analogous to renal medulla, which only receives 10% of the blood supply, and the cortex receives 90%). Fatty change is around zone 3 (part around central vein). Therefore, when asking about acetaminophen toxicity, which part is most susceptible? Around the central vein b/c it gets the least amount O_2, and therefore cannot combat free radical injury.

1. Alcohol related liver damage:

(a) MCC fatty change: alcohol.
(b) Metabolism of alcohol: NADH and acetyl CoA (acetate is a FA, and acetyl CoA can be converted to FA's in the cytosol). NADH is part of the metabolism of alcohol, therefore, for biochemical rxns: What causes pyruvate to form lactate in anaerobic glycolysis? NADH drove it in that direction, therefore always see lactic acidosis (a form of metabolic acidosis) in alcoholic's b/c increased NADH drives it in that direction. Also, in fasting state, alcoholic will have trouble making glucose by gluconeogenesis b/c need pyruvate to start it off. However, you have lactate (and not pyruvate) therefore alcoholics will have fasting hypoglycemia. Acetyl CoA can also make ketone bodies (acetoacetyl CoA, HMG CoA, and beta hydroxybutyric acid). See beta hydroxybutyric ketone bodies in alcoholic's b/c it's a NADH driven reaction. Therefore, two types of metabolic acidosis seen in alcoholics are lactic acidosis (b/c driving pyruvate into lactate) and increased synthesis of ketone bodies b/c excess acetyl CoA; main ketoacid = beta hydroxybutyric acid. Why does it produce fatty change? In glycolysis, around rxn 4, get intermediates dihydroxyacetone phoshphate (NADH rxn) and is forced to become glycerol 3-phosphate. Big time board question! With glycerol 3 phosphate shuttle, get ATP. Also imp to carbohydrate backbone for making tryglycerides (add 3 FA's to glycerol 3 – phosphate, and you get TG's). In liver, the lipid fraction if VLDL (endogenous TG is synthesized in the liver from glycerol 3 phosphate derived from glycolysis). Restricting fat will NOT decrease the synthesis of VLDL. Restricting carbs WILL decrease the VLDL synthesis b/c it is glucose intermediate it is made from. Glycerol 3 phosphate is a product of glycolysis which is why fatty liver is MC'ly due to alcoholism (this rxn)!

Audio file 3: Inflammation 1

2. Kwashiorker – kid with fatty change. The mechanism: when you make VLDL, and to be able to get it out of the liver, the VLDL must be surrounded by apoproteins. In kwashiorkor, there is decreased protein intake; they have adequate number of calories, but its all carbs. Therefore, they cannot get VLDL that they made in the liver out b/c there are no apolipoproteins to cover it and put it out in the bloodstream and solubilize it in water. Lipid and water do not mix; therefore it is necessary to put proteins around the lipid to dissolve it in water. Therefore, the protuberant abdomen in these pts is there for two reasons: 1) decreased protein intake which decreases oncotic pressure, leading to ascites. 2) The biggest reason is that they have huge livers related to fatty change. The mechanism for fatty change is different from alcohol b/c in alcohol; the mech is due to increased synthesis of VLDL. In this case, there is a lack of protein to put around the VLDL and export it out of the liver.

3. Hemosiderin and Ferrtin: brief discussion: Ferritin = soluble form of circulating Fe, and is a good marker for Fe in BM. It is the test of choice in dx'ing any Fe related problem – Fe def anemia, or Anemia of Chronic Dz or Fe overload dz's such as hemochromatosis and hemosiderosis (would be elevated). Ferritin is a soluble form of Fe, while hemosiderin is an insoluble form of Fe storage, and is stored in macrophages and BM. Stain it with Prussian blue.

V. Types of calcification: dystrophic and metastatic

A. Dystrophic calcification: means abnormal calcification. The damaged tissue gets calcified.
1. Example: Seen in enzymatic fat necrosis (chalky white areas on x-ray are a result of dystrophic calcification).

2. Example: football player with hematoma in foot, that becomes calcified dsystrophically (Ca binds and co-produces dystrophic Ca deposits). Serum Ca is normal, but damaged tissue becomes calcified. Occurs in atheromatous plaques (causes serious tissue damage), therefore they are difficult to dissolve (need to be on the ornish diet – a vegan diet).
3. MCC aortic stenosis (MCC: congenital bicuspid aortic valve) = dystrophic calcification (also leads to a hemolytic anemia). Slide: the aorta has only 2 valves doing the job of three, and gets damaged, leading to dystrophic calcification which narrows orifice of valve, leading to aortic stenosis.

B. Metastatic calcification: In cases of Hypercalcemia or hyperphosphatemia, Calcium is actually made to deposit in normal tissues, non-damaged tissues.
MCC hypercalcemia (outside of hospital) = primary hyperparathyroidism
MCC hypercalcemia (inside the hospital) = malignancy induced hypercalcemia.
With hypercalcemia, can put Ca in NORMAL tissues; this is called metastatic calcification. In dystrophic calcification there is damaged tissue with normal serum Ca levels. Metastatic calcification is when there is high Ca or phosphorus serum levels (actually when Ca is deposited into bone, it is the phosphorus part of solubility product that drives Ca into bone). High phosphate levels (very dangerous) will take Ca and drive it into normal tissue. This is why have to put a pt with renal failure on dialysis (have high phosphorus serum levels) therefore need to dialyze the phosphate b/c the phosphate will drive Ca into normal tissue – ie heart, conduction system, renal tubules, basement membrane (nephrocalcinosis) – all lead to damage.

VI. Cell Membrane Defects

A. RBC membrane defect: Spherocytosis is a defect in spectrin within RBC cell membrane; if you can't see a central area of pallor (if you don't see a donut) then it's a spherocyte. Absence of spectrin with in the RBC does not allow the RBC to form a biconcave disk; it is defective, and therefore forms a sphere.

B. Ubiquitin – stress protein. High ubiquitin levels are associated with high levels of stress. Some of the intermediate filaments (keratin, desmin, vimentin) are part of the superstructure of our cells ("frame of the cell", upon which things are built). When these intermediate filaments get damaged, the ubiquitin marks then for destruction. The intermediate filaments have been tagged (ubiquinated) and marked for destruction. Some of these products have names, for example: there are open spaces within the liver tisse, these spaces are fat and they are probably due to alcohol. The ubiquinited products of the liver are called Mallory bodies. These are the result of ubiquinated filaments called keratin and these are seen in alcoholic hepatitis. Another example: Silver stain of neurofibilary tangles – Jacob crutzfelt and alzheimers dz. Tau protein is associated with neurofib tangles; this is an example of a ubiquinated neurofilament. Example: Substantia nigra in Parkinson's Dz – include inclusions called Lewy bodies, neurotransmitter deficiency is dopamine. Lewy bodies are ubiquinated neurofilaments. Therefore, Mallory bodies, Lewy bodies, and neurofib tangles are all examples of ubiquintation.

VII. Cell Cycle- very very important: big big big time

A. Different types of cells:
1. Labile cells – cell where the division is via a stem cell. Three tissues that has stem cells: bone marrow, basement membrane of skin, and the base of crypts in the intestine. These cells have the tendency of being in the cell cycle a lot. In pharm: there are cell cycle specific and cell cycle nonspecific drugs. The cells that are most affected by these drugs are the labile cells b/c they are in the cell cycle. Complications of these drugs are BM suppression, diarrhea, mucocidis, and rashes on the skin (there are stem cells in all these tissues!).

2. Stable cells – in resting phase, G_o phase. Most of perenchymal organs (liver, spleen, and kidney) and smooth muscle are stable cells. Stable cells can ungo division, but most of the time they are resting, and something must stimulate them to get into the cell cycle and divide – ie a hormone or a growth factor. For example: estrogen in woman will help in the proliferative phase of the menstrual cycle. The endometrial cells are initially in the G_o phase and then the estrogen stimulated the cells to go into the the cell cycle. Therefore, they can divide, but they have to be invited by a hormone or a growth factor.

3. Permanent cells – can no longer get into the cell cycle, and have been permanently differentiated. The other types of muscle cells: striated, cardiac and neuronal cells. Only muscle that is NOT a permanent tissue = smooth muscle; hyperplasia = increase in #, while hypertrophy = increase in size. Would a permanent cell be able to under hyperplasia? NO, b/c that means more copies of it. Can it go under hypertrophy? Yes. A smooth muscle cell can undergo hyperplasia AND hypertrophy.

B. Different phases of cell cycle:
1. G_1 phase: The most variable phase of cell cycle is the G_1 phase. Compare with menstrual cycle: The most variable phase is the proliferative phase (not the secretory phase). The prolifertive phase varies with stress; however, once ovulation has occurred, it is 14 days. Therefore, proliferative phase is analogous to G_1 phase of the cell cycle b/c it can be shorter or lengthened; none of the other phases (S, G_2, and M phase) changes, they stay the same. Therefore, in cancer cells, ones with a longer cell cycle will have a longer G_1 phase, and cancer cells with a shorter cell cycle will have a shorter G_1 phase.

G_1 phase is the mastermind of everything. Cyclin dependent kinase (kinase = phosphorylation = activation). Phosphorylation usually involves sending a message to activate something. Glucagon is a phosphorylator, while insulin is a dephosphorylator. Glucagon will phosphorylate protein kinase and activate it, while Insulin would dephosphorylate protein kinase and inactivate it.

G1 to S phase: Inactive Cyclin d dependent kinase: Cyclin d activates it, and G_1 phase makes cyclin D. Once cyclin D is made in the G_1 phase, it then activates the enzyme: cyclin dep. kinase (therefore it is now active). Key area to control in

cell cycle: transition from G_1 to S phase. Because if you have a mutation and it goes into S phase, it then becomes duplicated, then you have the potential for cancer. Two suppressor genes that control the transition: (1) Rb suppressor gene: located on chromosome 13, which makes the Rb protein, which prevents the cell from going from the G_1 to the S phase. In general, to go from G_1 to S, the active cyclin dep kinase phosphorylates the Rb protein; when it is phosphorylated=activation, it can go from the G_1 phase to the S phase. A problem occurs if there is a mutation. Therefore the enzyme is checked by (2) p53 suppressor gene: located on chromosome 17, which makes a protein product that inhibits the cyclin d dep kinase. Therefore, it cannot go into the S phase; p53 is the number 1, most imp gene that regulates human cancer.

Example: HPV – inactivates Rb suppressor gene and p53 suppressor gene. HPV makes two genes products – E6 (which knocks off the p53) and E7 (which knocks of the Rb suppressor gene).

If you have a point mutation the Rb suppressor gene, the Rb suppressor gene is knocked off, there will be no Rb protein, and the cell will progress to the S phase b/c it is uncontrolled. This mutation in the Rb suppressor gene predisposing to many cancers, such as retinoblastoma, osteogenic sarcoma (ie kid with pain around knees, Codman's triangle – sunburst appearance on x-rays), and breast cancer (Rb suppressor can be involved). Depending on the age bracket, it hits in different areas. If you knock of p53 suppressor gene: the kinase will be always active, it will always phosphorylate the Rb protein, and that means that it will always go into the S phase, and this is bad. If you knock off any of those genes, the cell will go into the S phase. The p53 suppressor gene is the guardian of the genome, b/c it gives the cell time to detect if there are any defects/abnormalities in the DNA (splicing defects, codon thing, whatever, etc). DNA repair enzymes can splice out the abnormality, correct it, and the cell is ready to go to the S phase. If the cell has too much damaged DNA, then it is removed by apoptosis. Therefore this gene is imp b/c it gives the cell an opportunity to clean its DNA before going into the S phase.

2. S phase = synthesis phase, where everything is doubled, includes DNA and chromosomes (from 2N to 4N). For example: if it's in muscle, it will have double the number of contractile elements.

3. G_2 phase = where tubulin is made (imp to microtubule of the mitotic spindle); it is blocked by etoposide and bleomycin.

4. M phase = mitosis; where the cell divides into two 2N cells. The cell can either go into the G_o resting phase, or can continue dividing in the cycle, or can be permanently differentiated. p53 gene makes a protein to inhibit the kinase, therefore prevents the Rb protein from being phosphorylated, therefore stays in the G_1 phase. Therefore, when you knock it off, no one is inactivating the kinase, and the cell is constantly phosphorylated and that keeps the cell dividing, and then has the potential to lead to cancer.

C. Drugs that act on the cell cycle:

1. Drugs acting on S phase:
   a) Ergot alkaloids work on the mitotic spindle in S phase
   b) Methotrexate works in S phase: Example: pt with rheumatoid arthiritis has macrocytic anemia. Drug responsible for this is in what phase of the cell cycle? S phase b/c it is methotrexate blocking dihydrofolate reductase

2. Drugs acting on G_2 phase:
   a) Etoposide
   b) Bleomycin

3. Drugs acting on M phase:
   a) Gresiofulvin in M phase
   b) Paclitaxel specifically works in the M phase: Clinical scenario: this drug is a chemotherapy agent made from a yew tree? Paclitaxel (m phase)
   c) Vincristine and Vinblastine
   d) This drug used to be used for the treatment of acute gouty arthritis but b/c of all the side effects is no longer used. What drug and where does it act? Colchicine (m phase)

4. Clinical scenario that does not work on the cell cycle: HIV "+" person with dyspnea and white out of the lung, on a drug; ends up with cyanosis; which drug? Dapsone

VII. Adaptations to environmental stress: Growth alterations

A. Atrophy: Diagnosis: the decrease in tissue mass and the cell decreases in size. The cell has just enough organelles to survive, ie less mitochondria then normal cells, therefore, just trying to 'eek' it out until whatever it needs to stimulate can come back.

1. Example: hydronephrosis, the compression atrophy is causing thinning of cortex and medulla, MCC hydronephrosis is stone in the ureter (the pelvis is dilated). Question can be asked what kind of growth alteration can occur here. Answer is atrophy b/c of the increased pressure on the cortex and the medulla and produces to ischemia, blood flow decreases and can produce atrophy of renal tubules.

2. Example: Atrophied brain due to atherosclerosis (MC) or degeneration of neurons (alzheimers, related to beta amyloid protein, which is toxic to neurons).

3. Example: In muscle, many causes of atrophy – ie Lou Gehrig's Dz (amylateral sclerosis) knock off neurons to the muscle, so it is not stimulated, leading to atrophy.

4. Example: Endocrine related:
   a) Hypopituitarism will lead to atrophy of adrenal cortex: the zona fasiculata and retiucularis layers of the adrenal cortex; NOT the glomerulosa b/c ACTH has nothing to with stimulating aldosterone release. The fasiculata is where glucocorticoids (cortisol) are made, while reticularis is where sex hormones are made (17 ketosteroids and testosterone). ACTH is responsible for stimulating these, therefore zona fasiculata and zona reticularis are atrophied.

   b) Taking thyroid hormone will lead to atrophy of thyroid gland. This is due to a decrease of TSH and therefore nothing is stimulating the thyroid gland which leads to atrophy.

5. Example: Slide showing a biopsy of a pancreas in a patient with cystic fibrosis. What is growth alteration? Atrophy, b/c the CFTR regulator on c'some 7 is defective and has problems with secretions. The secretions become thicker and as a result, it blocks the ducts and so that means that the glands that were making the fluids (the exocrine part of the gland) cannot make fluids b/c of the back pressure blocking the lumen of the duct, which leads to atrophy of the glands, which then leads to malabsorption in all children with cystic fibrosis.

6. Example: Slide of an aorta, with atherosclerotic plaque, which leads to atrophy of the kidney and secondary HTN (renovasuclar HP, leading to high renin level coming out of the kidney). In the other kidney, it is overworked, therefore there is hypertrophy (renin level coming out of this vein is decreased and suppressed).

B. Hypertrophy increase of the SIZE of cell, not number

Scenario: A cell biology question: what is the N of this?

Hypertrophy of a cardiac muscle (permanent muscle), suppose there is a block just before the G2 phase. What is the number of chromosomes? Answer: # of c'somes is 4N, b/c it already underwent synthesis: already doubled.

1 N = sperm (23 c'somes)
2 N = normal (diploid cell)
3 N = trisomy
4 N = double the number

C. Hyperplasia – increase in the # of cells

In normal proliferative gland, there are thousands of mitoses, therefore see more glands with hyperplasia.

1. Example leading to cancer: With unopposed estrogen, you may end up with cancer, b/c if you didn't have progesterone (undoes what estrogen did-counteracts the estrogen), you will get cancer. The cells will go from hyperplasia, to atypical hyperplasia to endometrial cancer. Therefore hyperplasia left unchecked there is an increased risk of cancer. One exception: benign prostatic hyperplasia; hyperplasia of the prostate does NOT lead to cancer; just urinary incontinence.

2. Example: gravid uterus (woman's uterus after delivery). This is an example of 50:50: 50% hypertrophy of the smooth muscle cells in the wall of the uterus, and 50% related to hyperplasia.

3. Example: Bone marrow: normally should have 3X as many WBC's as RBC's. Slide shows few WBC's, and increased RBC's. Therefore, have RBC hyperplasia. This is not expected to be seen in Iron def anemia nor in thalassemias b/c in those, there a defect in Hb production. It is expected to be seen in chronic obstructive pulmonary dz (COPD) b/c the hypoxemia causes the release of hormone EPO (erythropoietin); which is made in the endothelial cells of the peritubular capillaries. So in the slide this is an example of EPO stimulated marrow.

4. Example: psoriasis on elbow –an example of hyperplasia (unregulated proliferation of squamous cells in the skin), leading to red skin, and raised red plaque, b/c excessive stratum corneum. This is why methotrexate works here, b/c it's a cell cycle specific for the S phase, and prevents the basal cells from proliferating.

5. Example: prostate gland and bladder – hyperplasia of prostate glands, it a hormone related hyperplasia; all hormone stimulated glands undergo hyperplasia, not hypertrophy. The wall of the bladder is too thick; b/c urine has to go out thru a narrow opening in the urethra, therefore the muscle has to work harder which leads to hypertrophy of smooth muscle cells of the bladder wall (more urine must go out against a greater force b/c of an increase in after load).

D. Metaplasia – replacement of one adult cell type by another

1. Example: Slide of an esophagus, part of if is all ulcerated away. On a section surrounding the ulcer (right at the edge of the muscosa) there are mucous secreting cells and goblet cells (these are grandular cells). These cells are not supposed to be present in lower esophagus; squamous cells should be there (not glandular cells). Metastatic grandular: Barrets esophagus is a precursor for adenocarcinoma. Adenocarcinoma has surpassed squamous cell carcinoma of mid-esophagus as the MC cancer of the esophagus. Therefore, GERD is the number one precursor to esophageal cancer (adenocarcinoma).

Audio file 4: Inflammation 2

2. Example: Lining of mainstem bronchus – ciliated columnar, pseudostatified columnar. In smokers, this would be an example of metaplasia would be squamous.

3. Example: There are increased goblet cells within mainstem bronchus of an old smoker, also see goblet cells in the terminal bronchial. Normally there are goblet cells in the mainstem bronchus but there are no goblet cells in the terminal bronchus, therefore this is an example of hyperplasia.

4. Example: Goblet cells in the stomach are abnormal (should be in the intestines, only). This is a glandular metaplasia, which is a precursor for adenocarcinoma of the stomach. H. pylori are a precursor for adenocarcinoma in the stomach. B/c H. pylori causes damage to pylorus and antral mucosa b/c it is a chronic gastritis which intestinal glandular metaplasia, which is a precursor for adenocarcinoma. MCC adenocarcinoma of the stomach = H. pylori.

5. Example: Cases where metaplasia causes an increased risk to caner:

a) Remember that if hyperplasia is left unchecked, could potentially lead to cancer. For example: in endometrial hyperplasia the MC precursor lesion to endometrial carcinoma due to unopposed estrogen. The exception is prostatic hyperplasia, which doesn't become cancer.

b) Metaplasia can also go through a process leading to cancer:

(1) In lung, ciliated columnar epithelium BECOMES squamous, therefore, this is called SQUAMOUS metaplasia; this will lead to squamous dysplasia, which then proceeds to cancer (squamous carcinoma);

(2) In distal esophagus, went from squamous to glandular epithelium b/c squamous epithelium cannot handle the acid, therefore it needs mucous secreting epithelium as a defense against cellular injury. However, the glandular metaplasia can go on to an atypical metaplasia, predisposing to adenocarcinoma of the distal esophagus.

(3) Parasites: 2 parasites produce cancer: clonesis sinesis leads to cholangiocarcinoma (Chinese liver fluke); and shistosoma hematoabia. The schistosomias hematobia causes bladder cancer by causing the transitional epithelium to undergo squamous metaplasia. This leads to squamous dysplasia, and then on to squamous cancer. Transitional epithelium leads to squamous epithelium (called metaplasia), then dysplasia, then on to cancer.

E. Dysplasia is really an atypical hyperplasia.

1. Example: Slide of a squamous epithelium is disorganized, with nuclei that are larger near the surface and the basal cell layer is responsible for the dividing; cells at top are bigger than the ones that are dividing, it has lack orientation. If it was found during a cervical biopsy in pt with HPV infection, or if it was found in the mainstem bronchus biopsy, you should be able to tell that it is dysplastic. Therefore dysplasia, whether glandular or squamous, is a precursor for cancer.

2. Example: There was a farmer with lesion on the back of his neck (can grow on any part of the body, due to sun exposure), which could be scraped off and grew back – actinic keratosis (aka solar keratosis) – is a precursor for sq. cell carcinoma of the skin. UV-b light damages the skin. Actinic keratosis does not predispose to basal cell carcinoma, even though basal cell carcinoma is the most common skin cancer.

CHAPTER TWO: INFLAMMATION

I. Acute Inflammation

A. Cardinal signs of inflammation

In the scenario with a bee sting: you will see redness (**Tubor**). The king of vasodilators is histamine and it vasodilates the arterioles. Therefore, histamine is responsible for the redness of acute inflammation (ie bee sting), and is working on arterioles. Now if we felt the area, it will be warm (**Calor** = heat), this is due to vasodilating the arterioles, which is caused by histamine. For example in endotoxic and septic shock, the skin is warm b/c you are vasodilated. **Tumor** is a raised structure caused by histamine. Histamine can lead to increased vessel permeability in the venules; is arterial thicker than venules? Yes. The venules are very thin; they basically have an endothelial cell with a basement membrane, all you have to is drill a hole through the BM and you are out. Therefore, increased vessel permeability occurs at the venule level, not the arterial level. Histamine contracts the endothelial cells, and leaves the BM bare, leading to increased vessel permeability, producing an exudate, and swelling of tissue, hence **tumor** of acute inflammation. The area may hurt (**Dolor** = pain) but hitamine does not have anything to do with this. Bradykinin is part of the kininogen system between factor 11 and Hageman factor 12. So when you activate the intrinsic pathway, you automatically activate the kininogen system. When you activate factor 12 (Hageman factor), it will activate 11 and the whole kininogen system. The end product is bradykinin. ACE degrades bradykinin. Complication of ACE inhibitor is angioedema. Also inhibit metabolism of bradykinin, which increases vessel permeability, producing the angioedema (swelling of the tissues). How bradykinin produces cough is not really understood. Bradykinin and PGE2 cause pain (**dolor**) and is the only one out of the four Latin terms of acute inflammation that is not due to histamine release.

B. Steps involved in Acute inflammation (this the normal sequence in acute inflammation)**:**

1. Emigration: includes margination, paveenting, rolling, adhesion, and transmigration

Neutrophils in circulation start to become sticky b/c of adhesion molecule synthesis. Endothelial cells begin to synthesize adhesion molecules. Eventatually, neutrophils will stick to endothelial cells, these steps are called pavmenting or margination. Then neutrophils look for bare basement membrane on the venules and then they drill a hole through it via type 4 collagenase. Cancer cells also have type 4 collagenase, that's how they metastasize. Cancer

cells attach to endothelial via adhesion molecules, usually against laminin in BM, and they have collagensae to get through the BM, therefore, cancer cells are pretty much like a neutrophil when invading tissue.

2. Chemotaxis:

When they pass BM of small venules, they emigrate but they have to know what direction to go. They get directions in a process called directed chemotaxis. C5a and LT-B4 (leukotriene B4) are the chemotactic agents. These chemotactic agents are also involved in making adhesion molecules on neutrophils). Therefore, they make adhesion molecules AND give direction by acting like chemotactic agents.

3. Phagocytosis via opsonization:

a) Example: in an acute inflammation with staph aureus, the bacteria are being processed by opsonins, which immobilize the particles on the surface of the phagocyte. The two main opsonins are IgG and C3b. They help with phagocytosis.

b) Example of an opsonization defect: Brutons agammaglobinemia: an x-linked recessive dz, where all the immunoglobulins are missing, including IgG. Therefore, MCC death in these pts is due to infection b/c cannot opsonize things. It produces hypogamma-globinemia, but the mechanism of infection is due to not having IgG to opsonize bacteria, therefore cannot phagocytose it.

Bacteria are opsonized by IgG and C3b, which means that neutrophils must have receptors for those. In acute inflammation the main cell is neutrophil and in chronic inflammation the main cell is macrophage/monocyte (monocytes become macrophages). These cells have to have receptors for these opsonins (IgG and C3b). Then they become phagocytosed or become phagolysomes. When they are phagocytosed, the lysosomes go to microtubules and empty their enzyme into this.

c) Example: In I-cell disease: in this dz, mannose residues cannot be phosphorylate in golgi apparatus therefore the enzymes are not marked with phosphorus, and the lysosome are empty.

4. Intracellular microbial killing:

a) Examples:
(1) Staph aureus in hottub surrounded by enzymes
(2)Chlamydia can get out of phagolysosome, mechanism unknown, but sometimes they have mucous and all kinds of things around them.

b) **O_2 dependent myeloperoxidase system** is the boards!!
Molecular O_2 is converted by NADPH oxidase, which is in the cell membrane of neutrophils and monocytes, but not macrophages. The most important cofactor is NADPH, which is synthesized in the pentose phosphate shunt. The enzyme responsible is glucose 6 phosphate dehydrogenase, which converts G6P into 6-phosphogluconate, generating NADPH and a neutralizing factor for free radicals (glutathione).

It is converting O_2 into a free radical, superoxide. Superoxide has an unpaired electron giving off energy, which is called a resp burst, which can be measured by radiation detectors; and by a negative NBT dye test. In the NBT test, you have a test tube, add the colorless NBT dye; and if neutrophils and monocytes are working normally, they will phagocytose it, will have a respiratory burst, and the free radical O_2 will cause the color to change to blue, indicating that the resp burst is working. If there is no color change, there is not a resp burst, therefore the pt has chronic granulomatous dz of childhood.

Free radical O_2 is converted by SOD (it's neutralizer) into peroxide. Peroxide itself could kill bugs, but it is used for another reason. Within the neutrophils and monocytes are reddish granules which are lysosomes, and are seen in the peripheral blood. Myeloperoxidase (one of the many enzymes in the granules) will catalyze the rxn. It will combine peroxide with chloride to from bleach. This **is the most potent bactericidal mechanism – O_2 dep myeloperoxidase system**, which is in NEUTROPHILS and MONOCYTES but NOT in macrophages, b/c macrophages lose the system when they convert from monocytes to macrophages and they use lysosomes to kill. Macrophages of the CNS are microglial cells, so the reservoir cell for CNS/AIDS is the microbial cell. Outside the CNS, it is the dendritic cell; it is a macrophage located in the lymph nodes.

c) In G6PD deficiency, infection is the MC precipitation of hemolysis b/c there is no NADPH, therefore there is no functioning O_2 dependent myeloperoxidase system, and therefore you are susceptible to infection, which will set of hemolysis of RBC'S.

d) Chronic granulomatous dz of childhood = X linked recessive dz where the mom gives the dz to the boy, and is an asymptomatic carrier, and they will transmit the dz to 50% of their son's. In this dz, there is a deficient activity of NADPH oxidase, and the NBT dye test is negative (doesn't show color of die), therefore no resp burst. Do they have superoxide? No. Peroxide? No. Myeloperoxidase? Yes. Chloride? Yes. Therefore, if they phagocytosed a bacteria that could make peroxide, and add it inside the phagolysosome, this is what the kid would need to kill the bacteria. These kids are missing PEROXIDE b/c there is no NADPH oxidase. ALL living organisms make peroxide (including ALL bacteria). However, not all bacteria contain catalase, which is an enzyme that breaks down peroxide. So, in chronic granulomatous dz, what can they and can't they kill? Cannot kill staph, but can kill strep. Why? B/c staph is Coagulase and CATalase "+"; so, ie, if it's staph. aureus and when it makes peroxide, it will also make catalase and neutralize it, therefore the child cannot kill staph, and will kill the kid. If it was a streptococcus organism that makes peroxide (does

not have catalase therefore peroxide can be used by the child), it adds what kid really needed to make bleach, and the bacteria is then wiped out. Therefore, can kill strep and not staph!

e) Myeloperoxidase deficiency: Do they have a resp burst? Yes b/c they have NADPH oxidase. Do they have peroxide? Yes. Do they have superoxide free radicals? Yes. Do they have chloride? Yes. Do they have myeloperoxidase? No. They have a normal resp burst and a normal NBT dye test, but they can't kill the bacteria b/c they cannot make bleach. This is called a myeloperoxidase defect. Other types of defects: (1) opsonization defects with brutons (missing IgG), C3 def's; (2) chemotactic defects where cells do not respond to chemotaxis; (3) microbiocidal defects, the defect in the ablility to kill bacteria, example: chronic granulmatous dz of childhood and myeloperoxidase deficiency are both microbiocidal dz, in that they cannot kill bacteria, but for different reasons. In myeloperoxidase def the problem is that they cannot make bleach (b/c of the missing enzyme), but do have resp burst, and is Autosomal recessive dz. In CGDz the problem is that they cannot make bleach either, but they have an ABSENT resp burst, and is a X-LINKED recessive dz.

f) Child has an umbilical cord that doesn't fall off when it should. When it was removed and looked at histologically, they did not see neutrophils in the tissue or neutrophils lining the small vessels. This is an adhesion molecule defect or beta 2 integrin defect. Umblilcal cord needs to have an inflammatory rxn involving neutrophils; they have to stick in order to get out. Therefore, if the neutrophils can't stick, they can't get out, and then they can't get rid of your umbilical cord – this is a classic adhesion molecule defect.

C. Chemical mediators:

1. Histamine: the king of chemical mediators of acute inflammation
   a) What does it do to arterioles? Vasodilates
   b) Venules? Increased vessel permeability

2. Serotonin:
   a) What amino acid makes serotonin? Tryptophan
   b) Is serotonin a neurotransmitter? Yes
   c) In a deficiency, you get depression (also decreased NE)
   d) a vasodilator and increases vascular permeability

3. Complement system: Anaphylatoxins – C3a, C5a. Function: stimulate mast cells to release histamine, leading to vasodilation and increased vessel permeablility. They also play a role in shock, b/c when there is inflammation the compliment system is activated, therefore there will be mast cells and histamine, therefore C3a, and C5a will both be there.

4. Nitric oxide – made mainly in endothelial cells, and is a potent vasodilator. It is used for treating pulmonary hypertension. It has a big time role in septic shock.

5. IL-1 associated with a fever, it is a pyrogen, therefore stimulates the hypothalamus to make PG's, which stimulate thermoregulatory system to produce fever. Aspirin works by inhibiting the synthesis of prostaglandins thereby reducing the fever.

6. Arachidonic acid metabolites:
   a) Corticosteroids inhibits Phospholipase A_2, therefore do not release arachidonic acid from phospholipids, therefore not making PG's or leukotrienes. This is the supreme antiflammatory agent b/c BOTH PG's and leukotrienes are blocked by blocking phospholipase A_2. Arachidonic acids make linoleic acid (omega 3), which is found in fish oils and walnuts. It is very good for you b/c it acts like aspirin, and blocks platelet aggregation, and that's how omega 3 protects your heart.

   b) Lipoxygenase pathway: Zileutin blocks 5-lipoxgenase, other drugs act by blocking the receptors, example: zirkufulast, etc. Leukotriene (LT) C4, D4, E4 (the slow reactor substances of anaphylaxis) seen in bronchial asthma. They are potent bronchoconstrictors; therefore it can be seen why zileutin works well in asthma b/c it blocks the leukotrienes, including these (LT-C4, D4, and E4). LT B4 is an adhesion molecule in chemotaxis.

   c) Cyclooxygenase pathway: Aspirin blocks cycoloxygenase, irreversibly in platelets. PGH2: where everything seems to be derived from. PGI2: derives from endothelial cells, it's also called prostacyclin synthase; is a vasodilator and inhibits platelet aggregation (exact the opposite of TxA2). Thrombaxane A2 (the enemy of PGI2) is made in the platelet; it's a vasoconstrictor, a bronchoconstrictor, and promotes platelet aggregation. What drug blocks thrombaxane synthase and is used to stress testing for CAD? Dipyrramidal blocks the enzyme, TxA2 synthase, therefore does not have to perform a treadmill stress test, all you have to do is use the drug dipyrramidal.
   PGE2: vasodilator in kidney; keeps patent ductus patent in baby heart; makes the mucous barrier in GI (stomach) thereby preventing ulcers; can cause dysmenorrhea woman and increased uterine contractility, and it an abortifactant, to get rid of fetal material.

   d) COX 2-make sure you know how this works!

   e) Corticosteroids blocks phospholipase A2, and it also decreases adhesion molecule synthesis, along with other steroids like epinephrine and NE. Decreased adhesion molecule synthesis, will lead to increased neutrophils on CBC; in immuno, 50% neutrophils are stuck to the endothelial vessels, and the other 50% are circulating, therefore, decreasing adhesion molecule synthesis will lead to doubled WBC (b/c the 50% of neutrophils that were stuck are now circulating). Corticosteroids destroy B-cells b/c they are lymphocytotoxic. Mechanism: decrease WBC's (B and T cells) via apoptosis; therefore, corticosteroids are the signal to activate the caspasases. Eosinophils, mainly seen in type one

HPY rxn, corticosteroids decrease them. When on corticosteroids, the only thing that is increased is neutrophils, via decreased adhesion molecule synthesis. Lymphocytes and eosinophils are decreased. Example: If have Addisons, do not have cortisol, therefore the neutrophil ct decreases and the eosinophil count will increase. Example: a person with MI with an 18,000 CBC most of which are neutrophils. Mechanism: Epinephrine decreases adhesion molecule sythesis and neutrophil count goes up.

D. Electron microscopy of inflammatory cells:

1. In lung, type II pneomocyte (black dots are lysosomes).
Lamellar bodies – structures where lecithin and phosphotidyl choline is located; if ask where macrophage, is, will ask which makes surfactant.

2. Monocyte: single nucleus with a grayish cytoplasm – has scavaged; can form foam cell in atherosclerotic plaque b/c it has phagocytized oxidized LDL's (which is a free radical); Vit E neutralizes oxidized LDL.

3. Lymphocyte – all nucleus and scant cyptoplasm, prob a T cell (60% of peripheral blood lymphocytes are T cells); ratio of helper to suppressor: CD4:CD8 is (2:1), therefore, more likely to be a Helper T cell, then a suppressor T-cell, and B cells (20%) are least likely.

4. RER looks like a thumbprint, have ribo's on it, and likes to make proteins, like Ig's (therefore it is a plasma cell). Multiple myeloma – has eccentrically located nucleus, cytoplasm is always sky blue, making plasma cells ez to recognize. Plasma cells are derived from B cells, and located in the germinal follicle.

5. Granules – eosinophil (have a red color similar to color of RBC's) – have crystals in the granules. Eosinophils are the only inflammatory cell that has crystals in the granules. They are called Charcot-Leiden crystals when it's seen in the sputum of asthmatic patient. They are degenerated eosinophils in sputum of asthmatic, and have formed crystals that look like spear heads. Basophils have granules that are more purplish and darker, while basophils have darker colors.

6. Mech for killing invasive helminthes–Type II HPY–major basic protein is involved. Remember that shistotosome eggs are coated by IgE Ab's. Eosinophils have IgE receptors; therefore, eosinophils hook into the IgE receptor and release chemicals; the main one released is major basic protein, which destroys the helminth, which is type II HPY, b/c it is a cell hooking into an Ab on the target cell. The effector cell is Type II HPY rxn is the eosinophils; don't get confused with Type I HPY rxn where the effector cell is the MAST CELL, and they release histamine (an eosinophil chemotactic factor), therefore they are invited to area of type I HPY b/c they have histaminase and arylsulfatase, which neutralizes leukotrienes. The purpose of eosinophils in type I HPY is to knock off chemical mediators produced in rxn; however, when an eosinophil kills an invasive helminth, it does so via type II HPY.

E. Cluster designations:

Helper t cell = CD4
Cytotoxic T cell = CD8
Marker for Ag recognition site for all T cells is CD3
Marker for histiocytes (including langerhan's cells) is CD1
Marker for MC leukemia in children = CD10 (calla Ag); positive B-cell lymphoma
CD15 and 30 = RS cell
CD21, Only on B cells – Epstein barr virus; hooks into CD21 on B cells, and actually the atypical lymphocytes are not B-cells but T-cells reacting to the infected B-cells.
Burkitts is a B cell lymphoma
CD45 is found on all leukocytes, is a common antigen on everything

F. Fever – IL-1 is responsible and PGE2 (this is what the hypothalamus is making) which stimulates the thermoregulatory center. Fever is good! It right shifts the O_2 dissoc curve. Why do we want more O_2 in the tissues with an infection? B/c of O_2 dependent myeloperoxidase system. Therefore, with antipyretics it's bad b/c thwarting the mechanism of getting O_2 to neutrophils and monocytes to do what they do best. Also, hot temps in the body are not good for reproduction of bacteria/viruses.

II. Types of inflammation (scenarios)

A. post partum woman, with pus coming out of lactiferous duct – this is staph aureus – supplerative inflammation

B. Bone of child with sepsis, on top of the bone, was a yellowish area, and it was an abscess – osteomyelitis – staph. aureus; if the kid had sickle cell, it is salmonella; why at metaphysis of bone? B/c most of blood supply goes here, therefore, mechanism of spread is hematogenous (therefore comes from another source, and then it gets to bone).

C. Hot, spread over face – cellulitis due to strep (play odds!) group A pyogenes
(called erysipilis, another name for cellulitis)

D. Diphtheria = psuedomembrane (corynebacterium diphtheria), a gram + rod, that makes an exotoxin, messing up ribosylation of protiens via elongation factor 2, the toxin damages mucosa/submucosa, producing a pseudomembrane; when bacteria doesn't invade, produces a toxin that damages the membrane; clostridium difficile also does this. It also produeces a pseudomembrane and a toxin, which we measure in stool to make the dx. Therefore, the answer is C. difficle.

E. Fibrinouis pericarditis, usually with increased vessel permeability; seen in (1)lupus, leading to friction rub; also seen in (2) the first week of MI, and then again 6 weeks later in dresslers's syndrome, (3) seen in Coxsackie

F. MC organism producing infection in third degree burns = pseudomonas auriginosa. Color of pus: green due to pyocyanin.

G. Basal cell layer on both sides of clot, proliferate, and go underneath it to clot. In a primary wound it's usually sealed off in 48 hrs (ie appendectomy). Key to wound healing is prescence of granulation tissue. Fibronectin is a very important proteoglycan and is involved in the healing of the wound. Fibronectin is an important adhesion agent and chemotactic agent, inviting fibroblast in helping healing process. The granulation tissue starts at day 3 and is on its prime by day 5. If you ever picked at a scar and it bleed like mad and you try to stop it but it still bleed like mad, that's granulation tissue. No granulation tissue means no healing of a wound. Type of collagen in initial stage of wound repair = type 3; type 4 collagen seen in BM; type 1 – very strong tensile strength; seen in bone, skin, tendons, ligaments.

After a few months, after months, the collagen type 3 is broken down by collagenases, and a metallic enzyme converts type 3 into type 1. Zinc is part of the metallic enzyme, this is why in a pt with zinc deficiency has poor wound healing b/c it screws up the collagenase (must replace type 3 with type 1). Max tensile strength after 3 months = 80%. MCC poor wound healing = infection

H. Ehlers Danlos – defect in collagen due to syn/breaking down; have poor wound healing.

I. marfan – defect in fibrilin; also have poor wound healing

J. Pt with scurvy – defect in hydroxylation of two aa's – proline and lysine via ascorbic acid. Remember it's a triple helix; what makes the triple helix stick together and increase tensile strength? Crossbridges. When you crossbridge things, they anchor into areas where you have hydroxylated proline and lysine. Therefore have weak abnormal collagen in scurvy b/c there are no crossbridges to attach, leading to not being able to heal wounds, hemorrhaging, hemarthroses….collagen has weak tensile strength b/c cannot crossbridge.

Audio file 5: Fluid and Hemodyn1

K. Granulation tissue with a lot of blood vessels due to lot of fibroblast G, with inflammatory cells from plasma cells and lymphocytes, necessary for wound healing (rich vascular tissue, which is absolutely essential for normal wound healing).

L. Keloid (hypertrophic scar) = excess in type 3 collagen deposition; which causes a tumor looking lesions, esp in blacks. In a white kid – keloid to due to third degree burns. In another example: in a chronically draining sinus tract of the skin, they tried to put antibiotics on it (didn't work), there was an ulceration lesion at the orifice of this chronically draining tract, and nothing worked. What is it? The answer is squamous cell carcinoma due to a lot of turnover; type 3 converted to type 1, and fibroblasts are involved. A lot of cell division occurring, which can presdispose to mutations and cancer, esp squamous cell cancer. Squamous cancer is imp b/c chronically draining sinus tracts, and predisposes to sqamous cell carcinoma. Hyperplasia predisposes to squamous cell carcinoma.

III. Chronic inflammation

A. Difference in Immunoglobulins:
   1. Acute Inflammation: IgM = main Ig first, and then IgG
      IgM = main Ig; need a lot of complement components in healing process; IgM is the most potent activator, and have activation of complement pathway (all the way for 1-9); IgM has 10 activating sites (pentamer).

      IgG can activate the classical system, but does NOT go passed C3 and stops and does not go onto C5-9.
      After 10 days, there is isotype switching, and the mu heavy chain is spliced out (mu chain defies specificity of an Ig); it splices in a gamma heavy chain, and IgG is made via isotype switching
   2. Chronic inflammation: IgG (as main Ig – IgM is coverted to IgG immediately)

B. Difference in Cell Types:
   1. Acute inflammtions = neutrophil
   2. Acute allergic reactions= eosinophils (mast cells are in tissues)
   3. Viral infections = lymphocytes are the main inflammatory cells
   4. Chronic inflammations = monocytes/macrophages are imp. And see a lot of plasma cells and lymphocytes; do not see pus-exudative (this is in acute inflamm – increased vessel permeability, and increased emigration of neutrophils into interstitial tissue, a protein rich fluid with >3 grams/dL, with a protein rich fluid = pus). Example: Cholecystis.

C. Type IV Hypersensitivity Reaction:
   Another example: Granuloma = chronic inflammation (never acute); ie caseious necrosis in someone with TB; roundish, pink, multinucleated giant cells = granulomas; pathogenesis = type IV hypersentistivity reaction – delayed HPY. The main actors are cytoxic T cells; when they kill neoplastic, virally infected cells, these are also type IV HPY (no Ab's involved). Poison ivy = type IV HPY. Back to TB infection, aleovlar macrophage phagocytoses it, and there is lymphohemotogenous spread; meanwhile the macrophage is processing the Ag. Then after weeks, it presents it to helper T cells. Therefore, the key players in Type IV hypersensitivity rxn are macrophages which process that Ag and presents that Ag via class II MHC sites to the helper T cells. These helper T-cells release cytokines: gamma IFN and macrophage inhibitory factor. Gamma IFN will activate the macrophage to kill the TB, Cryptococcus, histoplasmosis, etc. Therefore the gamma IFN is the trigger to active the macrophage; macrophage cannot kill without the activation from gamma IFN; b/c systmemic fungi and TB

have lipid in the cell wall, this leads to caseous necrosis. All the pink staining cells are 'epthiloid', which are activated macrophages (which have been activated by gamma IFN); when they die, they die in style – they fuse together and form multinucleated giant cells (like their 'gravestone'). Therefore, epitheloid cells are fused macrophages; black dots are helper T cells.

There are two types of helper T-cell:

a. Subset 1: involved in Type IV (delayed type) HPY; macrophages have IL-12; when it is secreted, the subset 1 helper T cells are presented with the antigen; then, subset 1 become MEMORY T cells. IL-12 is involved in activating the memory of subset 1 helper t cells. Most people in their primary dz usually recover with no problems, but the granulomas can calcify, as seen on x-ray. A calcified granuloma is not dead b/c they are resistant to dying. Therefore, most cases of secondary TB are due to reactivation TB. Granulomas necrosis is due to reactivation.

"+" PPD (purified protein derivative) – injected into the skin; the macrophage of the skin is a langerhan's cell (histiocyte) (marker: CD 1) – which have birbeck granules-look like tennis rackets on EM. They phagocyotose the Ag (the PPD), and process it very quickly; they present it to helper subset 1, which has memory of previous exposure. Therefore, it hooks in the MHC class II Ag sites (as all immune cells do), and once the Ag (PPD processed by the langerhan's cell) is presented, the helper T cell releases the cytokines producing the inflammatory rxn with induration called the "+" PPD.

Correlation: older people usually don't host a very good Type IV hypersensitity rxn: they have a less response to "+" PPD; therefore have to do a double test on them. In pt with AIDs, may not get any rxn. They don't have enough helper T-cells therefore don't have granuloma formation. Macrophage inhibitory factor keeps macrophages in that area; therefore, with HIV, b/c the helper t cell ct is decreased, you don't form granulomas at all. Therefore, they will have MAI (organisms) all over the body without granulomas b/c helper T cells are decreased. When you do "+" PPD, 5 mm induration is enough to say it's positive. .

IV. Tissue Repair

Scar tissue (b/c its permanent tissue); scar tissue (fibrous tissue) does not contract; therefore, if you have more scar tissue to free wall of left vetricle will lead to decreased ejection fraction (which is stroke volume divided by EDV).

A. Response of Kidneys to Injury: Kidney will form scar tissue; medulla is most susceptible to ischemia (b/c least amount of blood supply). What part of nephron most susceptible to tissue hypoxia? 2 places:

1. Straight portion of prox tubule b/c most of oxidative metabolism is located there, with brush borders – this is where most of reabsorption of Na, and reclaiming of bicarb is there.

2. Medullary segment of thick ascending limb – where the Na/K-2Cl pump is – which is where loop diuretics block. The Na/K-2Cl pump generates free water. The two type of water in urine: obligated and free. If the water is obligated, then the water is obligated to go out with every Na, K, and Cl (concentrated urea). Basically 20 ml's of obligated water for every Na, K, Cl (it's obligated) via Na/K/2Cl pump. The ADH hormone absorbs free water b/c the pump generates free water.

Let's say you absorb one Na, how much free water is left behind in the urine? – 20 mls; then reabsorbed another K, that is another 20, so its up to 40; another 2 Cl's are reabsorbed which is another 40; therefore, for absorbing one Na, one K, and 2 Cl's, you have taken 80 mls of free water from the urine – this is free water that is generated; its is this pump that loop diuretics block, which is in the thick ascending limb of the medullary segment.

B. Lung repair cell is type II pneumocyte (can also repair type I pneumocytes); it also synthesizes surfactant.

C. CNS – repair cell is the astrocyte; the astrocyte proliferates (b/c it's a stable cell, not a neuron), that can proliferate and produces protoplasmic processes – called gliosis (rxn to injury in the brain, which is due to astrocyte proliferation); this is analogous to fibroblasts laying collagen type 3 in the wound.

D. PNS – wallarian degeneration is the mech of axonal regeneration
In PNS, have Schwann cells, while in the CNS, have oligodendrocytes
(both make myelin). Tumor Schwann cell = schwannoma; if it involves CN VIII it is called acoustic neuroma. What genetic dz that is auto dominant has association? Neurofibromatous.

(Side note: myasthenia gravis – tensilon injection will increase Ach in synapses in eyelids, and myasthenic crisis will end)

V. Extra Side notes and Review of Inflammation:

A. ESR – putting whole blood into cylinder and see when it settles. The higher the density, or weight, therefore settle pretty quick and therefore have a increase sedimentation rate. When stuck together and looks like coins = roulouex. When aggregated together = increased sed rate, which is increased IgG and fibrinogen (includes every acute and chronic inflammation there is. What causes RBC's to clump – IgM, b/c the neg charge normally keeps RBC's from stick to e/o. IgM is a lot bigger; cold agglutinins are associated with IgM ab, leading to agglutinin. This is why in cold whether, you get Raynaud's phenomenon (lips, nose, ears, toes, fingers turn blue). The IgM ab can cause cold agglutinins, leading to ischemia. Another type of clumping of IgM are Cryoglobulins – Ig's congeal in cold weather; IgM ab's do the same thing. High assoc of hep C with cryoglobulins. Mult myeloma = increased esr b/c increased IgG; with waldenstroms, will see increased IgM (Waldenstrom's Macroglobemia).

B. Acute appendicitis – get CBC, and want to see absolute neutrophilic leukocytosis, meaning that you have an increase of neutrophils in the peripheral blood; also looking for toxic granulation, and a LEFT SHIFT. Assuming you start from myeloblast on

the left, and eventually form a segmented neutrophil on the right; normally go left to right on maturation; therefore, with a left shift, its means that we go back to immature neutrophils; the definitions is greater than 10% band neutrophils is considered a LEFT SHIFT (all the neutrophils are bands); if you have just one metamyelocyte or one myelocyte, its is automatically considered a LEFT SHIFT. In acute appendicitis, there is an absolute increase in neutrophils, with toxic granulation and a left shift.

C. Most potent system for killing bugs = O_2 dependent myeloperoxidase system;
Myeloperoxidase is located in azurophilic granules, which are lysosomes.
Want a lot of lysosome in an acute inflammatory rxn, b/c therefore there is more myeloperoxidase around for killing bugs – this is what toxic granulation.
Therefore, toxic granulation ensures that there is enough myeloperoxidase to work that potent system to kill bugs (O_2 dep myeloperoxidase system).

CHAPTER 3: FLUID AND HEMODYNAMICS

I. Edema – excess fluid in the interstitial space, which is extracellular fluid (ECF); this is outside the vessel

A. Types of Edema

1. Non-Pitting edema – increased vessel permeability with pus in the interstial space (pus=exudates). Lymphatic fluid is another type of non-pitting edema. Blockage of lymphatics leads to lymphatic fluid in the interstial space. Pits early, but eventually becomes nonpitting. Exudates and lymphatic fluid does not pit.

2. Pitting edema – transudate with right heart failure, swelling of the lower extremities, fluid in the interstial space. Transudate does pit.

3. So there are three things that cause edema: exudates, lymphedema, and transudate, and transudates are the only one that has pitting edema.

B. Transudate/Pitting Edema

Transudate deals with starling forces:

1. What keeps fluid in our blood vessels? Albumin, and this is called oncotic pressure. 80% of our oncotic pressure is related to the serum albumin levels. Anytime there is hypoalbuminemia then we will have a leaking of a transudate (protein of less than 3 g/dL) leaking into interstial space via capillaries and venules (pitting edema);

2. Normally, hydrostatic pressure is trying to push fluid out. Therefore, in a normal person, oncotic pressure is winning. Therefore, a decrease in oncotic pressure and an increase in hydrostatic pressure will lead to transudate (pitting edema).

3. Albumin is made in the liver. With chronic liver dz (cirrhosis), have a decreased albumin level. Can you vomit it out? No. Can crap it out (malabsorption syndrome), or can pee it out (nephrotic syndrome), can come off our skin (3rd degree burn b/c losing plasma), another possibility of low protein ct (low-intake) is seen in kids – Kwashiorkor – kid has fatty liver and decreased protein intake, leading to low albumin level.

4. Examples:

a. Person with MI 24 hrs ago and he died and he has fluid coming out– transudate b/c increased hydrostatic pressure and left HF due to MI so things backed up into the lungs. B/c the CO decreased, the EDV increases and pressure on left ventricle increases, and the pressure is transmitted into the left atrium, to the pul vein, keeps backing up, and the hydrostatic pressure in the lung approaches the oncotic pressure, and a transudate starts leaking into the interstitial space, which leads to activation of the J receptor, which will cause dyspnea. Leads to full blown in alveoli and pulmonary edema, which is what this is.

b. venom from bee sting on arm leads to exudate due to anaphylactic rxn (face swelled), with histamine being the propagator, and type one HPY, causing tissue swelling. Rx – airway, 1:1000 aqueous epinephrine subcutaneously

c. cirrhosis of liver, with swelling of the legs: transudate, mechanism: decreased oncotic pressure b/c cannot syn albumin, and increased hydrostatic pressure b/c portal HTN; there is cirrhosis of the liver, and the portal vein empties into the liver; in this case, it cannot, and there is an increase in hydrostatic pressure, pushing the fluid out into the peripheral cavities (so there are 2 mech for acites). Pitting edema in legs: decreased in oncotic pressure

d. Pt with dependent pitting edema: pt has right heart failure, and therefore an increase in hydrostatic pressure; with right heart failure, the blood behind the failed right heart is in the venous system; cirrhosis of liver is due to decrease in oncotic pressure.

e. modified radical mastectomy of that breast, with nonpitting edema: lymphedema. Other causes – w. bancrofti, lymphogranulomon venarium (subtype of chylamdia trachomata– scarring tissure and lymphatics, leading to lymphedema of scrotum lymphatic). Inflammation carcinoma of breast (p'eau de orange of the breast) deals with dermal lymphatics plug with tumor; excess leads to dimpling, and looks like the surface of an orange. MCC lymphedema = postradical mastectomy; can also run risk of lymphangiosarcoma.

II. Renal Physio

A. ECF/ICF
ECF (1/3) = extracellular fluid of two compartments – vascular (1/3) and interstitial (2/3)
ICF (2/3) = intracellular fluid compartment

Example: how many liters of isotonic saline do you have to infuse to get 1 liter into the plasma? 3 Liters (2/3:1/3 relationship); 2 liters in interstial space, and 1 L would go to the vascular space; it equilibrates with interstial/vascular compartments.

B. Osmolality = measure of solutes in a fluid; due to three things: Na, glucose, and blood urea nitrogen (BUN) – urea cycle is located in the liver, partly in the cytosol and partly in the mitochondria; usually multiply Na times 2 (b/c one Na and one Cl).

Audio file 6: Fluid and Hemodyn 2

Normal Na is 135-140 range, times that by 2 that 280. For glucose, normal is 100 divide that by 18, let's say it's roughly 5, so that's not contributing much. BUN: located in the liver, part of the cycle is in the cytosol and part of it is in mitochondria. The urea comes from ammonia, that's ammonia is gotten rid of, by urea. B/c the end product of the urea cycle is urea. The normal is about 12; divide that by 3, so we have 4. Therefore, in a normal person Na is controlling the plasma osmolality. To measure serum osmolality: double the serum Na and add 10.

C. Osmosis
2 of these 3 are limited to the ECF compartment; one can equilibrate between ECF and ICF across the cell membranes – urea; therefore, with an increased urea, it can equilibrate equally on both sides to it will be equal on both sides; this is due to osmosis. B/c Na and glucose are limited to the ECF compartment, then changes in its concentration will result in the movement of WATER from low to high concentration (opposite of diffusion – ie in lungs, 100 mmHg in alveoli of O_2, and returning from the tissue is 40 mmHg pO_2; 100 vs. 40, which is bigger, 100 is bigger, so via diffusion, O_2 moves through the interspace into the plasma to increase O_2 to about 95mmHb). Therefore, in diffusion, it goes from high to low, while in osmosis, it goes from low to high concentration.

1. Example: In the case with hyponatremia – water goes from ECF into the ICF, b/c the lower part is in the ECF (hence HYPOnatremia); water goes into the ICF, and therefore is expanded by osmosis. Now make believe that the brain is a single cell, what will we see? cerebral edema and mental status abnormalities via law of osmosis (the intracellular compartment of all the cells in the brain would be expanded)

2. Example: hypernatremia – water goes out of the ICF into the ECF, therefore the ICF will be contracted. So in the brain, it will lead to contracted cells, therefore mental status abnormalities; therefore, with hypo and hypernatremia, will get mental status abnormalities of the brain.

2. Example: DKA – have (1000mg) large amount blood sugar. Remember that both Na and glucose are limited to the ECF compartment. You would think that glucose is in the ICF but it's not. You think that since glycolysis occurs in the cytosol therefore glucose in the ICF (again its not) b/c to order to get into the cell (intracellular), glucose must bind to phosphorus, generating G6P, which is metabolized (it's the same with fructose and galactose, which are also metabolized immediately, therefore, there is no glucose, fructose, or galactose, per se, intracellularly). So, with hyperglycemia, there is high glucose in the ECF, so water will move from ICF to ECF. Therefore, the serum Na concentration will go down – this is called dilutional hyponatremia (which is what happens to the serum sodium with hyperglycemia).

Therefore the two things that control water in the ECF are Na and glucose; but a normal situation, Na controls. Urea does not control water movements b/c its permeable, and can get through both compartments to have equal concentrations on both sides.

D. Tonicity – isotonic state, hypotonic state, and hypertonic state
We have all different types of saline: Isotonic saline, hypotonic saline (1/2 normal saline, ¼ normal saline, 5% dextrose in water), and hypertonic saline (3%, 5%); normal saline is 0.9%. We are referring to normal tonicity of the plasma, which is controlled by the serum Na. These are the three types of tonicity (iso, hypo, and hyper). Serum Na is a reflection of total body Na divided by total body H_20. For example: hypernatremia is not just caused by increased total body Na; it can also be caused by decreasing total body water with a normal total body Na, therefore there is an increase in serum Na concentration. It is really a ratio of total body Na to total body H_20. To determine serum Na, just look at serum levels. With different fluid abnormalities, can lose or gain a certain tonicity of fluid.

1. **Isotonic loss of fluid** – look at ratio of total body Na and water; in this case, you are losing equal amounts of water and Na, hence ISOtonic. This fluid is mainly lost from the ECF. The serum Na concentration is normal when losing isotonic fluid. ECF would look contracted. There would be no osmotic gradient moving into or out of the ECF. Clinical conditions where there is an isotonic loss of fluid: hemorrhage, diarrhea.

If we have an **isotonic gain**, we have in equal increase in salt and water; ie someone getting too much isotonic saline; normal serum Na, excess isotonic Na would be in the ECF, and there would be no osmotic gradient for water movement.

2. **Hypotonic solutions** – by definition, it means hyponatremia. Hypoglycemia will not produce a hypotonic condition. MCC of low osmolality in plasma is hyponatremia. How? Lose more salt than water, therefore, serum Na would be decreased. If losing more salt than water, kidney is probably the location of where/why it is happening. Main place to deal

with sodium (either to get rid of it or to get it back) is in kidney, esp when dealing with diuretics (furosemides and HCTZ). The tonicity of solution you lose in your urine is HYPERtonic, so that's how you end up with hyponatremia with a hypotonic condition. ECF concentration is low with hyponatremia, therefore the water will move into the ICF compartment. (Osmosis- remember low to high)

Example: If you gained pure water, and no salt, you have really lowered your serum Na: MCC = SIADH – in small cell carcinoma of the lung; you gain pure water b/c ADH renders the distal and the collecting tubule permeable to free water. With ADH present, will be reabsorbing water back into the ECF compartment, diluting the serum Na, and the ECF and ICF will be expanded. The ECF is expanded due to water reabsorption, and the ICF is expanded b/c it has a high concentration levels (its levels are not diluted). This can lead to mental status abnormalities. Therefore, the more water you drink, the lower your serum Na levels would be. The treatment is by restricting water. Don't want to restrict Na b/c the Na levels are normal. When ADH is present, you will CONCENTRATE your urine b/c taking free water out of urine; with absent ADH, lose free water and the urine is diluted. Therefore, for with SIADH, water stays in the body, goes into the ECF compartment, and then move into the ICF compartment via osmosis. The lowest serum sodium will be in SIADH. On the boards, when serum Na is less than 120, the answer is always SIADH. Example: pt with SIADH, not a smoker (therefore not a small cell carcinoma), therefore, look at drugs – she was on chlorpropramide, oral sulfylureas produce SIADH.

Example: Gain both water and salt, but more water than salt, leading to hyponatremia – these are the pitting edema states – ie RHF, cirrhosis of the liver. When total body Na is increased, it always produces pitting edema. What compartment is the total body Na in? ECF What is the biggest ECF compartment? Interstial compartment. Therefore, increase in total body Na will lead to expansion of interstial compartment of the ECF, water will follow the Na, therefore you get expansion via transudate and pitting edema; seen in right HF and cirrhosis.

Example: hypertonic loss of salt (from diuretic) leads to hyponatremia

Example: SIADH (gaining a lot of water) leads to hyponatremia

Example: gaining more water than salt will lead to hyponatremia: pitting edema

3. **Hypertonic state** – by definition, have too much Na (hypernatremia) or have hyperglycemia (ie pt with DKA has a hypertonic condition, which is more common than hypernatremia). With hypernatremia, what does ICF look like? It will always be contracted or shrunken.
Primary aldosteronsim – gain more salt and water.

Diabetes insipidus – Lose pure water (vs. gaining pure salt in SIADH). If you lose more water than salt in the urine, you have osmotic diuresis – mixture. When there is glucose and mannitol in the urine, you're losing hypotonic salt solution in urine.

Example: Baby diarrhea = hypotonic salt solution (adult diarrhea is isotonic), therefore, if baby has no access to water and has a rotavirus infection, serum sodium should be high because losing more water than salt, leading to hypernatremia. However, most moms give the baby water to correct the diarrhea; therefore the baby will come in with normal serum Na or even hyponatremia b/c the denominator (H_2O) is increased. Treatment is pedialyte and Gatorade – these are hypotonic salt solution (just give them back what they lost). What has to be in pedialyte and what has to be in Gatorade to order to reabsorb the Na in the GI tract? Glucose b/c of the co-transport. With the co-transport, the Na HAS to be reabsorbed with glucose or galactose. Example: cholera, in oral replacement, need glucose to reabsorb Na b/c co-transport pump located in the small intestine. Gatorade has glucose and sucrose (which is converted to fructose and glucose).

Sweat = hypotonic salt solution; if you are sweating in a marathon, you will have hypernatremia

E. Volume Compartments

Arterial blood volume is same as stroke volume and CO (cardiac output). When CO decreases, all physiologic processes occur to restore volume. With decrease CO (ie hypovolemia), oxygenated blood will not get to tissues, and we can die. Therefore, volume is essential to our bodies.

We have baroreceptors (low and high pressure ones). The low pressure ones are on the venous side, while the high pressure ones are on the arterial side (ie the carotids and arch of aorta). They are usually innervated by CN 9 and 10 (the high pressure ones). When there is a decrease in arterial blood volume (decreased SV or CO), it will under fill the arch vessels and the carotid; instead of 9^{th} or 10^{th} nerve response, you have a sympathetic NS response, therefore catecholamines are released. This is good b/c they will constrict the venous system, which will increase blood returning to the right side of the heart (do not want venodilation b/c it will pool in your legs). Catecholamines will act on the beta adrenergic receptors on the heart, which will increase the force of contraction, there will be an increase in stroke volume (slight) and it will increase heart rate ("+" chronotropic effect on the heart, increase in systolic BP). Arterioles on the systemic side: stimulate beta receptors in smooth muscle. Diastolic pressure is really due to the amount of blood in the arterial system, while you heart is filling with blood. Who controls the amount of blood in arteriole system, while your heart is filling in diastole? Your peripheral resistance arterioles – that maintains your diastolic blood pressure. So, when they are constricted, very little blood is going to the tissues (bad news); good news: keep up diastolic pressure – this is important b/c the coronary arteries fill in diastoles. This is all done with catecholamines. Renin system is activated by catecholamines, too; angiotensin II can vasoconstrictor the peripheral arterioles (therefore it helps the catecholamines). AG II stimulates 18 hydroxylase, which converts corticosterone into aldosterone, and stimulates aldosterone release, which leads to reabsorption of salt and water to get cardiac output up.

With decreased SV, renal blood flow to the kidney is decreased, and the RAA can be stimulated by this mechanism, too. Where exactly are the receptors for the juxtaglomerlur apparatus? Afferent arteriole. There are sensors, which are modified smooth muscle cells that sense blood flow. ADH will be released from a nerve response, and pure water will increase but that does not help with increasing the cardiac output. Need salt to increase CO.

Example: bleeding to death and there is a loss of 3 L's of fluid – how can you keep BP up? Give normal saline is isotonic therefore the saline will stay in the ECF compartment. Normal saline is plasma without the protein. Any time you have hypovolemic shock, give normal saline to increase BP b/c it stays in the ECF compartment. Cannot raise BP with ½ normal saline or 5% dextrose; have to give something that resembles plasma and has the same tonicity of plasma. Normal saline is 0.9%.

Peritubular capillary pressures: you reabsorb most of the sodium in the proximal tubule (60-80%). Where is the rest absorbed?; in the distal and collecting tubule by aldosterone. The Na is reabsorbed into the peritubular capillaries. Starling forces in the capillaries must be amenable to it. Two starling forces: oncotic pressure (keeps fluids in the vessel) and hydrostatic (pushes fluids out of vessel).

Example: When renal blood flow is decreased (with a decreased SV and CO), what happens to the peritubular capillary hydrostatic pressure? It decreases. Therefore, the peritubular oncotic pressure is increasing (ie the force that keeps fluids in the vessel), and that is responsible for reabsorption of anything into the blood stream from the kidney. This is why PO (peritubular oncotic pressure) > PH (hydrostatic pressure of peritubular capillary), allows absorption of salt containing fluid back into blood stream into the kidney.

Tonicity of fluid reabsorbing out of proximal tubule is isotonic (like giving normal saline). ADH is reabsorbing isotonic salt solution, but not as much as the proximal tubule. ADH contributes pure water, therefore, with all this reabsorption you have an isotonic sol'n add the ADH effect and the pt becomes slightly hyponatremic and hypotonic, therefore absorbs into the ECF compartment when there is a decreased CO.

Opposite Example: increased SV, and increase arterial volume, will lead to stretch of baroreceptors (innervated by 9th and 10th nerve), and a parasympathetic response will be elicited, instead of a sympathetic response. There will not be any venuloconstriction nor any increase in the force of contraction of the heart. This is fluid overload; therefore we need to get rid of all the volume. There is increased renal blood flow, so the RAA will not be activated. Fluid overload does not ADH be released. The peritubular hydrostatic pressure is greater than the oncotic. Even of the pt absorbed salt, it wouldn't go into the blood stream, and it would be pee'd out. Therefore pt is losing hypotonic salt solution with increased in arterial blood volume.

Need to know what happens if there is decreased CO, what happens when ANP is released from the atria, and give off diuretic effect; it wants to get rid salt. ANP is only released in volume overloaded states.

Example: pt given 3% hypertonic saline: what will happen to osmolality? Increase. What will that do to serum ADH? Increase – increase of osmolality causes a release of ADH.
Example: What happens in a pt with SIADH? decreased plasma osmolality, high ADH levels.
Example: What happens in a pt with DI? no ADH, therefore, serum Na increases, and ADH is low

How to tell total body Na in the pt: Two pics: – pt with dry tongue = there is a decrease in total body Na, and the pt with indentation of the skin, there is an increase in total body Na. Dehydration: Skin turgur is preformed by pinching the skin, and when the skin goes down, this tells you that total body Na is normal in interstial space. Also look in mouth and at mucous membranes.

If you have dependent pitting edema that means that there is an increase in total body Na.

SIADH – gaining pure water, total body sodium is normal, but serum Na is low; have to restrict water.

Right HF and dependent pitting edema – fluid kidney reabsorbs is hypotonic salt solution with a decreased CO (little more water than salt), therefore serum Na will low. Numerator is increased for total body sodium, but denominator has larger increase with water.

What is nonpharmalogical Rx of any edema states? (ie RHF/liver dz) – restrict salt and water

What is the Rx for SIADH = restrict H_2O

What is the Rx for any pitting edema state? Restrict salt and water
Pharmacological Rx for pitting water – diuretics (also get rid of some salt).

III. Shock

A. Causes of hypovolemic shock – diarrhea, blood loss, cholera, sweating, not DI (b/c losing pure water, and not losing Na, total body Na is NORMAL! Losing water from ICF; no signs of dehydration; when you lose salt, show signs of dehydration).

Example: lady with hypovolemic shock – when she was lying down, her BP and pulse were normal; when they sat her up, the BP decreased and pulse went up. What does this indicate? That she is volume depleted. This is called the TILT test. Normal BP when lying down b/c there is no effective gravity, therefore normal blood returning to the right side of the heart,

and normal CO. However, when you sit the patient up, and impose gravity, you decrease the venous return to right heart. So, if you are hypovolemic, it will show up by a decrease in BP and an increase in pulse.
Cardiac output is decreased, and the catecholamine effect causes this scenario. How would you Rx? Normal saline.

Audio file 7: Fluid and hemodyn 3

Example: pt collapses, and you do a tilt test: 100/80 and pulse of 120 while lying down. Sitting up, it was 70/60 and pulse of 150. The pt is severely hypovolemic, therefore Rx is normal saline. Treatment: One liter in, showed no signs, put another liter and the BP becomes normal, and is feeling better, but still signs of volume depletion (dry mouth). We have the BP stabilized, but the pt lost hypotonic salt solution, therefore we need to replace this. So on IV, give hypotonic salt sol'n (b/c was losing hypotonic salt solution). We do not give 5% dextrose and water b/c there's not any salt in it. Therefore, we will give ½ normal saline. The treatment protocol is: when a pt loses something, you replace what they lost. And when pt is hypovolemic, always give isotonic saline.

Example: DKA, have osmotic diuresis; tonicity of fluid in the urine that has excess glucose is hypotonic. Hypotonic fluid has a little more fluid than salt. So the pt is severely hypovolemic; therefore the first step in management is correction of volume depletion. Some people are in hypovolemic shock from all that salt and water loss. Therefore need to correct hypovolemia and then correct the blood sugar levels (DKA pts lose hypotonic solution). Therefore, first step for DKA pt is to give normal saline b/c you want to make them normo-tensive. Do not put the pt on insulin b/c it's worthless unless you correct the hypovolemia. It can take 6-8 liters of isotonic saline before the blood pressure starts to stabilize. After pt is feeling better and the pt is fine volume wise. Now what are we going to do? The pt is still losing more water than salt in urine, therefore still losing a hypotonic salt solution, therefore need to hang up an IV with ½ normal saline (ie the ratio of solutes to water) and insulin (b/c the pt is loosing glucose).

So, first thing to do always in a pt with hypovolemic shock is normal saline, to get the BP normal. Then to correct the problem that caused the hypovolemia. It depends on what is causing the hypovolemia (ie if pt is sweating, give hypotonic salt solution, if diarrhea in an adult give isotonic salt sol'n (ie normal saline), if pt with DI (ie stable BP, pt is lucid) give water (they are losing water, therefore give 5% dextrose (ie 50% glucose) and water).

B. Four kinds of shock:

1. Hypovolemic shock: blood loss, diarrhea (adult or child), basically whenever you are lose salt, you could end up with hypovolemic shock
2. Cardiogenic shock: MC due to MI
3. Neurogenic shock: assoc. with spinal cord injuries
4. Septic shock: MC due to E. coli; also MCC sepsis in hospital and is due to an indwelling of the urinary catheter. Staph aureus is not the MC cause of IV related septicemia in the hospital, E.Coli wins hands down. Endotoxin in cell wall is a lipopolysacharide, which are seen in gram negative bacteria. The lipids are endotoxins. Therefore, gram negatives have lipids (endotoxins) in their cell wall, gram positive do not. SO if you have E.Coli sepsis, you will have big time problems, and is called septic shock.

5. Classical clinical presentations:

a) Hypovolemic and cardiogenic shock: you would see cold and clammy skin, b/c of vasoconstriction of the peripheral vessels by catecholamines (release is due to the decrease in SV and CO) and AG II. These will vasoconstrict the skin and redirect the blood flow to other important organs in the body like brain and kidneys, leading to a cold clammy skin. BP is decreased, pulse is increased.

b) Pouseau's laws: is a concept that teaches you about peripheral resistance of arterioles which control the diastolic blood pressure.

$$TPR = V/r^4$$

TPR = Total peripheral resistance of the arterioles
V = Viscosity
r = radius of the vessel to the 4^{th} power

The main factor controlling TPR is radius to the 4^{th} power
What controls the viscosity in the blood? Hb. So if you are anemic, viscosity of blood is decreased (ie low hemoglobin), and if you have polycythemia (high hemoglobin), viscosity will be increased. Therefore, TPR in anemia will decrease, and in polycythemia will increase.

c) Septic shock – There is a release of endotoxins which activates the alternative complement system. The complement will eventually release C3a and C5a which are anaphylatoxins, which will stimulate the mast cells to release histamine. The histamine causes vasodilation of arterioles (the same ones of the peripheral resistance arterioles). Therefore blood flow is increased throughout the peripheral resistance arterioles and the skin feels warm. The endotoxins also damage the endothelial cells; as a result, two potent vasodilators (NO and PGI_2) are released. Therefore, 2 or 3 vasodilators are released, and affect the TPR to the fourth power. Therefore, the TPR will decrease (due to vasodilation).

TPR arterioles control your diastolic BP b/c when they are constricted; they control the amount of blood that remains in the arterial system while your heart is filling up in diastole. Therefore, when the TPR arterioles are dilated, the diastolic BP will pan out.
Think of a dam (with gates): if all the gates are wide open all that water will come gushing through. This is what happens to the arterioles when they are dilated. The blood gushes out and goes to the capillary tissues, supposedly

feeding all the tissues with O_2. Think in the context of fishing: when the dam wall opens, all the water rushes thru causing turbulent waters, therefore this would be a bad time to go fishing. The fishes would be trying to save themselves. That is what the O_2 is doing. Therefore, with all this blood going by, the tissues cannot extract O_2 b/c it is going too fast and b/c it isn't a controlled release of blood. Therefore, the blood is coming back to the right side of the heart faster than usual, b/c all the arterioles are widely dilated. Due to the blood going back to the heart faster, the cardiac output is increased. This is seen in septic shock and the skin feels warm b/c the vessels are dilated. Therefore, with septic shock, there is a HIGH output failure, with warm skin.

However, in hypovolemic and cardiogenic shock, the cardiac output is decreased (b/c the vessels are constricted by catecholamines and angiotensin II), and the skin feels cold and clammy.

C. Swan ganz catheter is inserted in the right side of the heart and it measures all parameter that is taught in physiology. All of these things are measured in a swan ganz catheter.

1. Cardiac Output: measured by swan ganz

2. Systemic vascular resistance: this is a calculation. The basically measures the TPR, ie measures what arterioles are doing

3. Mixed venous O_2 content. You know normally that the O_2 content is equal to = 1.34 x Hb x O_2 sat'n + pO_2. Measured in RA with swan ganz catheter; this is the BEST TEST for evaluating tissue hypoxia.

Cardiac output in cardiogenic and hypovolemic shock is low, therefore, blood not being pushed ahead with a great deal of force. So, tissue will have a lot of time to extract O_2 from what little blood that is being delivered. As a result, mixed venous O_2 content in hypovolemic and cardiogenic shock will be decreased ie very low b/c the blood going through the vessels is very slow (no force is helping to push it through). Therefore, it extracts more O_2 than normal. Mixed venous O_2 content in septic shock (when blood is passing through vessels at a very fast rate) will lead to a HIGH mixed venous content (b/c tissues unable to extract O_2).

4. Pulmonary capillary wedge pressure – measures Left ventricular end diastolic volume and pressure (EDV and EDP). Catheter in right heart will tell you what the pressure is in the left ventricle.

5. Differences between Hypovolemic, Cardiogenic, and Septic Shock using swan ganz catheter:

CO in hypovolemic and cardiogenic? both decreased
CO in septic shock? Increased

Systemic vasc resistance (TPR) is a measure of what the ARTERIOLES are doing.
What is TPR in hypovolemic and cardiogenic shock? Increased due to vasoconstriction
TPR in septic shock? Decreased due to vasodilation.

Mixed venous in hypovolemic and cardiogenic? Low.
Mixed venous in septic shock? High.

How do we separate hypovolemic and cardiogenic?
Pulmonary capillary wedge pressure (measures left ventricular EDV)
In Hypovolemic, what is LVEDV? Low.
In Cardiogenic, what is LVEDV? High.
In Endotoxin shock it's decreased.

D. Examples:

1. Example: Of all organs in the body, which suffers the greatest due to decreased BP? Kidneys. What part? Medulla. Not the brain b/c with decreased CO, the circle of willis will distribute blood flow to certain areas in the brain, especially the areas where there are neurons. Someone with hypovolemic, or cardiogenic, or septic shock: oliguria, and an increased in BUN/Creatine causes sugars in the body. This occurs b/c the patient is going into acute tubular necrosis. Nephrologists want to correct the renal blood flow, so that you can prevent ATN b/c a pt can die. What type of necrosis? Coagulation necrosis. The dead renal tubules will slough off and produce renal tubular casts in the urine which will block urine flow, thereby producing oliguria. There is also a decrease in GFR, leading to ATN (chances of survival are zero). So it is the kidneys that are the most affected when the cardiac output is decreased, ie decreased blood flow. Brain would be a close second to necrosis. The heart has a bit of a collateral circulation as well.

2. Example: Pt with the sickle cell trait can get kidney dz; b/c the renal medulla's O_2 tension is low enough to induce sickling. Therefore if you have a young black woman with microscopic hematuria coming to the office, what is first test you should do? Sickle cell screen, b/c she probably has the sickle cell trait. Therefore, sickle cell trait has problems, b/c O_2 tension in renal medulla is low enough to induce sickling in peritubular capillaries, which produces microinfarctions in the kidneys. Therefore, don't want to produce Coagulation necrosis (aka ATN)

IV. Acid-base and Blood Gas

Acidosis – increase in H^+ ions, therefore decrease in pH
Alkalosis – decrease in H^+ ions, therefore increase in pH

$pH = [HCO_3^-] / pCO_2$

A. New equation for acid/base physio by Goljan:

> Increase in bicarb = increase pH = metabolic alkalosis
> Decrease in bicarb = decrease pH = metabolic acidosis
>
> Increase pCO_2 = decrease pH = respiratory acidosis
> Decrease pCO_2 = increase pH = respiratory alkalosis

B. Compensation = bodies attempt to try to maintain a normal pH (which it never does). So if you want to keep pH roughly normal (assuming you could).

1. Example: if you have metabolic alkalosis (increase in bicarb: which is in the numerator), then have to increase denominator (pCO_2) to keep it normal, therefore, compensation is due to respiratory (pCO_2) acidosis. A nice way of memorizing it is what is the opposite of metabolic? Respiratory and what is the opposite of acidosis? Alkalosis, and vice versa.

2. Example: if you have metabolic acidosis (decrease bicarb) what do we have to do with the pCO_2? We have to get rid of it. If we decrease the nominator, we have to decrease the dominator in order for the equation to stay the same. Therefore, we have to blow off the CO_2 (hyperventilation).

3. Ventilation is a CO_2 term!
Hyperventilation = Increase in respiratory rate allows for the blowing off of CO_2, therefore results in respiratory alkalosis. For the treatment of respiratory alkalosis is to give the pt a paper bag and ask to breath in it, b/c then they are re-breathing their own CO_2.

Hypoventilation = Decrease in respiratory rate allows for the retention of CO_2, therefore results in respiratory acidosis.

Full compensation does not exist; you never bring back the pH to the normal range. There is one exception: chronic respiratory alkalosis in high altitude; ie mountain sickness (ie peru).

C. Respiratory conditions: acidosis and alkalosis

1. Things that deal with CO_2:

a) Respiratory center is in medulla oblongata, which controls the breathing rate

b) Upper airways – if obstructed, there will be a problem getting rid of CO_2.
c) Chest bellows – most imp muscle of respiration is diaphragm. On inspiration: the diaphragm goes down, the negative intrathroacic pressure increases, and air is sucked into the lungs and blood is sucked into the right side of the heart (this is why neck veins collapse on inspiration). Negative vacuum sucks blood and air into your chest. On expiration, there is a "+" intrathrocic pressure, pushing things out. It helps the left heart to push blood out and it also helps the lungs by pushing out air.

2. Examples:

(a) Barbiturates or any drug that depresses the respiratory center will leads to respiratory acidosis

(b) CNS injury to medulla oblongata – resp acidosis

(c) Anxiety = MCC resp alkalosis. When you take a test, sometimes you feel strange, and get numb and tingly, especially around mouth and on the tips of fingers, and become twitchy (b/c you are in tetany) its all caused by being alkalotic and ionizing calcium level gets lower and you really are getting tetany. Therefore you become twitchy and paresthesias (ie carpal pedal sign or trousseau's sign are both signs of tetany). All due to tetany b/c of breathing too fast from anxiety.

(d) Pregnant woman have resp alkalosis b/c estrogen and progesterone over stimulate the respiratory center. Located in the lungs are spider angiomas due to AV fistulas related to high estrogen, therefore clear more CO_2 per breath than a normal woman. A lot of shunting occurring within lungs. These spider angiomas go away after delivery of the baby.

(e) Endotoxins over stimulate the system. All pts in endotoxic shock have resp alkalosis. They are also in anaerobic metabolism, producing lactic acid, therefore are also in metabolic acidosis. Therefore, endotoxic resp alkalosis due to overstimulation, and metabolic acidosis due with normal pH.

(f) Salicylate overdose – overstimulate resp center, leading to resp alkalosis. Salicylic acid is an acid, hence metabolic acidosis, and pH will be normal b/c they balance e/o out. (Tinnitus in salicylate OD – also a MIXED disorder!)

(g) 6 y/o child with inspiratory strider – do a lateral x-ray, and see thumbprint sign, with a swollen epiglottis. The diagnosis is acute epiglottitis, due to H. influenza; vaccination has decreased incidence, hence you don't see any ids with H. meningitis b/c of the vaccination. The MC of meningitis in 1 month – 18 yrs = N. meningitis.

(h) 3 month old – croup, a larygiotracheobronchitis dz due to parainfluenza virus. Want to do a lateral x-ray and see a steeple sign. Where is the obstruction in croup? Trachea
(i) Pt shoving food in their mouth (café coronary) – Heimlich maneuver; if they can talk, leave alone and let them cough it out.

(j) Diaphragm innervated by the phrenic nerve – ie erb Duchene palsy, with brachial plexus injury, and child has resp difficulty, and diaphragm on right side is elevated. Paralysis of the diaphragm will lead to increased CO_2.

(k)Lou Gehrig's dz – amyotrophic lateral sclerosis dz, a LMN's and UMN's gone therefore cannot breath b/c no innervation to the diaphragm (ie diaphragm and intercostals are paralyzed)

(l)Guillain-Barre – ascending paralysis in a patient who a week ago had a respiratory infection. The spinal fluid shows increased protein, slight increase in lymphocytes, and a gram stain negative. Dz: Guillain-Barre, demyelinating dz

(o) Polio – destroys LMN's and eventually UMN's. Therefore, anything that paralyzes muscle of resp will lead to resp acidosis.

(p) LUNGS: obstructive and restrictive lung dz's
Obstructive lung dz – problem getting air out, compliance increased and elasticity is decreased, therefore, have a resp acidosis.
In restrictive lung dz, ie Sarcoidosis and pneumonocionioses, there is a problem in getting air in therefore has a resp alkalosis (?)

Day 2

Caisson's Disease –Underwater: for every 30 ft, increase 1 atm, (ie 760 at level, but 30 ft lower it will be 2 atm); the reverse is true when you go to high altitudes – ie at top of mt everst, the atmospheric pressure is 200 atm; still breathing 21% O_2; breathing the same, but atmospheric pressure is different, depending on where you are.

Formula for calculating: alveolar O_2 = (0.21 x atmospheric pressure) – PCO_2 / .8

High Altitude: (.21 x 200) – 40mmHb/.8 = 2mmHg of air in alveoli, therefore will have to hyperventilate at high altitudes, b/c lower pCO_2= increased PO_2 (you HAVE to hypverventilate otherwise you die).

However, when you go under, the atm pressure increases, and the nitrogen gases are dissolved in your tissues, leading to an increase in pressure. Ie 60 ft below, want to get up fast; like shaking a soda bottle; as you ascend, the gas comes out of fat in bubbles; the bubbles get into tissues and BV's; this is called the bends; leads to pain, and quadriplegia, loss of bladder control. Rx = hyperbaric O2 chamber.

CHAPTER 4: NUTRITION

I. Eating disorders – includes obesity, anorexia, bulimia

Difference between anorexia and bulimia?

A. Anorexia

Distorted body image; women with anorexia can have distorted image; control issue; they have lost control of everything in their life, and the only thing that they can control over is what they put in their mouth. With a decrease of body fat and wt, GnRH decreases, therefore FSH and LH also decrease, leading to low estrogen; as a result, amenorrhea occurs, AND predisposes to osteoporosis, as if pt is postmenopausal. Anorexic people will eventually develop osteoporosis.
Rx – convince person to gain enough wt to bring period back; not birth control.
(ie first step in management of HP/diabetes = wt loss; as you lose adipose, you upregulate insulin resistance). In anorexia, usually die to cardiac dz (heart failure: heart just stops).

B. Bulimia Nervosa

1. Metabolic Alkalosis: It's not a body image problem – they can be obese, normal or thin (no weight issue); however, they binge (eat a lot), then force themselves to vomit. Pic on boards: from vomiting, wear down enamel on teeth; so, brownish stuff seen on teeth is just dentine (erosions seen on teeth). Metabolic alkalosis from forced vomiting will be seen. Metabolic alkalois is bad b.c there is a left shift curve, and the compensation is resp acidosis, which drops pO_2, therefore will get hypoxia with metabolic alkalosis, and the heart do not like that. The heart already with low O_2 will get PVC's (pre-mature ventricular contractions), RRT phenom, then V-fib, then death. Therefore, met alkalosis is very dangerous in inducing cardiac arrythmias, and this commonly occurs in bulimics due to forced vomiting. Pt can also vomit out blood – Mallory Weiss Syndrome – tear in distal esophagus or proximal stomach.

2. Borhave syndrome, which is worse. In the syndrome, there is a rupture and air and secretions from the esophagus get into the pleural cavity; the air will dissect through subcutaneous tissue, come around the anterior mediastinum, which leads to Hemimans crunch – observed when dr looks at pt's chest, puts a stethoscope down, and you hear a 'crunch'. The "crunch" is air that has dissected through interstial tissue up into the mediastinum, indicating that a rupture occurred in the esophagus; this is another common thing in bulimics.
So, there are 2 things imp in bulimics: 1) Metabolic alkalosis from vomiting (which can induce arrthymias 2) Borhave's syndrome

C. Obesity: With obesity, using a diff method: BMI: kg's in body wt/meters in body

ht'2. If your BMI is 30 or greater, you are obese; if your bmi is 40 or greater, you are morbidly obese. Main complication of obesity = HTN; with HTN, leads to LVH, and potentially heart failure. MCC death in HTN = cardiac dz. Other complications of obesity include: gallbladder dz, cancers with a lot of adipose, you aromatize many 17-ketosteroids like androstenedione into estrogens. Therefore, will hyperestrinism (all obese women have hyperestrinism), you are at risk for estrogen related cancers – ie breast cancer, endometrial carcinoma, colon cancer.

II. Malnutrition

Protein-calorie malnutrition:

1. Marasmus – total calorie deposition, and wasting away of muscle; however, high chance of survival if they get food
2. Kwashiorkor – prob gonna die; have carbs, but no protein; also have anemias, cellular immunity probs (ie no rxn to ags), low albumin levels, ascites, fatty livers.

These kids are apathetic and need to be force-fed; therefore, kid with kwashiorkor is more likely to die than child with Marasmus. Example: kid with edema, flaky dermatitis, reddish hair (Cu def) – kwashiorkor

III. Vitamins

A. Difference between fat and water soluble vitamins:

1. Fat soluble vitamins dissolve in fats, indicating that they are taken up by chymlomicrons. The chymlomicron will have A, D, E, and, K b/c these are the fat soluble vitamins. Fat soluble are more likely to be stored in fat, so the toxicity is much greater, b/c if it is water soluble, we just pee it out.
MCC bright yellow urine = vitamins
2. Water soluble vitamins are all cofactors for biochemical rxn's.

B. Fat soluble vitamins:

1. Vitamin A

a. Function: Is very imp in children for growth and can have failure to thrive in vit A def. Very important in iodopsin/rhodopsin within the eye and the first sign of vit A def is night blindness which is called nictolopia. Vit A also prevents sq metaplasia.

b. Example of Vit A def: eye with sq metaplasia, goose bumps on back of arm called follicular hyperkeratois. Eye is lined with cuboidal epithelium; when you get sq metaplasia, will get white spots on the eye. If become extensive, grow over eye, and can lead to softening of the cornea (keratomalacia), and leads to blindness. 2nd MCC blindness globally = vit A def. MCC blindness globally = trachoma; MCC blindness in USA = diabetes. Therefore, vit A will prevent sq metaplasia, if you are Vit A deficient and a nonsmoker, a person can end up with sq metaplasia in mainstem bronchus and bronchogenic carcinoma.

c. Toxicity: Hypervitaminosis A – ex. big game hunter that eats bear liver and has headaches. Increased vit A causes cerebral edema, also get papilloedema (which causes the headache), can alsp lead to herniation and death. There is also an increase of retinoic acid (used from treating acne and acute progranulocytic anemia). The retinoic acid toxicity can lead to severe liver toxicity. Therefore, hypervitaminosis of vit A affects 2 areas: 1) cerebral edema (brain) 2) liver. Example: if have young lady pt on retinoic acid for acne, need to check liver enzymes and ask for headaches (can be developing papilloedema or cerebral edema related to vit A toxicity). Massive amount of vit A in bear livers, and hunter dies with massive headaches or liver failure

2. Vitamin D = VERY imp on the boards; MC source of vit D is from sunlight.

a. Cholesterol is the
1. Main component of our cell membranes
2. Starting point for making bile salts and bile acids
3. First compound that starts the synthesis of steroid hormones in the adrenal cortex
4. And the 7-dehydrocholesterol in the skin is photoconverted to vitamin D.

Therefore we need cholesterol! (makes bile salts, hormones, cell membranes, and vit D).

b. Source: Sun is the most imp source of vit D. take baby out to expose to sunlight (no vit D or vit K in breast milk, therefore must be supplemented – expose to sun for vit D).

c. Synthesis of Vitamin D: Reabsorbed in the jejunum. Undergoes 2 hydroxylation steps; first is in the liver, where it is 25 hydroxylated and the 2nd is in the kidney and its 1 alpha hydroxylase. What hormone puts 1-alpha hydroxylase in the proximal tubule? PTH. PTH is responsible for synthesis of 1-a-hydroxylase and is synthesized in the proximal tubule. (ACE is from the endothelial cells of the pulmonary capillary, EPO is from the endothelial cells of the peritubular capillary). 1-a-hydroxylase is the 2nd hydroxylation step, and now it is active (the first was in the kidney).

d. Vit D function: reabsorb Ca and phosphorus from the jejunum. It HAS to reabsorb both of these, b/c its main job is mineralizing bone and cartilage. Have to have appropriate solubility product to be able to do that; Ca and phosphorus are necessary to mineralize cartilage and bone (like the osteoid making bone). Therefore, it makes sense to reabsorb Ca and phosphorus b/c it needs to make sure that both of them are present in adequate amounts to have an adequate solubility product to mineralize bone.

e. Parathyroid Hormone (PTH) – Functions: (1)is somewhat related to Vitamin D metabolism, it helps last step for hydroxylation of vit D syn. (2) PTH will lead to reabsorption of Ca in the early distal tubule (this is also where Na is reabsorbed, and thiazides block this channel). At that location, there is a Ca channel; PTH helps reabsorption of the Ca

in this location. Ca has to 'take turns' with Na, usually more Na, reabsorbed; therefore Ca has to sneak through channel, with help of PTH. Therefore, with thiazides, Na is blocked, leaving the Ca channel completely open, and the thiazides will lead to hypercalcemia. Therefore, use in Ca stone formers – most of stone formers have hypercalciurea; these pts have too much Ca in their urine; when they are on thiazides, the drug takes Ca OUT of the urine, so they do not form stones. (3) PTH will decrease reabsorption of phosphorus in the prox tubule, and (4) decrease the reaccumulation of bicarb, too.

f. Vitamin D and PTH and how they work together:
Vit D's main function is mineralizing bone, and osteoblasts (bone builders) are involved with this process, therefore the receptor for Vit D is located on the osteoblast. When vit D hooks into the receptor, it causes the release of alkaline phosphatase. So, when you are growing bone or rehealing of a fracture, you expect to see an increase in alkaline phosphatase, which makes the appropriate solubility product to mineralized cartilage and bone. Knowing that **PTH** breaks down bone (maintains Ca levels in the blood stream) you would think that its receptor would be on the osteoclast (cell normally breaks bone down). However, only one hormone has a receptor on ostoeclasts and that is **calcitonin**. When calcitonin hooks into the osteoclast receptor, it inhibits the osteoclast, and therefore is used to treat hypercalcemia. Calcitonin also used in treating osteoporosis. The receptor for PTH is on the osteoblast, but not sharing the same one as vit D. When PTH hooks on the osteoblast, it releases IL-1. Another name for IL-1 is osteoclast activating factor (other functions of IL-1 are also involved in fever, stimulates Ab synthesis, and B cell stimulation). So, IL-1 (released from the osteoblast) activates osteoclasts via IL-1 release from osteoblast, and osteoclast is signaled to break down bone to maintain Ca levels in our bloodstream. Sex hormones keep IL-1 in check; in women, estrogen levels keep a check on IL-1 (do not want too much osteoclast activation); in men, it is testosterone that keeps IL-1 in check (puts inhibitory effect on IL-1 release from the osteoblast after PTH hooks in). Therefore, in women, can see why they get osteoporosis – lack of estrogen = IL-1 not in check and breaking more bone down than making (this is the mechanism of postmenopausal osteoporosis).
PTH is more involved in maintaining Ca levels in our blood, while Vit D is more involved in mineralizing our bones and cartilage.

g. Vitamin D deficiency: Many reasons: lack of sun, poor diet, liver dz, renal dz.

Example: Pt on phenytoin and pt has hypocalcemia, why? Phenytoin, alcohol, barb's, rifampin all induce the cyt p450 system located in the SER. Therefore, get SER hyperplasia; therefore, you metabolize drugs and other things made in the liver, including 25-hydroxyvitamin D. Therefore, anything that rev's up the p450 enzymes will cause a decrease in vit D, and any other drugs being taken.

Example: woman on birth control pills and taking phenytoin, and she got pregnant, why? The phenytoin rev'ed up the p450 system, which increased the metabolism of estrogen and progesterone in the birth control pills, therefore not enough levels to prevent pregnancy.
Example: what is the enzyme in the SER that increases when the p450 is rev'd up? Gamma glutamyl transferase (GGT) – enzyme of SER! (look at in alcoholics)

Example: MCC chronic renal dz in USA: diabetes mellitus – tubular damage, so no 1-a-hydroxylase, therefore inactive vit D. Therefore, pts with chronic renal failure are put on 1-25-vit D.

Example: if someone gets OTC vit D, what steps does it go through to become metabolically active? 25 hydroxylated in liver, and 1-a-hydroxylated in your kidney (it is NOT 1, 25 vit D – this is a prescription drug, and extremely dangerous). Many people have the misconception that the vitamin D is already working. This is not the case; pt must have a functioning liver and kidney.

With vit D def in kids = rickets; vit D def in adults = osteomalacia (soft bones).
If you can't mineralize bone, you cannot mineralize cartilage, and they will both be soft, therefore pathologic fractures are common.

Kids have different a few things that are different in rickets – ie craniotopies, soft skulls (can actually press in and it will recoil). They can also get ricketic rosaries, b/c the osteoid is located in the costochondral junc, and b/c they are vit D def, there is a lot of normal osteoid waiting to be mineralized, but not an appropriate Calcium/phosphorus solubility product; will have excess osteoid with little bumps, which is called ricketic rosary. Not seen in adults' b/c they are getting fused.

So, 2 things you see in kids and not adults: 1) craniotopies 2) ricketic rosaries; rhe rest is the same, with pathologic fractures being the main problem.

h. Toxicity/Hypervitaminosis of vit D: hypercalcemia, therefore risk of having too many stones in the urine, and stones is a MCC complication.
Type 1 rickets – missing the 1-a-hydroxylase
Type 2 rickets – missing the receptor for vit D

3. Vitamin E
a. Main function: maintain cell membranes and prevent lipid peroxidation of the cell membranes; in other words, it protects the cell membranes from being broken down by phospholipase A (lipid peroxidation, which is free radical damage on the cell membrane, and is prevented with vit E). Other function: neutralized oxidized LDL, which is far more atherogenic than LDL by itself. When LDL is oxidized, it is way more injurious to the cell then when it is not

oxidized. Vit E will neutralize oxidized LDL, therefore is a cardioprotectant (vit E and C both neutralize oxidized LDL). In summary: vit E func = 1) protects cell mem from free radical damage. 2) Oxidizes free LDL (this is the LDL that macrophages phagocytose to produce foam cells, and leads to atherosclerotic plaques).

b. Deficiency of vitamin E: Is seen but is very uncommon, and if seen if would be in kids with cystic fibrosis; from birth, kids have resp probs and pancreas problems. (look at in robbins, too). A kid that has cystic fibrosis will have malabsorption problems; therefore what four vitamins should you give him? Cystic fibrosis pt has a malabsorption of fat; therefore they will have malabsorption of fat soluble vitamins – A, D, E, and K. Vit E def in USA is usually seen in cystic fibrosis patients.

c. Clinical presentations: One of the features of vit E def is hemolytic anemia (vit E normally maintains the integrity of the membrane); this pt is now susceptible to free radical damage, damaged mem of RBC leads to hemolysis of RBC and hemolytic anemia. Another feature of vit E are things related to myelin: posterior column dz, spinal cerebellar probs. Therefore, with vit E def, have neurological problems and hemolytic anemia.

d. Vitamin E toxicity: anything more than 1100 units (average capsule is 400 units, therefore, if take 3 pills, already toxic). Vitamin E toxicity will inhibit synthesis of
Vit K dependent Coagulation factors (2, 7, 9, 10, protein C, protein S); in other words, you are antiCoagulated. Example: pt with MI – take antioxidants, and aspirin; with anterior MI, they antiCoagulate the pt, and pt goes home on three months of warfarin. Normal INR ratio, and takes lots and lots of vit E and other vitamins. Take a lot of vit E and will help warfarin, leading to over antiCoagulated state, (remember that warfarin blocks gamma carboxylation of vitamin K dep factors). Vit E will prevent the SYNTHESIS of these factors. Therefore, vit E toxicity is synergistic in activity with warfarin. Example: pt on warfarin, came home from MI, INR ratio is huge; why? Taking vit E.

4. Vitamin K

a. Sources: Can come from what we eat, but most is synthesized by our colonic bacteria (our anaerobes in our gut) – this is why we give vit K injections to our baby when they are born; they only have 3 days worth of vit K from mom, but after that, they won't have any b/c its not in breast milk; therefore, a very low level of vit K between days 3-5; also, they don't have bacteria to make the vit K. Therefore, can get hemorrhagic dz of the newborn (this is why we give vit k when they are born); after 5 days, the bacteria colonize, and vit is made by the baby.

b. Metabolism: Bacteria make vit K in an inactive form – K2. K2 (inactive form must be converted by epoxide reductase to K1 (K1 is the active form of vitamin K). K1 will gamma carboxylates the vit K dependent factors (2, 7, 9, 10, protein C and S). Gamma carboxylates requires the same understanding as Vitamin C, in vit C If you don't hydroxylate pro and lys then the crosslinks are weaker (anchor pt). Gamma carboxylation of vit K dep factors actually activates them to become functional. Vit K dep factors all have something in common: (1)have to be activated by vit K1 and (2) they are the only Coagulation factors that are bound to a clot by Calcium (Ca); so they have to be bound by Ca in order to work and form a clot; if you can't bind, then you are antiCoagulated. That is what gamma carboxylation: glutamic acid residues are gamma carboxylated on the vit K dep factors (which is done with K1), and allows Ca to bind the factors; therefore, it keeps them together and you are able to form a clot; therefore, if they are not gammacarboxylated, they are useless b/c Ca can't grab them to form a clot (so, gammacarboxylation is the anchor pt, so Ca can bind to form a clot, similar to hydroxylation of proline and lysine in collagen synthesis).

Warfarin blocks epoxide reductase, so all the vit K pt has is K2 and no gammacarboxylation will occur. Therefore, the patient is anticoagulated.

c. Vitamin K deficiency: MCC vit K def (in hospital) = broad spectrum Ab's. 2nd MCC = poor diet, being a newborn, malabsorption. Def vit K = hemorrhagic diathesis (bleeding into skin or brain). Know why newborn has vit K def: Example: kid with rat poison –rat poison is warfarin; when rats eat it, they get antiCoagulated and die. Treat with intramuscular Vitamin K. Example: kid lived with grandparents and developed hemorrhagic diathesis: why? B/c the elderly were on warfarin, and kid ate the warfarin, and led to toxic levels.

C. Water Soluble Vitamins: all are cofactors in major biochemical pathway

1. Vitamin C:

a) Classic example of Vitamin C deficiency: older person on tea and toast diet – indicating that they are malnourished; pt gets bleeding of the gums = scurvy, due to vit C def. Vit C is responsible for hydroxylation of proline and lysine, and this occurs in the Golgi apparatus b/c that's where post-translational modification occurs. Pts have weak Type I collagen b/c cannot crossbridge it; therefore, BV's are unstable and gums bleed. Get bleeding of the gums, inflammation, and may loose teeth.

b) Associated question: what complication is associated with severe hemophilia A? Hemearthroses, and caused by Vit C deficiency (b/c the BV's are unstable and they rupture).

c) Physical diagnosis of Vitamin C deficiency: Along with the tea and toast diet, there is also perifollicular hemorrhage (hemorrhage around the hair follicles). See ring sideroblast (nucleated RBC, and has too much iron in the mitochondria), ring around the hair follicle and also see cork screw hairs due to vit C def. The tongue looks like it hurts and patients with vit C have a smooth tongue – glossitis, with kelosis around ankles, plus a hemorrhagic diathesis = scurvy.

d) Excess vitamin C: very common b/c pts take way too much vit C (6-8gm), main complication is Renal stones (increased uric acid stones, and other kinds of stones). Vitamin C and D both have toxicity stones.

e) Vitamin C is used in ancillary Rx for methemoglobinuria; it is a reducing agent and a great scavenger hunter for free radicals (knocks them off).

f) Cofactor in biochemical pathway: Vit C is a cofactor for converting the catecholamine NE into Epi.

2. Vitamin B_1 (Thiamine):

a) Involved in many biochemical reactions: transketolase rxn's in the pentose phosphate shunt; and pyruvate dehydrogenase; alpha keto glutarate dehydrogenase; and alpha keto acid dehydrogenase. All the dehydrogenase rxns require thiamine as a cofactor. Pyruvate dehydrogenase is the main rxn that converts pyruvate into acetyl CoA. Pyruvate can also be converted to OAA with a carboxylase enzyme. When you combine acetyl CoA with OAA, you make citrate, and you are in the TCA cycle.

b) So, if thiamine def, b/c it is involved in the pyruvate dehydrogenase rxn (which converts pyruvate to acetyl CoA), you will not have a lot of acetyl CoA around, therefore, won't have much citrate around, therefore, you won't have the TCA cycle working efficiently, and LESS ATP. Therefore, the problem with thiamine def is ATP depletion. When you go from pyruvate to acetyl CoA, you generate 2 NADH's and since this is in the mito, you get 6 ATP (so, just from going from pyruvate to acetyl-Coa, gives 6 ATP); and then with TCA, get 24 ATP's. 6 + 24 = 30 ATP; the total you can get from completely metabolizing glucose is 38 ATP; so, if you are thiamine def, you are out 30 ATP's; so, the main prob of thiamine def is ATP depletion.

c) In thiamine def you'll see foot drop (dry beriberi), and pitting edema (wet beriberi). How does this explain wet/dry beriberi?

1) Dry beriberi = peripheral neuropathy, and refers to Wernicke's korsakoff psychosis (can't remember old and new things – like an exam – ie "used to know that, but can't remember now"; a memory problem). It takes a lot of ATP for synthesis of myelin; without myelin, you will get peripheral neuropathy and foot drop (due to common peroneal palsy), can get wrist drop (radial nerve palsy), and claw hand (ulnar nerve palsy). Wernicke's encephalopathy is confusion, ataxia, and nystagmus. All of these are due to demyelization.
2) Wet beriberi = heart failure; MCC thiamine def = alcohol (not polished rice). Alcoholics are the MC people with thiamine def. Wet beriberi is referring to cardiomyopathy – cause: LHF went into RHF which lead to pitting edema. Heart needs ATP to function, therefore, the pt with have congestive cardiomyopathy; their heart will have biventricular enlargement (the whole chest will be heart), with left and right HF (pitting edema is a sign of right HF due to increased hydrostatic pressure behind the failed heart). If you give IV thiamine, can reverse; and in some cases it's related to toxicity of alcohol, and cannot work.

d) Example: pt in ER given IV of 5% dextrose and normal saline; all of sudden, pt develops confusion, nystagmus, and ataxia, and opthalmaplegia. Diagnosis: subclinical thiamine deficiency. As soon as the glucose was hung up, the pyruvate went to acetyl CoA and used the rest of thiamine...then went into acute Wernicke's encephalopathy. Therefore, moral of the story: give IV thiamine before hanging up IV glucose, especially in ER.

f) When people come in comatose or semicomatose, several things you always do: 1) 50% glucose if a hypoglycemia problem 2) naloxone (OD) 3) IV thiamine

3. Vitamin B_3 (Niacin):

Slide: Rash in sun exposed area = pellagra (aka dermatitis), due to niacin def (also diarrhea, dermatitis, dementia); hyperpigmentation in sun-exposed areas = Cassel's necklace (dermatitis/pellagra);

NAD/NADP rxns (N stands for nicotinamide, and the nicotinamide was derived from niacin). Therefore, all the oxidation rxns rxn's are niacin dependent. Example: pyruvate to acetyl CoA = went from NAD to NADH and niacin is involved here.

Tryptophan can used in synthesizing niacin and serotonin (why it's an essential aa); but it's not the main source of niacin, but a good source.

Nicotinic acid = least expensive lipid lowering drug; see the flushing assoc with it; supposed to take aspirin with it to remove the flushing related to nicotinic acid (used in treating familial hyperlipidemia), it is the DOC for elevated hyperTGemia.

4. Vitamin B_2 (Riboflavin):

FAD/FMN – rxns are riboflavin cofactor rxns (therefore, whenever you have FAD and FMN rxns, these are riboflavin cofactor rxns).
(Niacin for NAD/NADP rxns, and riboflavin for FAD/FMN rxns).
Also, the first rxn: glutathione reductase converts oxidized glutathione into glutathione which riboflavin is a cofactor for.

5. Vitamin B_6 (Pyridoxine):

We're talking about microcytic anemia. First rxn in the synthesis of heme involves succinyl Coa, plus glycine. The enzyme is ALA synthase, and the cofactor is B_6. Therefore, it is imp to the synthesis of hemoglobin and heme proteins. The cytochrome system is the heme system, too. Myoglobin is different from Hb (has one heme group), while Hb has

four heme groups. There is also heme in the liver, in the cytochrome system. Pyridoxine is involved in the synthesis of heme, which is in porphyrin. Pyridoxine is in the transaminases rxn. Most abundant substrate from making glucose in the fasting state = alanine (aa from muscle – aa's broken down from muscle to get glucose, via gluconeogenesis). How can an aa be used to make glucose? Transamination. Transaminations (SGOT, SGPT) from the liver can take transaminases; they take amino groups out and put them into other things; if you take the amino group out of alanine, this produces pyruvate (an alpha keto acid). If you take aspartate and take the aa out, you have OAA, which is a substrate for gluconeogenesis. If you take pyruvate, and add an amino group, can synthesize alanine. If you take OAA, and add an amino group, you can make aspartate. This is what the transaminases do, with B_6 as a cofactor. B_6 is also involved in the synthesis of neurotransmitters. Therefore, a child that is B_6 deficient, they end up with severe neurological problems b/c no neurotransmitters (B_6 imp to synthesizing the neurotransmitters). Important in transamination, neurotransmitter, and heme synthesis.

MCC def B_6 def = isoniazid; without B_6, will develop neurologic problems and sideroblastic anemia related to heme problem.

D. Other important co-factors

1. Pantothenic acid is related to FA synthase; not the rate limiting rxn, but imp in making palmitic acid (a 16 C FA), and helps in making CoA (ie acetyl CoA, HMG CoA); pantothenic acid is the cofactor for these rxns.

2. Biotin

Cofactor for other rxn of pyruvate to acetyl Coa via pyruvate dehydrogenase = thiamine is the cofactor, while biotin is the cofactor for Pyruvate decarboxylase to OAA. Therefore, thiamine helps form acetyl CoA from pyruvate, while biotin helps form OAA from pyruvate.
If you are def, need to eat 20 raw eggs/day
Deficiency: get a rash and go bald (alopecia). If biotin def, cannot form OAA, and cannot from citrate either (this is the first step in gluconeogenesis, therefore you can end up with fasting hypoglycemia). If you build pyruvate, it will be forced to go to lactic acid.

3. Trace elements

a) Chromium = glucose tolerance factor, and helps insulin do its job.
Oatmeal can also decrease glucose with all the fiber; good for a type II diabetic to be on chromium.

b) Copper – lysl oxidase – puts crossbridge between collagen fibrils and elastic tissue. Therefore, if Cu def, have weak collagen and weak elastic tissue, predisposing to dissecting aortic aneurysm. Red hair in kwashiorkor also due to Cu def.

c) Fluorine needed to prevent dental carries; too much fluorine leads to white, chalky teeth, also in Colorado b/c water has too much fluorine. It will also get calcification of the ligaments, where ligaments go into bone; the calcified ligaments are subject to rupture; any good radiologist can detect fluorine toxicity.

d) Selenium – in pentose phosphate shunt, form glutathione, and have riboflavin helping that enzyme. Glutathione can neutralize peroxide, and this requires glutathione peroxidase; selenium is the cofactor for this reaction. Therefore, in other words, it is an antioxidant b/c if you are def in it; the glutathione cannot breakdown the peroxide. (Vit E usually comes with selenium – so one works on glutathione, while the other protects the lipid membrane from free radical damage and scavenges oxidized LDL).

e) Zinc – Example: older person with dysgusia (abnormal taste) and anosmia (lack of sell); smell and taste are both def in zinc def. Zinc is a metalloenzyme; therefore it has a trace metal as a cofactor. Collagenase is a metalloenzyme b/c it has zinc in it, and it breaks down the type 3 collagen, so you can form type 1 collagen. Therefore, if deficient in it, will have poor wound healing, and you get a rash on the face. So, rash on face, dysgusia, anosmia, poor wound healing = zinc deficiency!!! Diabetics are zinc def, unless taking supplements.

4. Dietary fiber (insoluble and soluble) – soluble fiber can lower cholesterol (not the insoluble fiber). How it works (ie oatmeal): oatmeal has insoluble fiber, when it's in the gut, it will suck up water into it from the colon, and also suck up bad things – lipopolic acid. 95% of bile acids and bile salts are reabsorbed in the terminal ileum. The 5% are lipopolic acids, which are carcinogenic (produces colon cancer). So, fiber (insoluble and soluble), it sucks the lipopolic acid up, into the interior of the stool, so it has no contact with the bowel mucosa. Plus, defecate more often and therefore lipopolic acids have even less contact with the stool. Women are lucky b/c they recycle estrogens; main way of excreting estrogens is in bile and out of your stool, but a small % of estrogens are recycled back into the system. You may not necessarily need that, so, when on fiber, increased estrogen is passed out, therefore, decreasing chance of breast cancer, ovarian cancer, and uterine cancer b/c fiber in the diet.

IV. Special diets – protein restriction

What 2 dz's would you restrict protein in?

1) Renal failure b/c excess protein broken down to ammonia and other things – the ammonia is metabolized in the urea cycle, will have increase urea and the kidney will have to get rid of more urea.

2) Cirrhosis of the liver – defective urea cycle therefore cannot metabolize ammonia; most of the ammonia that we have in our bodies comes from bacteria in our colon that have urease in them (H. pylori); and they breakdown urea to ammonia in our

colon. Ammonia is reabsorbed, and supposed to go back to our liver and go into the urea cycle, become urea and get rid of it. But with cirrhosis, no urea cycle, so the ammonia levels increase in the blood, leading to hepatic encephalopathy, mental status abnormalities, asterixis; also caused by octpaneme, benzoic acid, neurotransmitters.

So, two situations to restrict protein: cirrhosis and chronic renal failure.

CHAPTER 5. NEOPLASIA

I. Nomenclature: B9 vs. malignant

A. Main difference – B9 usually does not metastasize, malignant has the capacity to metastasize. Exception: B9 tumor that metastasize: invasive mole (metastasize to lungs, but goes away).

B. Slides:

a) MC skin cancer INVADES but does not metastasize: basal cell carcinoma.
b) Uterus: leiomyoma; MC B9 tumor in woman is MC located in which organ? Uterus – it's a leiomyoma; tumor of smooth muscle!
c) Fibroids – smooth muscle; become very hard
d) MC B9 tumor in male (yellow) = lipoma
e) B9 tumor of glands = adenomas (ie adrenal adenoma – thin adrenal cortex b/c it is functional; it could be making cortisol, therefore suppressing ACTH, and the fasiculata and reticularis would undergo ATROPHY…leads to Cushing's. If tumor secreting mineralocorticoids – it is Conn's syndrome, causing atrophy of the zone glomerulosa (GFR – salty sweet sex)

f) Tubular adenoma = MC precursor lesion for colon cancer (looks like strawberry on a stick)

C. Carcinoma vs. sarcoma

1. Carcinoma – malignancy of epithelial tissue (3 epithelial tissues – squamous, glandular, and transitional)

a) Squamous carcinoma – how to recognize? Little swirls of increased redness (bright red) called squamous pearls;

b) Glandular carcinoma – Round glands, with something in the middle = adenocarcinoma

c) Transitional cell carcinoma – from bladder, ureter, renal pelvis (from genital urinary tract) – all with transitional epithelium

Therefore 3 carcinomas = squamous, adenocarcinoma, and transitional cell carcinomas.

d) Example: Malignant melanoma – first step in management? Excision (b9 version = nevus), both are derived from melanocytes. This is the most rapidly increasing cancer in the USA, not MC. They are S-100 Ag "+" tumors – aput tumors

e) Aput Tumors: S-100 Ag "+" tumors – aput tumors; aput is precursor uptake decarboxylation, meaning that they are of neurosecretory or neural crest origin. Therefore, on EM, have neurosecretory granules. S-100 Ag is used to stain things of aput origin or neural crest origin (most, not all, will take up that Ag).

Examples of aput tumors: melanoma; small cell carcinoma of the lung; bronchial carcinoid; carcinoid tumor at the tip of the appendix; neuroblastoma (secretory tumor), ie 2 y/o with tumors all over skin, and on biopsy, it is S-100 "+", tumor was from adrenal medulla, metastasize to skin.

2. Sarcomas –are malignancy of MESENCHYMAL tissue (not epithelial).

Sarcoma of smooth muscle = leioymyosarcoma; Striated muscle = rhabdomyosarcoma; Fat = liposarcoma; (these are malignancies of mesenchymal tissue, while carcinoma's are of epithelial tissue).

Examples:
a) Bone, see metaphysis, see Codman's triangle, and sunburst appearance on x-ray b/c this tumor actually makes bone. Dx = osteogenic sarcoma (bone making sarcoma).

b) Biopsy from girl having necrotic mass coming out of her vagina, Vimentin and keratin "-", and desmin "+", dx? Embryonal rhabdomyosarcoma (see striation of muscle). This is the MC sarcoma of children (vagina in little girls and penis in little boys)

c) Movable mass at angle of jaw = mixed tumor (in parotid); 'mixed' b/c two histologically have two different types of tissue but derived from SAME cell layer (not a teratoma, which is from three cell layers),. MC overall salivary gland tumor (usually b9) = mixed tumor

d) Teratoma = tooth, hair, derived from all three cell layers (ectoderm, mesoderm, and endoderm) Aka germ cell tumors – b/c they are totipotential, and stay midline. Ex. anterior mediastinum, or pineal gland; therefore, teratomas are germ cell, midline tumors.

e) Cystic teratoma of the ovaries: 16 y/o girl with sudden onset of RLQ pain (don't confuse with appendicitis, Crohn's dz, ectopic pregnancy, follicular cyst). On x-ray, see calcifications of the pelvic area! – Cystic teratoma (the calcifications can be bone or teeth). Usually develop in midline – germ cell tumor.

II. Nomenclature: Leukemia and lymphoma

MC on the boards: Auer rod from myeloblast, and hypersegmented neutrophil from B12 and folate deficiency.

A. Leukemia = malignancy of stem cells in the **BM**, and they can metastasize (like all cancer) and to lymph nodes, leading to generalized lymphadenopathy and hepatosplenomegaly. Derived from stem cells in the marrow and metastasize.

B. Malignant lymphoma: arise from **LYMPH nodes**, and can metastasize anywhere, include BM.

The MC site in body for lymphoma NOT developing in lymph node: **stomach**
Most extranodal (outside lymph node) primary lymphomas occur in the stomach;
H. pylori can produce these.
2nd MCC location (lymphoid organ in the GI tract) = **Payer's patches** (located in the terminal ileum).

MC lymphoma = follicular B cell lymphoma. This is an example of knocking off apoptosis gene -14:18 translocation of a heavy chain; when you get the translocation, B cells will make bcl-2, which inactivates apoptotic gene in the B cell, therefore, the apoptotic gene is immortal, leads to cancer.

III. Nomenclature of Trophoblastic Tumors

A. Hydatidiform mole, presents with cluster of grapes. It manifests in the first trimester with signs of preeclampsia (HP, proteinuria, edema in the first trimester). On ultrasound, will see uterus too large for its gestational age, with a snowstorm appearance = classic complete mole; and can progress to choriocarcinoma.

B. Choriocarcinoma mole is a benign tumor of the chorionic villus; chorionic villi are lined with trophoblastic cells, including synctiotrophoblast on the outside (has contact with the blood, from which O_2 is extracted); under the synctiotrophoblast is the cytotrophoblast, then have warten's jelly in the chorionic villus, then have vessel that becomes the umbilical vein, which has the most O_2 in the vessels of the fetus.

So, hydatidiform mole is a B9 tumor of the WHOLE chorionic villus, and it looks like grapes b/c it's dilated up. Choriocarcinoma is a malignancy of the lining of the chorionic villus: the synctiotrophoblast and the cytotrophoblast (not the actual chorionic villus). Which makes hormones? The syncytiotrophoblast synthesizes B-HCG and human placental lactogen (growth hormone of pregnancy – it gives aa's and glucose from mom to baby). So, when gestationally derived, and even when they metastasize to the lungs, they respond well to chemotherapy (methotrexate, chlabucil). Therefore, these are highly malignant tumors, but go away with chemotherapy.

IV. Things that end in "–oma":

Everything that end in –oma is not necessarily b9 – ie melanoma (malignant tumor of melanocytes), lymphoma (malignant tumor of lymph nodes)

Also, all that ends in –oma is not necessarily a neoplasm – ie hemartoma = overgrowth of tissue that is normally present in that area. Example: A bronchial hemartoma seen lung which is b9 cartilage and a solitary coin lesion is seen in lung (also wonder if it's a granuloma). The polyp in Peutz Jeghers syndrome is a hemartoma (not even a neoplasm), that's why there is no increase in risk of poly cancer. Hyperplastic polyp (MC polyp in GI) is a hemartoma, it's a B9 tissue in place it is not suppose to be (ie pancreatic tissue in the stomach) – this is called a choristoma, or heterotopic ret.

Meckel's Diverticulum
MC complication of Meckel's Diverticulum = bleeding from a gastric mucosa that is ulcerated, or pancreatic tissue that is ulcerated. Should gastric mucosa be in the meckel's diverticulum? No, b/c it is in the small bowel (about 2 ft from the ileocecal valve). Hemartomas are non-neoplastic, and therefore do not have cancer producing potential.

V. Malignant Cells

Increased mitotic rate does not mean cancer. What makes mitosis malignant is having an atypical mitotic spindle (they are aneuploid and have more than the normal 46 c'somes**). Key thing that determines if it is malignant is its ability to metastasize**. Malignant cells usually have a longer cell cycle than the cells they derived from. **How many doubling times does it take to get a tumor that can be detected clinically? 30 doubling times** means that the tumor goes through the cell cycle 30 times, and a tumor of one sonometer in size is produced; 10^9 in mass. Malignant cells are immortal – they don't like each other and lack adhesion; if they were stuck to each other, they would have problems infiltrating tissue. Malignant cells have simple biochemical systems, typically anaerobic metabolism, and have many enzymes such as proteases (used to break through tissue), collagenases (used to break through BM). This is what makes a malignant cell malignant.

VI. Mechanisms of Metastasis: lymphatic, hematogenous, seeding

A. Lymphatic metastasizes:

How do **carcinomas** usually metastasize? Lymph nodes – they drain to their regional lymph nodes; ie breast cancer goes to axillary nodes or internal mammary nodes. For colon cancer, go to nodes around them (the local lymph nodes); same with carcinoma of the esophagus. What part of the lymph node do metastases go to? Subcapsular sinus. If they can get through the lymph node, they go to the efferent lymphatics which drains into the thoracic duct, and then into the subclavian, and then they become hematogenous. Therefore, carcinoma can become hematogenous, this means that they 1st went through the lymph nodes; now, they can spread to other organs (ie bone, liver, etc). This is better than sarcoma b/c can feel the lymph nodes by clinical exam and pick up before it spreads.

B. Hematogenous metastasizes:

On the other hand, **sarcomas** do not like to go to lymph nodes. They go right through BV's and are characterized by hematogenous spread, and that's why lungs and bones are common sites of sarcomas. They don't like to go to lymph nodes. Therefore, they are a little worse b/c they immediately go hematogenous, and do not give a clue that they are spreading. Example: have angiosarcoma of the breast; would you do a radical dissection of the axilla? No, b/c angiosarcoma does not go to the lymph nodes, therefore, do a simple mastectomy. If it is breast carcinoma, take breast and lumpectomy and local axillary lymph nodes and complete the dissection.

Exceptions: Follicular carcinoma of the thyroid (thinks it's a sarcoma) – skips lymph nodes and goes straight to BV's, and takes the hematogenous route.
Renal adenocarcinoma – goes to renal veins (also determines prognosis)
Hepatocellular carcinoma – like to attack the vessels

In general, carcinomas 1st like to go to lymph nodes, and the have the potential to become hematogenous. Sarcomas go hematogenous, making them dangerous.

C. Seeding: Classical Example: cancers that are in cavities and have a potential of seeding, like little malignant implants. Most ovarian cancers are surface derived cancers, therefore derived from lining around the ovary, and they seed like little implants. Therefore, easy to throw out these implants and for it to metastasize to the omentum, and into the pouch of Douglas. The pouch of Douglas is posterior to the uterus and anterior to the rectum and is felt by digital rectal exam. The pouch of Douglas is to a woman, as the prostate gland is to the man. If you do a rectal on a man, and push forward, you will feel the prostate. If you do a rectal on a woman and push forward, this is the pouch of Douglas. This is an imp area b/c it's the most dependent area of a woman's pelvis and many things go here – clotted blood in a rupture ectopic pregnancy, where endometrial implants go in endometriosis, and where seeding goes in ovarian cancers (pouch of Douglas). So, seeding of ovarian cancer to the omentum and can actually invade. Can also seed in the pleural cavity, for example: peripherally located lung cancer that can seed into the pleural cavity. GBM (MC primary malignancy of the brain in adults) can seed into the spinal fluid and implant into the entire spinal cord, as can a medulloblastoma in a child.

So, the 3 mechanisms for metastasis are lymphatic, hematogenous, and seeding.

VII. Most Common (MC) cancers

The first question is to ask: "Is the metastasis more common than primary cancer?"

In most cases, metastasis is the MC cancer in an organ (not a primary cancer). Exception: renal adenocarcinoma (which is more common than metastasis to it).

Lung: MC cancer is metastasis from the breast cancer. Therefore, MC cancer in the lung is breast cancer. Therefore, women are more likely to get lung cancer.

Bone: MC cancer in bone is metastasis (not multiple myeloma or osteogenic sarcoma). MC cancer that metastasis to bone is breast cancer b/c the batsom system; it is a venous complex going from base of the skull down to the sacrum, and has no valves in it. The little tributaries communicate with the vena cava and also go right into the vertebral bodies. Then they collect around the spinal cord and go up. For example: a lady has a little plug of tumor in the intercostal vein, and bends down to pick up something off the ground, which causes the cancer to be dislodged from the vein to the vena cava to the batson plexus in the vertebral bodies, and 3 months later she is complaining of lower back pain. All of a sudden, she is stage four cancer.

MC bone metastasis TO the vertebral column. 2nd MC is the head of the femur (in a woman, this is due to breast cancer – ie breast cancer in head of femur, when they thought it was degenerative arthritis).

MC organ metastasis to = lymph nodes (carcinomas are more common than sarcomas, and carcinomas like to go to lymph nodes, meaning it is the MC metastasis to)

Liver: MC cancer of liver = metastasis from lung into liver (not colon – colon is 2nd b/c portal vein drainage).

Testicular Cancer: Where would testicular cancer metastasize first? Paraortic lymph nodes; NOT the inguinal lymph nodes b/c it derived from the abdomen, and then descended. Example: seminoma (malignant) will metastasize to paraortic nodes b/c that is where it came from

Left supraclavicular node, aka Virchow's node. The MC primary metastasize to Virchow's nodes = stomach cancer! There is a mass in the left supraclavicular nodes along with wt loss and epigastric distress.

Bone: Best test looking for bone mets? Radionucleide scan. Example: everywhere that is black in a woman is mets from breast cancer. MC bone metastasis to = vertebral column!

Mets that are **lytic** (break bone down) and mets that are **blastic** (mets go into bone and induce osteoblastic response).

A. Lytic Metastasis:
For lytic mets, they can lead to pathologic fractures and hypercalcemia.
Multiple myeloma with punched out lesions b/c all malignant plasma cells have IL-1 in them (aka osteoclast activating factor)

B. Blastic metastasis:
For blastic mets, **alkaline phosphatase** will be elevated. Example: this is a male with prostate cancer (prostate cancer is blastic!); it is making bone and will release alkaline phosphatase

MC location for mets = lumbar vertebrae
Example: 80 y/o man with lower lumbar pain with pt tenderness; what is first step in management? Digital rectal exam would be the first thing to do b/c this would be stage four dz, and the prostate is palpable; so, this is the easiest and cheapest test (not PSA, or radionucleide bone scan to make sure its not mets).

Lytic mets – have lucency (absence of bone) – ie vertebrae collapse
Blastic mets – have entity on x ray

If you see any specimen with multiple lesions in it, it is METS (primary cancers are confined to one area of the organ).

MC cancer brain = mets
MC cancer killer in men and women = lung cancer
MC primary site for cancer in brain = lung
MC cancer in lung = mets from breast

MC mets to adrenal = lung – therefore they always do a CT of the hilar lymph nodes, and adrenal glands in the staging of all lung cancers.
Bone = blastic, therefore the most likely cause is prostate cancer.

VIII. Stains and EM used to help dx dz:

Stains: desmin – good stain for muscle – ie used for rhabdomyosarcoma
Stain for keratin (most carcinomas have keratin in it, therefore stain for that)
Stains help ID diff types of tumors
Vimentin- mesenchymal cells

EM: Used when nothing else helps
Auput tumor – see neurosecretory granules.
Histiocyte tumor (ie histiocytosis X) – see birbeck granules, with CD 1
Muscle – see actin and myosin filaments
Vascular malignancy – Wibble palad bodies (have vWF in them); they are of endothelial origin
Know gap junc (which communicate, which don't)

IX. Oncogenesis:

A. Big picture of oncogenesis

1) Initiation (mutation – ie within the cell cycle)
2) Promotion (where multiple copies of the mutation are made)
3) Progression (sub-specializing) diff types of cancer cells have diff func – malignant cells with one purpose – to kill you. Diff cells with diff func: some stay where they are; some invade (and are given special things for it to be able to invade); some have special receptors to home in to specific organs; some resist chemo, some spread, some make enzymes to penetrate tissues.

2 sets of genes involved with cancer:
1) Involved in growth process (cell cycle related)
2) Genes that suppress things (suppressor genes)

B. Things that are involved in trying to get a cell to divide:
GF's (epidermal derived GF); protooncogenes – normal genes, which haven't been activated, and have normal function. When they have been activated, they become oncogenes, which are bad and become cancerous. Certain protooncogenes code for growth factors – ie sis, whose func is to make GF's.

All GF's have to hook into a receptor; therefore certain protooncogenes whose main job is to make receptors – ie erb-2 = breast cancer, which codes for a receptor and ret = seen in MEN syndrome (MEN I and IIa and IIb).

We have to send a message to the nucleus, so have another set of genes, whose job is to send the message; some located in the cell membrane. Example: ras protooncogene sends a GTP (a phosphorylated protein message), therefore it's a cell membrane located messenger system. Another example: abl protooncogene which lives in the cytosol, very close to the nuclear membrane and also is involved in messages.

Who is the messenger sent to? The message is sent to a group of protooncogenes in the nucleus. Once that message is sent to them, there is stimulation of nuclear transcription of that message; in other words, the cell divides and makes whatever it is supposed to make. **Classic protooncogenes there are – myc protooncogenes = n-myc and c-myc (n-myc is for neuroblastoma, and c-myc is for Burkitts lymphoma).**

So, the protooncogenes involved make GF's, growth factor receptors; send messages (which are often phosphorylated proteins). Example – ie insulin hooks into receptor on adipose and activated tyrosine kinase (located right on the receptor), which makes a

phosphorylated product, goes to the nucleus (to divide), and also goes to GA and attaches to GLUT-4, which is made from golgi apparatus, goes to the cell membrane and there's the receptor for glucose. Therefore the messages go to nuclear transcribers in the nucleus and these are myc oncogenes.

The suppressor genes are controlling the cell cycle. The 2 most imp are Rb suppressor gene and p53 suppressor gene. Normally, they control the cell cycle and do not let cell cycle progress to S phase. If unregulated, cells go to S phase and become 'initiated'.

How do we initiate a cell? Mutations–mechanisms: usually a point mutation ie substitutes aa for e/o. The p53 suppressor gene and the ras oncogenes is a pt mut'n. All suppressor genes are due to pt mut'n. Other mutations include:
Amplification – make multiple copies (erb-2 is an amplification system) and

Translocation (putting in another place and can't go back) classic: CML translocation of abl (non receptor tyrosine kinase activity from c'some 9 to 22. On c'some 22, it fuses on a cluster region of the fusion gene, and b/c of the tyrosine kinase activity, it sends a message and stem cells keep dividing; aka Philly c'some. Another example: Cancer assoc with Epstein Barr virus – translocation of myc nuclear transcriber gene from c'some 8 and puts it on c'some 14; it doesn't like it there, so it leads to Burkitts lymphoma. Receptor for Epstein barr virus on all B cells – CD 21; when it hooks on to receptor, it causes B cells to become plasma cells and make Ab (therefore, this virus is an amazing stimulating of Ab synthesis, as is the CMV virus.)
The more a cell divides, the worse it is if something happens to it; ie EBV virus , 8,14 translocation of myc oncogenes from 8 to 14 and all of a sudden you are making multiple copies, and leads to lymphoma (greater chance that you do something, the greater chance that you will screw up).

Follicular B cell lymphoma – translocation of 14:18; inactivation of suppressor gene.

Translocation 15:17 = acute progranulocytic leukemia; Rx – Vit A (retinoic acid) b/c it matures the blasts, therefore the malignant cell becomes B9.

C. Suppressor genes
Suppressor genes suppress, therefore if knocked off, whatever they were suppressing keeps on going**. Key suppressor genes: p53, Rb gene, adenomatos polyposis coli (familial polyposis), neurofibromatosis, wilm's tumor gene, brca1 and 2** (both involved in DNA repair, and one is on c'some 13 while the other is on c'some 17); brca1 can be breast cancer, ovarian cancer, or others; **brca2 is TOTALLY related to breast cancer.** Only 15% of breast cancers have genetic assoc with these genes, therefore, most cases are sporadic.

X. Common things that predispose mutations:
Protooncogenes are activated, while suppressor genes are inactivated
3 main ways this occurs: chemicals, viruses, radiation

A. Chemicals:
Which of the three is most common in initiating a cell producing a mutation? **Chemicals – smoking = MCC death in USA due to polycyclic hydrocarbons.**
By itself, smoking is MC than virally induced or radiation induced cancers. Smoking causes lung cancer, squamous cancer of the mouth, larynx, lung, pancreas, bladder, and if it's not the #1 cause, it's often #2, such leukemias, cervical ca, and colon.

MCC papillary tumor of the bladder = transitional cancer (smoking)
What if you worked in a dye industry? Aniline

What if you had Wegener's granulomatosis, put on a drug and got hematuria, did cytology and saw cells, what drug is pt on? Cyclophosphamide (hemorrhagic cystitis); prevent with mesna, and can cause transitional cell carcinoma (therefore acts as a carcinogen!)

Lung cancer – MCC = polycyclic hydrocarbons from smoke; most often assoc with smoking is small cell and squamous;

B. Viruses:
Virus assoc cancer: a virus with nonpruritic raised red lesions. Dx? Kaposi's sarcoma (due to HHV 8)

Burkitts; due to Epstein barr varies which also causes nasopharyngeal carcinoma, esp. in Chinese

liver – Hepatocellular carcinoma due to hepatitis B from Asia; also due to a mold – *aflatoxin B;* combo of hep B, cirrhosis, plus aflatoxin makes is common in Asia; can also be caused by hep C

HIV is assoc with primary CNS lymphoma. They will ask: the rapidly increasing incidence of primary CNS lymphoma can be directly attributed to what? HIV

HPV causes squamous cancer of cervix, vagina, and vulva, and anus of homosexuals due to unprotected intercourse; due to HPV 16, 18, 31. This virus causes anal squamous cell carcinoma in homosexuals. The virus works by making two proteins, **E6 which knocks off p53, while E7 knocks of Rb**.

C. Radiation
MC cancer assoc with radiation = leukemia

MC leukemia assoc with radiation = CML (9, 22 translocation of abl)

Papillary carcinoma of thyroid is also commonly seen as a result of radiation. Example: pt had radiation in head and neck, and has nontender nodular masses in cervical region = metastatic papillary carcinoma of the thyroid related to ionizing radiation.

Example: osteogenic sarcoma

Example: which medical profession is most subject to leukemia? Radiologist, leukemias are commonly caused by radiation and it's the radiologist that are commonly involved with this.

Example: if you have Jacob Crutzfelt dz, what dr are you? Neuro-Pathologist (bc work with brains and prions)

Example: basal cell carcinoma (pic), multifocal; this is non ionizing radiation (ionizing radiation is the bad stuff). This is UV B light (b is bad); UV A light is for fluorescing superficial dermatophytes (wood's light) or green's patches in tuberous sclerosis (therefore used by dermatologists), aka black light. UV B light is what you protect yourself from to prevent getting skin cancers (basal cell = MC, then squamous cell, then melanoma). UV D = thymidine dimmers

Example: lesion in sun exposed areas that is scraped off and grows back – aka solar (actinc) keratosis; it predisposes to squamous dysplasia. Arsenic is a metal that is associated with skin cancer**. Bangladesh has bad water supply which contains arsenic, therefore they have a high number of squamous skin cancers, and with time it can lead to cancer of the lung, and angiosarcoma of the liver.**

Example: kid with white eye reflex – retinoblastoma – c'some 13. This dz is sporadic and familial. It takes the sporadic dz 2 separate mut'n to become retinoblastoma (knock off on each c'some 13). If it is familial, which is Autosomal dominant it takes just one mut'n, b/c you are born with one already inactivated, therefore only need one more mutation on the other chromosome in order to develop retinoblastoma. **White eye reflex is not MC due to retinoblastoma – the MCC is congenital cataract (which can be due to CMV, rubella, or any congenital infections). Which drug predisposes to cataracts? Corticosteroids; therefore a person with Cushing's dz may develop cataracts.**

XI. Genetic dz

Xeroderma pigmentosa – sun exposed areas, auto recessive, can cause all skin cancers (BCC, SCC, and melanomas), and **the defect is in DNA repair enzymes**. Other DNA repair defects are associated with BRCA1 and BRCA2, p53, they splice out the defects, this group is called the chromosomal instability syndromes – wiskott Aldrich, Blooms, Ataxia Telangiectasias, and Fanconi's, all have probs with DNA repair.

Basic rule of thumb for BCC and SCC:
Upper lip and up is basal cell carcinoma;
lower lip and down is squamous cell
(therefore, lesion on lower lip = sq cell; lesion on upper lip = basal cell)

Example: inside nose is BCC, b/c above the upper lip

Example: keloid – sq cell carcinomas and 3rd degree burns and sq cell carcinoma developing in areas of drainage from the sinus and ulcer that doesn't heal from antibiotics. So, wherever there is constant irritation, and division of cells related to irritation, there is an increase susceptibility to cancer. This does not hold true for scar cancer tissue related cancers of the lungs or adenocarcinoma (just applies to things on the skin – ie burns and draining of sinus tracts).

Only bacteria assoc with cancer? H. pylori – adenocarcinoma and low grade malignant lymphomas.

XII. Grade vs Stage

A. Grade = **what does it look like?** The term well differentiated means that the tumor is making something like keratin or glands, and if it's identifiable it's called low grade. When the cells are anaplastic, poorly differentiated under the microscope, and if you cannot tell what it is, then it's called high grade.
Example: sq cell carcinoma can see keratin pearls; can ID it, so it's a low grade cancer. Example: see gland like spaces, can ID so its low grade

B. Stage = (TNM) MC staging system; goes from least imp to most imp (TNM)
Example: breast cancer with axillary node involvement; therefore, the N=1, but the "M" is worse, b/c it indicates that cancer has spread to other organs like bone, etc.
Just b/c it goes to lymph nodes doesn't mean it is the most imp prognostic factor.

T=size of tumor; if tumor is over 2 sonometers, it has a chance of mets
N=nodes (next most imp for prognosis)
M=mets outside of nodes (most imp prognostic factor)
Stage is more important than grade for prognosis; and within staging, M is the most imp factor for prognosis
Example: pt with prostate cancer, which of following has it the worst? The answer choices were cancer limited to prostate, it went into seminal vesicles, it involved the wall of bladder, went to lymph nodes, or bone? Answer = bone (bone represents the "M" of the TNM system – this ie is stage 4 by definition=mets)

Example: a slide of a colon cancer and a lymph node: what is most important – size of tumor or lymph node involvement? Lymph node. If it was also in the liver, what is most imp? Liver specimen is the most imp prognostic factor.

XIII. Host defenses – most important is Cytotoxic CD8 T cell
Others – NK cells, Ab's, macrophages, type 2 HPY
In hospital, they look for altered MHC class I Ag's in the cancer pt, b/c cancer wants to kill T cells; they do this by putting in perforins, which activate caspasases, and this leads to apoptosis (the signal, from the perforins, activate the caspasases, which have proteases, which break down the nucleus and mitochondria, and cell dies, without any inflammatory infiltrate).

XIV. Other diseases seen in malignancy:

A. Cachexia – cause is TNF alpha; it is irreversible
Once you see a pt with disseminated cancer about to go into catabolic state, can give then total nutrition, but still won't help. (Will not get muscle mass back, and this is due to TNF-alpha)

B. Many hematologic causes of anemia seen in malignancy

MC anemia in malignancy is Anemia of chronic disease (this is the overall most common)

Colon cancer: left side obstructs w/ right side bleeds; if you have RT side bleed in colon cancer, Fe def anemia is very common.

Mets to BM and replace BM

Or, use chemotherapy drugs that are cell cycle specific or cell cycle nonspecific – they wipe out the marrow

Can have autoimmune mechanism with certain malignant dz.

C. Associations with disseminated cancers:

1. Most pts with disseminated cancers are **hypercoagulable**, meaning that they have a tendency for forming clots. Classic Example: a pt with painless jaundice, left supraclavicular node (this is a distracter), had light color stools, lesions that jump from one part of body to next – trousseau's sign: a superficial migratory thrombophlebitis due to carcinoma of the head of the pancreas). Pancreatic cancers can ALSO mets to left supraclavicular node (virchow's node), and often describe trousseau's sign, which is a vascular problem in the veins that jumps from one place to the next.
2. Another common thing seen is disseminated cancers is **thrombocytosis** – an elevated platelet count. Other causes of thrombocytosis: Fe def, splenectomy (ie see scar on abdomen), TB, anemias. If you cannot find any obvious cause of thrombocytosis then the cause is cancer.
   40% of disseminated cancers are thrombocytosis
   Or a do a stool guaic for colon cancer

D. MCC fever in malignancy = gram neg. infection. An E. coli if you have an indwelling catheter; Pseudomonas if you have a respirator, staph aureus can also be the cause from an indwelling catheter, but this is gram "+".
MCC death in cancer = infection

XV. Paraneoplastic syndromes
These are signs and sometimes symptoms saying that you may have an underlying cancer present. Its important b/c when you recognize the signs and symptoms, then you can catch the cancer before it metastasize.

MC Paraneoplastic syndrome = hypercalcemia
2 mechanism for hypercalcemia in malignancy:

1) mets to bone, produce a chemical (IL-1, PGE_2, both of which activate osteoclasts) that produces lytic lesions in bone, and you get hypercalcemia

2) renal adenocarcinoma or squamous carcinoma of mainstem bronchus that sits there and makes PTH-like peptide and causes hypercalcemia b/c it acts like PTH and breaks down bone. This is Paraneoplastic, but it's not the most common one.

Example: 2 black lesions – both are markers for gastric adenocarcinoma; usually under the arm – called acanthosis nigricans, and other is called seborrheic keratosis (these are not neoplasms); however, when these suddenly develop overnight, you get multiple outcroppings (lesserr tree-ar sign), and the outcroppings is a phenotypic marker for **gastroadenocarcinoma**; this is easy to remember b/c 2 black lesions are markers from gastroadenocarcinoma.

Example: **clubbing** – inflammation beneath on the bone called periostitis; inflamm of underlying bone causes proliferation of the soft tissue around it, which leads to clubbing (called hypertrophic osteoarthropathy). Clubbing is not always assoc with cancer; also assoc with bronchiectasis, IBS. But, if it's a malignancy, it is due to primary lung dz.

Example: least common collagen vascular dz, but the most often assoc with a certain cancer. They have an elevation of serum CK; this is dermatomyositis; raccoon eyes, so you see inflammation of skin and muscle; high assoc with leukemias, lymphomas and lung cancer. patches of knuckles – goltrin's patches (seen in dermatomyositis).

Example: vegetations (sterile) on the mitral valve – assoc with mucous producing cancers such as colon cancer; this is called marantic endocarditis-aka nonbacterial thrombotic endocarditis; they are not infections and these marantic vegetations are assoc with mucous secreting colon cancers. Can they embolize? Yes. You will need history to separate from rheumatic fever, but history will relate more to colon cancer (ie polyarthritis)

Example: hyponatremia or Cushing's – cancer in the lung = small cell carcinoma, which is secreting either ADH or ACTH; also, for small cell, they are aput tumors,
S-100 Ag positive, neural crest origin, neural
secretory granules.
Example: Hypercalcemia or secondary polycythemia: renal adenocarcinoma (can make PTH like peptide and/or EPO).

Example: Hypoglycemia or secondary polycythemia: Hepatocellular carcinoma (they can make EPO or insulin-like factor).

Example: Hypocalcemia or Cushing's: auto dominant, and the rare tumor marker that can be converted to amyloid (calcitonin) – medullary carcinoma of the thyroid.

XVI. Tumor markers

A. 2 markers associated with Testicular cancer – alpha feto protein (AFP) (which is really the albumin of a fetus) and HCG. AFP is a maker for–yolk sac tumor (endodermal sinus tumor). So the tumors in kids are yolk sac tumors (alpha feto protein)

AFP is also assoc with Hepatocellular carcinoma, increased in neural tube defects (must be on folate while pregnant to prevent neural tube defects). In Down's syndrome AFP is decreased.

Marker for malignancy in bone, assoc with monoclonal spike: Bence Jones Proteins (light chain Ig), assoc with Multiple Myeloma.

Tumor marker for prostate cancer: PSA; not sp for cancer b/c it can be also increased in hyperplasia; it is sensitive but not specific. If you do a rectal exam, it is not increased. PSA is NOT an enzyme; it is an Ag and is within the actual cell. It will not increase with a rectal exam.

Breast cancer (surface derived) – 15, 3.
CEA–125: Ovarian cancer
CEA –Ag for colon cancer; and sometimes used for small cell, and breast ca. CEA can be a part of an immune complex, and will get CEA: anti-CEA immune complexes which deposit in the kidney, and lead to nephrotic syndrome – this is diffuse membranous glomerulonephritis = MC overall cause of nephrotic syndrome. Many of these are related to malignancy b/c CEA can be the Ag that is deposits in the glomeruli.
woman with a trophoblastic mole, what would you get? Beta HCG

What is MC primary tumor of the brain in kids? Cerebellar cystic astrocytoma (B9). It's not medulloblastoma. All astrocytomas are B9 (if asked what is the most common malignant primary tumor, and then the answer is medulloblastoma, which derives from cerebellum). MC actual tumor of the brain – cerebellar tumor derived from astrocytes;

MC childhood cancer = ALL leukemia (other childhood tumors include CNS tumors, neuroblastomas (in the adrenal medulla), Burkitts, Ewing's (tumor of bone with onion skinning), embryonal rhabdomyosarcoma.)

Adults: incidence:
in woman: breast, lung, colon
In men: prostate, lung, and colon

Killers: lung is #1 in both (followed by prostate/breast and colon)
2nd MC cancer and cancer killer in men and women combined = colon

Therefore, from age 50 and on, you should get a rectal exam and a stool guaic.
After 50, MCC cancer of "+" stool guaic is colon cancer.

MC gyn cancer: endometrial (#2 is ovarian, and #3 is cervix)
Cervix is least common b/c Pap smear. When you do a cervical pap, picking up cervical dysplasia, not cervical cancer (therefore the 'incidence' isn't the highest).
B/c cervical pap smears; the incidence of cervical cancer has gone down significantly b/c the detection of the precursor lesion, cervical dysplasia. So, b/c cervical Pap smear, incidence of cervical cancer has gone down dramatically (picking up the precursor lesion); with mammography, the incidence of breast cancer decreases, same with PSA.

MC Gyn cancer killer: ovarian (#2 = cervical, #3 = endometrial); therefore to remember, the MC has the best prognosis – endometrial is MC and has the best prognosis.

What is the only known existing tumor vaccine? HBV …why?
MC infection transmitted by accidental needle stick in the hospital = Hepatitis B

B/c viral burden of Hepatitis B is greater than any infection, even more so than HIV.

So, with the Hepatitis B vaccine, you won't get three things (1) Hepatitis B, (2) Hepatitis D (requires Hep B), and (3) hepatocellular carcinoma (related to Hepatitis B related cirrhosis).

How do you eradicate hepatocellular carcinoma? Vaccination (ie in the Far East).

CHAPTER 6. HEMATOLOGY: RBC

I. Think big picture.

A. MCV < 80: Microcytic anemia's: Fe def = MC and Anemia of chronic dz, thalassemias, sideroblastic anemias
B. MCV > 100: Macrocytic anemia's: B12/Folate def = MC; usually folate def in an alcoholic
C. MCV 80-100: Normocytic anemia's: low reticulocyte ct corrected: aplastic anemia, renal dz; high corrected reticulocyte ct: hemolytic anemias – hereditary spherocytosis, sickle cell, G6PD def, autoimmune hemolytic anemia, microangiopathic

II. Reticulocyte count: Reticulocyte count next to CBC is the first step in the work up of any anemias. What is reticulocyte? Young RBC. In 24 hrs, a reticulocyte will become a mature RBC with a biconcave disk.

If you have an anemia, the reticulocyte count is imp b/c it tells you where the problem is: is the prob in the BM in making the RBC, or is it a prob outside the BM causing the problem? To determine this, look at reticulocyte ct. If the BM was the prob, then the reticulocyte ct would not have an appropriate response. What is an appropriate response? You would have a BM with hyperplasia, that has rev'd itself up, and making RBC's and should be putting reticulocytes out prematurely, therefore working correctly to correct the anemia. Therefore, it tells whether the BM is responding appropriately or not. If you have blood loss right now, do not expect reticulocyte ct to be elevated in 24 hrs; it takes at least 5-7 days to get the response of making more reticulocytes (like the kidney making bicarb, which takes a few days (3-4) to make). If nothing is wrong with the BM, then it should host a normal reticulocyte response; if there is something wrong, will not have a normal response (imp b/c might decide whether you have to do a BM exam or not). Therefore, if you have a normal reticulocyte ct, do not do a BM exam.

Have to correct the reticulocyte count for the degree of anemia.
Corrected reticulocyte ct = Hct of the pt ÷ 45 × reticulocyte ct that you are given
Example: pt's Hct is 15% (which is very severe anemia), and the reticulocyte ct that was initially measured is 9% (which is increased – anything over 3% is increased).
This 'looks' like the BM is responding correctly b/c the ret ct is 9% (but have to correct for the degree of anemia). 15/45 X 9 is 3; so, when we correct for the anemia, we have 3%; that's what the corrected is – therefore, 3% or greater = good response; 3% or less = bad response; so, this figure is saying that it is a reasonable response occurring in the pt.

Slide of a reticulocyte (know what it looks like) – need to do a special giemsa stain to see the black filaments (which are RNA filaments); b/c they are RNA filaments, the reticulocyte is still synthesizing Hb. So, in about 24 hrs, 25% the normal Hb is being synthesized and need RNA filaments; cannot see these without doing a special stain (look like little black worms in the RBC – do not confuse with Heinz body). Another slide using right giemsa stain of reticulocyte with bluish stain – polychromasia. These are younger blood cells than the 24 hr old reticulocytes. They still have the basophilia, which is not normally present in the peripheral blood; so, when we see them, it means that the BM is really responding, and pushing even the younger ones out. Therefore, whenever the boards say's 'polychromasia', they are talking about these cells and these cells take 2-3 days before they become a mature RBC. Why is this imp? B/c we have to make an additional correction – why? When we are working up an anemia, we do a corrected ret ct and want to know how the BM is responding right now at this day. Not interested about what will happen in 2-3 days, but what will happen right now. Here's the prob: when they do a reticulocyte stain, these guys will also have RNA filaments and will be counted in the ret ct and it will show a falsely elevated ret ct (we don't want these b/c they take 2-3 days b4 they become a mature RBC) instead we want the normal guys there. So, how do we factor them out? Divide by 2. So, make the first correction for the degree of anemia (did it with 3% in this case), look at CBC and see nothing that says polychromasia. Let's say the CBC ct says 'polychromasia present' – then have to make an additional correction by dividing by 2. All of a sudden, it is now 1.5% and this is not a good reticulocyte response! **So, when you see the term "polychromasia", then you have to make an additional correction by dividing by 2.**

Example: reticulocyte – cannot see with right giemsa stain; use special giemsa stain to see RNA filaments, and ribosomes (look like dots – BASOPHILIC STIPPLING, seen in lead poisoning).

III. Side notes:

When looking at CBC you can make many dx's.
Rule of 3 is good: Hb x 3 should roughly equal the Hct
Example: for previous ie, had 15% Hct, therefore the Hb was a 5

Transfusion of packed RBC's – for every unit transfused increase the Hb by 1 and the Hct by 3%. Example: pt with 5 gram Hb, and given 3 units of packed RBC's. The following day the Hb is 6 and the Hct is 18, is that an appropriate response? NO, it should've been 8, with Hct of 24. It wasn't 8 b/c the pt has a GI bleed (pt was bleeding).

MCC anemia worldwide = Fe def anemia
MCC cause of Fe def (overall) = GI bleed
Therefore, the MC reason why Hb and Hct don't go up after transfusion is b/c blood loss, MC due to GI tract bleed.

IV. RBC indices – MCV – how big is the cell? Best way to classify is with MCV (mean corpuscular volume) Small, normal or big? The machine has the RBC's pass through an aperture and sizes it. And then takes an average; this is the best way for classifying an anemia

MCV: < 80, it is microcytic (if you play odds, its Fe def)
MCV (normal): 80 -100 =; have Normocytic anemia;
MCV above 100 = macrocytic (b12 or folate)

If you have small and large cells (dimorphic popcorn of RBC's) it will be Normocytic
(Like the met acidosis, and resp alk, but normal pH). So, how could you have a Fe def anemia and a folate def anemia at the same time? Know where these things are reabsorbed – Fe reabsorbed in the duodenum, Folate is reabsorbed in the jejunum, and B12 is reabsorbed in the terminal ileum. So if you have all these, you have **small bowel dz (ie celiac dz)**; pt has malabsorption that affects diff areas of the bowel. Example: celiac sprue (MCC malabsorption) – involves duodenum and jejunum, therefore will have def of Fe and folate, and will have small cells and large cells. Example: if it involves the jejunum and terminal ileum, you will have folate and B12 def.

V. RDW – RBC Distribution Width

This machine looks at the RBC's and tells if the RBC's coming out of the aperture are all uniformly small, normal, macrocytic, or different in size. So, the RDW detects a change in size of the RBC's and it reports it as a number. Example: microcytic anemia, with an increased RDW; this tells us that is microcytic, and there are different sized microcytic cells. Example: if you develop microcytic anemia overnight and all the cells are Fe def, the cells don't become microcytic immediately; they are normocytic first before they become microcytic, and there will be a size variation picked up by the RDW.

Here's the trick: when you look at the CBC, and it shows **decreased MCV with an increased RDW, this is Fe def anemia** (not thalassemias b/c that is genetic and ALL the cells are microcytic).

Slide with high RDW – has large and small cells. Another slide with spherocyte (have too little membrane, and therefore cannot hold a biconcave disk - an anorexic cell), and target cell (has too much membrane and too much Hb collects in there and looks like a bull's-eye – an obese cell). Target cells are imp markers for alcoholics b/c they have altered cell membrane due to an altered cholesterol concentration of the membrane and markers for hemoglobinopathies (ie thalassemias, SCD, HbC).

Mature RBC looks like biconcave disk and is thin in the middle b/c there is less Hb there, and more is concentrated at the edges; this is why there is a central area of pallor in a normal RBC when it lying flat. All microcytic anemias have one thing in common: decreased Hb synthesis; with less Hb, the redness of the cell with decrease and see greater area of pallor will increase (and if you play odd it's IDA). Spherocyte – too lil mem, therefore it's a sphere; NO central area of pallor! (All red, no central area of pallor). Microcytic anemias all have a PALE, blank color to them; therefore, it is very easy to ID spherocyte and microcytic cells with hypochromia and IDA of chronic dz.

Audio Day 3: Hematology File 2

VI. Normocytic Anemia:

For normocytic anemia, you need to look at the reticulocyte count. First, you have to correct for the degree of anemia (Hct/45 X ret ct). Then look to see if there is polychromasia, if there is polychromasia (then divide by 2); 3% or higher = BM responding normally, and 2% or lower = not responding properly.

Physical signs of anemia: – spoon nails = Fe def (aka kelosis), riboflavin def
Pallor of conjunctiva = have 6 grams or less of Hb
Palmer crease – works for white people – if don't see red, pt is anemic
Ie women, often due to Fe def
Lead line – discoloration in gums due to lead poisoning
Neurologic exam very imp in B12 def b/c the posterior columns are knocked off and lateral corticospinal tract, therefore have propioception abnormalities and decreased vibration sensation and babinski (lateral cortical).

VII. Microcytic anemias

A. Fe studies – four Fe studies:
1. Serum Fe (normal = 100, like the alveolar O_2),
2. Serum ferritin. best test – this is a soluble, circulating form of Fe storage; it rep the amount of Fe stored in the BM, so, if you had to pick one test for dx of Fe def, anemia of a chronic dz, or Fe overload, you would pick serum ferritin b/c this is the best screening test.
3. TIBC (total Fe binding capacity); the carrying protein for Fe is transferrin (trans = 'carrys') and it is made in the LIVER.
4. % saturation= serum Fe divided by TIBC

B. 3 rules:
1. Transferrin and the TIBC is the SAME! (Remember transferrin is what carries Fe).
2. There is a relationship of Fe stores in BM with the transferrin synthesized in the liver. When the Fe stores in the BM are deficient (ie Fe def anemia), that is the signal for the liver to make more transferrin, so it's increased; therefore, TIBC will also be increased in Fe def. Therefore, low Fe stores = increased transferrin synthesis and increased TIBC (an inverse relationship); also, if Fe stores increase, transferrin and TIBC will decrease (ie Fe overload – hemochromatosis, transfusions)

3. % saturation is a calculation = serum Fe/TIBC (normal serum Fe is 100 and normal TIBC is 300, therefore, the % sat'n is normally 100/300 = 33% - therefore, 1/3 of the binding sites are occupied with Fe.
These are the terms and Fe studies we use, esp for microcytic anemias (related to Fe problems).

C. Pathogenesis of microcytic anemias

All microcytic anemias are microcytic (b/c they have a problem making Hb). When the RBC is developing in the marrow, it's the Hb concentration within the RBC that determines the number of cell divisions. Therefore, if the Hb synthesis is decreased, it is a signal in the marrow to increase the number of mitoses. When cells mitoses, they go from something originally big to something small. So b/c of the decrease in Hb syn, there are extra divisions and therefore the cell is smaller.

All four groups of microcytic anemias have a decrease in Hb.
Hb = heme + globin; Heme = Fe + protoporphyrin; Globin is made by the body – alpha ( ), beta ., delta ( ), gamma ( ); HbA –2 2 ; HbA2–2 2 ; HbF– 2 2
We can dispense 2 of the 4 microcytic anemias immediately:
Fe def = don't have Fe, therefore there is no Fe to form with protoporphyrin to form heme; so, **no Fe = no heme = no Hb**

D. Pathogenesis of Anemia of chronic dz

When we have inflammation, our bodies respond to inflammation as if it is an infection. In micro, bugs increase their reproduction with Fe, therefore, the more Fe they have, the more they reproduce. Same concept: with anemia of chronic inflammation and body assumes it is subject to a bacterial infection, the object is to keep Fe away from the bacteria. How does it do that? Its like a safety deposit box, and you have the key – Fe is normally stored in macrophages in the BM – this is where transferrin goes (to the macrophage) to pick up the Fe and take it to the RBC. If you don't want bacteria to have access to the Fe, it will be locked away in the macrophages in the BM and the 'key' to the macrophages will be lost; therefore, there is lots of Fe in the macrophages of the BM, but cannot get it out. However, the good news is that you are keeping it away from the bugs so they don't reproduce. Bad news – keeping it away from the RBC's, and therefore have an decrease in Hb synthesis. However, unlike Fe deficiency, where there is no Fe in the macrophages of the BM, there is PILES of Fe, but the 'key' have been lost and you cannot get it out. So, irrespective of that, your serum Fe is decreased b/c it is all locked in the macrophages, and you don't have enough Fe to make heme. So, it's the same mechanism as Fe def, but for different reasons: (1) you have no Fe (IDA) and (2) you have lots of it, but its locked in the safety deposit box and you cannot get it – so, either way, you cannot make heme and therefore you cannot make hemoglobin. **To distinguish between IDA and ACDz, there are high ferritin levels in ACDz, whereas there is a high TIBC in Fe def anemia**

E. Heme synthesis

Certain rxns in biochem occur in the cytosol, the inner mito membrane (ox phos), mito matrix (beta ox of FA's, TCA), and in the cytosol AND the mitochondria (gluconeogenesis, which starts in the mito and ends up in the cytosol, urea synthesis, which starts in the mito and goes to the cytosol and back into the mito, and heme syn – in mito, then cytosol, and then again in the mito). So, there are 3 biochemical rxns in the mito and cytosol.

First part of heme syn (aka porphyrin syn) begins in the mito. First rxn is succinyl coA (substrate in TCA cycle and substrate for gluconeogenesis), which can be put together with glycine (which is an inhibitory neurotransmitter of muscle, blocked by tetanus toxin rhesus sardonicus and tetanic contraction – so when glycine is inhibited, the muscles are in a tonic state of contraction). Know all RATE LIMITING Enzyme's (RLE) for every biochemical rxn. (RLE in cholesterol syn = HMG CoA reductase).

RLE in heme synthesis = ALA synthase, cofactor = pyridoxine. So, protoporphyrin is made and goes back to the mito. So you have protoporphyrin plus Fe, so you have a metal plus protoporphyrin. Chelatase puts these together; so, it is called ferrochelatase, with combines Fe with protoporphyrin and forms heme. Heme has a feedback mechanism with ALA synthase (all RLE's have a feedback mech). So, with increased heme, it will decrease syn of ALA synthase, and when heme is decreased, it will increase ALA synthase syn.

F. Pathogenesis of Sideroblastic anemias (least common of the microcytic anemias). "sidero" = Fe. Rarest of microcytic anemias = **sideroblastic anemias**; they have 3 causes:

1. Alcohol (sideroblastic anemia is NOT the MC anemia in alcohol, MCC of sideroblastic anemia is alcohol; MC anemia overall = ACDz, followed by folate def). Alcohol is a mitochondrial poison and uncouples ox phos, and damages inner mito membrane, allowing protons to go in and drain them off. On EM of the mito of an alcoholic is huge b/c they are damaged (called megamitochondria). Therefore, any process that occurs in the mito is screwed up. This, therefore, includes heme synthesis. So, Fe is delivered to the RBC by transferrin and doesn't know where to go. Some is stored as ferritin, while most of it goes to the mito, which is BAD news! Why? B/c it can get in, but CANNOT get out. So, there is damaged mitochondria that were damaged by alcohol, Fe goes in and now cannot go out. So, there will lots of Fe caught and Fe builds up within the mito. Mito is located around the nucleus of an RBC in the BM, leading to a ringed sideroblast. This is the marker cell for sideroblastic anemia; also in Fe overload dz – will excess iron, and will not get heme b/c mito destroyed (so alcohol is the MCC).

2) G6PD def – pyridoxine def; ie not taking Vit B6 during Rx of TB. So, no Vit B6 = no heme, and the first rxn will not happen. But Fe doesn't know that; again, Fe goes to the mito, waiting for porphyrin, leading to ringed sideroblast.

3) lead poisoning – so lead leads to sideroblastic anemia. Lead is a denaturer. All heavy metals denature proteins (enzymes are proteins). Lead's favorite enzyme to denature is ferrochelatase, so it won't work, and no heme = no Hb, leading to microcytic anemia. Less of inhibitory effect, but does have a little one on aminolevulinic acid dehydratase. But is

MOST commonly knocks off ferrochelatase. So, when Fe comes into mito, it cannot bind to protoporphyrin to form heme. **No heme = decreased Hb = microcytic anemia**.
Example: if ferrochelatase is decreased/inhibited, heme decreases, but what happens to protoporphyrin before the block? It increases (used to be screening test of choice for lead poisoning). Not used anymore. Why? B/c if you don't have Fe b/c ACDz/Fe def, what will happen to the protoporphyrin in the mito? It will increase. So, they found out that many people had an increase in RBC protoporphyrin, and got "-" test for lead poisoning, and then knew that the pts had either Fe def or ACDz, and concluded that it was not a good screening test.

So, now blood lead level is the screening and confirmatory test for lead poisoning, not RBC protoporphyrin (too many false "+"'s)

G. Pathogenesis of Thalassemias: Auto rec dz's

1. Alpha thalassemias – who do we see alpha thalassemias in? Asians (Far eastern) and blacks (all genetic hematologic dz's are seen in the black pop'n – alpha/beta thal, G6PD def, SCDz).

1. Hb electrophoresis – separates things based on size and charge, therefore you can clearly separate HbA, HbF, and HbA2 clearly on cellulose acetate b/c they have different migrations. So, they fluoresce it, and HbA, HbF and HbA2 all settle down. Then they stain the cellulose acetate to see how much is there. Then, it produces density, and the density correlates with the concentration of each of the Hb's. How will they know the percent? With a densitometer – it converts the density of the stain to the percentage. It turns out that HbA (2 2) is the predominant Hb in an adult (95-95%). HbA2 is 1-2%; HbF = 1%. These are the normal, which are expressed as a percentage.

2. Alpha thalassemias, auto rec, has a problem in making alpha globin chains. Do HbA2 and HbF require HbA to be made? Yes. Therefore, all will be equally decreased. This will NOT show up on an electrophoresis, b/c all are equally decreased, therefore, it shows to be totally normal. There are four genes that control alpha globin synthesis. Deletion of one of these four will not cause anemia. Deletion of 2 genes = problem b/c minimally decreased, and therefore a mild anemia. It is microcytic b/c the globin part is decreased, meaning you will get a microcytic anemia (decrease in Hb conc'n, which will be the stimulus). This called alpha thalassemia minor, seen in the far eastern pop'n and black pop'n.
With a three gene deletion, that's not good, and pt is really decreased (there is also a hemolytic component to it). The beta chains get irritated that there is no alpha chains around, so they from their own beta globin chains. So, four beta chains get together and form HbH. If you do an electrophoresis, there will be a different result. HbH is a diff Hb, and therefore will not migrate to the same place as other Hb's. So, you can dx this alpha thalassemia with Hb electrophoresis (why its called HbH dz). Four gene deletions – spontaneous abortions (usually, therefore not usually born alive – aka hydrops fetalis). Gamma chains form together (like the beta chains did earlier) and form a Hb with 4 gammas, which is called Hb Barts. This will show up on electrophoresis, but won't matter b/c baby is dead already. What is the spontaneous abortion rate in far east? High b/c this is where alpha thalassemia is most commonly located. Therefore, if the incidence of spontaneous abortions is increased, what cancer risk is increased? Choriocarcinoma (increased hydatidiform moles, which leads to choriocarcinoma). So, there is a high incidence of choriocarcinoma in the far east b/c of alpha thalassemia. Rx – DO NOT give Fe (will Fe overload them). So, just leave them alone. (2nd MCC jaundice = Gilbert's dz – esp with lack of food).

2. Beta thalassemia – blacks, Greeks, Italians. B (by itself) = making normal beta chains; B (with a "+") = making beta chains, but not enough; B (with a "0") = not making beta chains at all. Beta thal is auto rec, and has to do with splicing defects, stop codons. The most severe form is due to stop codon (therefore terminate synthesis of beta chains, and don't even make them). **Mild thalassemia**: slightly decreased beta chains, prob due to a splicing defect; beta chains are slightly decreased, alpha chains are okay, delta chains are okay, gamma chains fine (confined to fetus). So, HbA will decrease, and delta will get together (hence increase in HbA2) and gamma chains get together (hence increase in HbF). Therefore, see a decrease in HbA and an increase in HbA2 and HbF; this WILL show up on electrophoresis. This happened b/c beta chain is decreased, and it showed a decreased HbA. It is just a mild thalassemia and is very common. So, only way to dx Beta thal is with Hb electrophoresis. Cannot do anything about it. Hopefully it is not the severe type, where not making any beta chains – aka Cooley's anemia and will not live past 30 y/o. Will have a constant transfusion requirement; many of these pts die from Fe overload, or Hep C or multiple transfusions or HIV.

MC in black pop'n – beta-delta thalassemia (decreased beta chains and decreased delta chains, so what's left are alpha and gamma chains). What will the electrophoresis show? HbF. This called hereditary persistence of HbF. No anemia, just dominant HbF.

For thalassemias, know they are genetic, what groups of people they are in, and that you DON'T do anything to them, esp giving Fe b/c all their Fe studies are normal.

H. Iron Deficiency Anemia (IDA):

1. Causes of Fe def anemia – look at age brackets:
   a) Prematurity – everyday a baby is not in utero, it is losing Fe (all their Fe stores are decreased, so baby must be given Fe supplements).
   b) Newborn – check stool for their blood; need to know it's not mom's blood, which can be swallowed. This is done with the apt test. Most of blood that comes out of baby's meconium is blood the baby swallowed from mom, and it has HbA in it. However, if it was HbF blood that came out, the MCC is bleeding meckel's diverticulum. Therefore, bleeding meckel's diverticulum = MCC Fe def in a newborn and child. Meckel's diverticulum is NOT the cause of Fe def in an adult, b/c most have bled by four years of age, and already would have known pt has it.

c) Woman under 50 – MCC Fe def = menorrhagia, therefore need to get a good menstrual hx; due to anovulatory cycles (between 20-40 y/o, due to ovulatory cycles, inadequate luteal phase, pregnancy related bleeds, endometrial polyp that is bleeding).
d) Men under 50 – MCC Fe def = PUD (usually duodenal ulcer).
e) Men and women over 50 – MCC Fe def = Colon cancer

2. Lab Test –serum Fe = low, TIBC = high, % sat'n (Fe/TIBC) = low
If you don't have Fe, sat'n is decreased b/c no Fe to put on it. Serum ferritin level = low

I. ACDz – related to inflammation. Fe is locked in safety deposit box, so you have plenty, but cannot get it out
Serum Fe=low; TIBC=low (high Fe STORES = decrease transferrin syn)
% sat = low, serum ferritin = high
Therefore, main test to distinguish ACDz from Fe def = serum Ferritin!

J. Mild alpha and beta thal – NORMAL Fe studies b/c nothing to do with Fe, but globin chains.

K. Sideroblastic - ie smear without appropriate amount of Hb in the cells, therefore, they are more than likely to be a microcytic anemia (Fe def, ACDz, thalassemia, lead poisoning). Slide: ringed sideroblast (only seen in BM, and is stained with Prussian blue, which stains Fe b/c mito around the nucleus, all filled up with Fe – called a ringed sideroblast – this is pathognomonic of a sideroblastic anemia). So if you think that B6 is causing the anemia, need to prove it. Need to get BM; if you think alcohol is the cause, you have to prove it.

L. Lead poisoning If you suspect lead poisoning; just do a lead level (not a BM exam). – cells with blue spots – called basophilic stippling. Do not need a special stain to see basophilic stippling (shows up on giemsa stain). See blue dots – lead denatures ribonuclease, and the purpose of ribonuclease is to break down ribo's; if is denatured, and doesn't breakdown, ribosome persists. Therefore, they give a great marker in the peripheral blood – basophilic stippling. If it's an RNA filament, talking about reticulocyte. If we were talking about persistent ribo = lead poisoning. On x-ray – epiphyses of finger of child; only heavy metal that can deposit in the epiphysis of bone is lead (mercury cannot, arsenic cant, only lead can). Therefore, can see deposits in epiphyses. This is why they have failure to grow. If you screw up the epiphyses of the kid, they will not be able to grow properly. Clinical scenario – child eating paint/plaster leads to lead poisoning, have severe abdominal colic, prob with cerebral edema, convulsions, severe microcytic anemia, see lead in intestines (flat plate). You'll see Fe in the intestines; three things can cause this is Fe tablets ingested in a kid, lead, mercury). Also, there is a failure to thrive. Mechanism of cerebral edema? Related to increased vessel permeability of brain and buildup of delta-lemavinylinic acid. If you block ferrochelatase, everything distal to the block will increase (protoporphyrin, deltalemavinylinic acid) this is toxic to neurons, leading to cerebral edema.

Example: guy at an automobile shop, complains of abdominal colic and diarrhea. This is lead poisoning b/c exposure to batteries. In plants, there is exposure to incineration of batteries, and pts are exposed to lead in auto factories

Example: moonshine – make alcohol in old radiators, leads to lead poisoning

Example: pottery painter – pottery is commonly painted with lead based paints. A lot times they lick the tip of the brush, and leads to lead poisoning.

Example: in certain country, they use lead-based pottery for dishes, which leads to lead poisoning. Adults will get the neuropathies – slapping gait (perineal palsy), wrist drop (radial palsy), claw hand (ulnar palsy), lead lines in teeth (usually get with colic and diarrhea)

M. Fe/TIBC/%sat/ferritin:
Fe def: l, h, l, l
ACDz: l, l, l, h
Alpha/beta thal: n, h, h, h, do nothing about it
Lead poisoning (and sideroblastic anemias – Fe overload like hemochromatosis):
H, l, h, h (TIBC is low b/c Fe stores are high!) – in Fe overload everything is high, TIBC is LOW

Anemia	Iron	TIBC	% saturation	Ferritin
Iron Deficiency Anemia	LOW	HIGH	LOW	LOW
Anemia of Chronic Disease	LOW	LOW	LOW	HIGH
Alpha and Beta Thalassemias	NL	HIGH	HIGH	HIGH
Lead overload w/ hemochromatosis	HIGH	LOW	HIGH	HIGH

Audio Day 3: Hematology File 3

VIII. Macrocytic anemias
B12 and folate are involved in DNA synthesis, therefore, if you are B12 and/or folate def, you cannot make DNA, specifically b/c you have a prob with making DMP (deoxythymidine monophosphate). Therefore, if you cannot make that, you cannot mature the nucleus (immature nuclei do not have a lot of DNA in them, but as you make more DNA, the nuclei become more matured, and the nucleus becomes smaller and more condensed). B/c DNA cannot be made, then you have large nucleus, and all nucleated the cells in your body are big – why they are called **MEGAloblastic anemias**. A good pathologist can dx B12 and

folate def in a cervical pap smear, when looking at the squamous cells (cells look big – any cell with a nucleus has DNA in it, so any cell with DNA will be big – not just the hematopoeitic cells that are huge, ALL nucleated cells in the body are big – ie GI, squamous cells)

B12 aka cobalamin; B12 has cobalt in it. Circulating form of folate is methyltetrahydrofolate (tetra = four). Purpose of cobalamin (B12) is to take the methyl group off of methyltetrahydrofolate. Then it's called tetrahydrofolate. If you don't get the methyl group off of folate, you will not make DNA. So, if you are B12 def, you can't get the methyl group off and cannot make DNA. If you are def in folate, you can't make DNA.

Cobalamin adds a methyl to group homocysteine; when you add a methyl group to homocysteine, it becomes methionine. Methionine = aa for 1 carbon transfer rxns. (Methyl = CH_3). If you are B12 or folate def, what are the serum homocysteine levels? High. With a **high serum homocysteine, it produces thromboses, including MI's; it damages endothelial cells, leading to thromboses, and predisposing to MI.** So, what is MCC of increased homocysteine? It is NOT homocystinuria (rare auto rec dz), but B12 def or folate def, and folate is MC than B12. Therefore, the MCC of increased homocysteine is folate def, and have an increased incidence of thrombosis and MI. This is why cardiologists order serum homocysteine levels. In folate def, no methyl group to add to homocysteine (so homocysteine increases); with B12 def, no methyl group to add to methionine to make homocysteine therefore methionine increases.

Tetrahydrofolate is the start of the cycle, and leads to production of thymidilate synthase – this is where DNA is made. DUMP is converted to DDT, making DNA. Therefore, this substrate is necessary to make DNA. So, it is used in the making of DNA by an enzyme called dihydrofolate reductase which converts oxidized dihydrofolate to tetrahydrofolate. Many drugs block dihydrofolate reductase – methotrexate, TMP-SMX. The drugs block DNA synthesis (ie decreasing DNA synthesis) thereby leading to macrocytic anemia. So, the functional B12 takes the methyl group from tetrahydrofolate and gives it to homocysteine to make methionine. And tetrahydrofolate will start the cycle for making DNA.

A. B12

1. B12 Reactions: B12 is humiliated by having to transfer methyl groups. This is an odd request – so whoever he asked said that they can take care of even chained FA's, but we have a problem with ODD chained FA's b/c we can only break down till proprionyl CoA, which leads to dementia and proprioception loss. **B12 helps in odd chain FA metabolism**. Therefore, it is involved in proprionate metabolism, which is metabolism of an odd chain FA. Proprionate forms methylmalonyl CoA, where B12 comes in and helps convert methylmalonyl CoA to succinyl CoA, which can go into the TCA cycle. In B12 def, certain things will build up, such as proprionate and methylmalonyl CoA. Methylmalonyl CoA becomes methylmalonlylic acid, which is a sensitive and specific test for B12 def. So, with B12 def, get a methylmalonlylic acid test (which will be increased). Reason for neurological problems is b/c proprionate metabolism; without B12, cannot convert odd chain FA's into succinyl CoA, and they build up, and it screws up myelin (cannot syn myelin) – and leads to demyelination of posterior columns, and of the lateral corticospinal tract, along with dementia. B/c it is a posterior column dz, you will have probs with proprioception, vibration; b/c you knock off the lateral cortical spinal tract, you will get UMN lesions (spasticity, babinski), and then dementia.

Will always tell you that you can have B12 def, and correct the anemia with high doses of folate, but cannot correct the neurologic dz. Therefore, must make the specific dx. B/c if you think its folate def and give folate, you will correct the hematologic problem, but not the neurological problem, therefore have B12 def. So, in **differential of dementia**, include B12 def (along with Alzheimer's). You don't have to have anemia with B12, but can have neurological probs. So, with dementia, get a TSH level (to throw out hypothyroidism), and a B12 level to rule out B12 def b/c these are REVERSIBLE causes of dementia.

Pure vegan vs. ovo-lactovegan: In ovo-lactovegan taking dairy products (which are animal products), therefore, do not have to take B12 supplements. However, a pure vegan does have to take B12 supplements.

2. Normal sequence of B12 absorption: Have to eat meats or dairy products to get B12. The first thing B12 does is binds to R factor in saliva. R factor protects B12 from destruction by acid in the stomach. Intrinsic factor (IF) made by parietal cells in the body fundus; they also make acid. IF is not destroyed by acid, therefore does not need anything to protect it. So the B12/R factor complex goes into the duodenum, where there is IF waiting for it. R factor must be cleaved off, which is done with enzymes from the functioning pancreas. Then, IF and B12 bind to e/o and take a long trip. Do not go to duodenum (Fe country), do not go to ligamentum of trietz in the jejunum (folate country); so they go all the way to the terminal ileum, where there are receptors for IF, and it is reabsorbed. This is the same place bile salts are reabsorbed, and the same place the Crohn's dz hits. Therefore, it is fair to say that with Crohn's dz, you also have bile salt reabsorption problems and B12 def.
3. Causes of B12 deficiency:

a) MCC B12 def = pernicious anemia; this is an autoimmune dz with destruction of the parietal cells; autoAb's attack the parietal cells and there are autoAb's against IF and destroys the parietal cells which are located in the body and fundus. Everything gets destroyed leading to an atrophic gastritis of the body and fundus. No parietal cells = no acid = achyloridria, and no IF. Achyloridria is a major predisposing factor for gastric adenocarcinoma.

b) Causes of B12 def: pure vegan; chronic pancreatitis seen in alcoholics (this leads to B12 def b/c can't cleave off the R factor); D. latum (fish tapeworm that eats B12 (rarest) – from fish in lake trout in lakes of Chicago); terminal ileum dz (Crohn's). And bacterial overgrowth due to peristalsis prob and/or diverticular pouches and/or stasis. Whenever there is stasis you'll get bacterial infection (also bladder infection); bacteria love B12 and bile salts with bacterial overgrowth. All of these will lead to B12 deficiency.

B. Folate

Folate is seen in animal and plant products, therefore not seen in vegans. Folate has many pharm ties (ie dihydrofolate reductase). When you eat folate, it's in a polyglutamate form, meaning you cannot reabsorb it in the jejunum; therefore it has to be converted to a monoglutamate form. Intestinal conjugase (in the small intestine) is responsible for this. **What drug blocks intestinal conjugase? Phenytoin.** So, if they ask about pt on Phenytoin, with macrocytic anemia, hypersegmented neutrophils, neurological effects are NOT present – therefore folate def (b/c there are no neurological problems, this r/o b12 def.) Now you have monoglutamate, which is absorbed in the jejunum. There are 2 things that inhibit its absorption: (1) birth control and (2) alcohol **(MCC folate def = alcoholism)**. With B12, have 6-9 year supply in liver, therefore its uncommon to get. Folate only has 3-4 month supply – so, even if you have an excellent diet, you can have folate def if you are taking one of these two things.

Summary: circulating form of folate is methyltetrahydrofolate, and B12 takes the folate off, and gives it to homocysteine which becomes methionine; the methyltetrahydrofolate becomes tetrahydrofolate, and with the help of dihydrofolate reductase, DNA is made.

Example: pic with hypersegmented neutrophil (definition: 5 or more lobes!). Hypersegmented neutrophil indicates B12 or folate def, even if you don't have anemia. It is the first thing that comes up before anemia. And if the neurological test is normal, it's a folate def. Test for proprioception: Rhomberg test – if you have post column dz, prob with proprioception b/c do not know where your joints are; does not show cerebellar ataxia (will have these with eyes opened AND closed). Use vibrating tuning fork to see if pt has proprioception on the malleous.

Hematopoetic cells are made outside the sinusoids in the BM. It's analogous to the cords of bilroth in the spleen (where there are fixed macrophages and then, the RBC's and WBC's have to get back into the sinusoids and circulate through holes. They get through, and are in sinusoids). The same thing occurs in the BM – they have a place equivalent to the cords of bilroth and that is where they are made. To get into the circulations, they have to fit through lil, narrow holes to get into the sinusoids in the BM and into the blood stream. Something very big will not be able to get through the lil holes and into the sinusoids. Therefore, macrophages will want to feast on the macrocytic cells (WBC's, RBC's, platelets) that cannot get into the sinusoids. So, the macrophages kill them all. So in the peripheral blood, will see NOTHING – pancytopenia; severe macrocytic anemia, neutropenia, thrombocytopenia – which is characteristic of B12 /folate def. (everything in the marrow is too big and cannot get out into the circulation).

Schilling's test – good test for localizing B12 def. We know now that it's a B12 deficiency, and we want to know what caused it. Steps for schilling test: Give radioactive B12 by mouth; they then collect the 24 hr urine to see if any comes out in the urine and nothing comes out, therefore prove that they have a problem absorbing B12.

1st step: give radioactive B12 and IF, collect urine for 24 hrs, and piles in the urine = Pernicious anemia; b/c added what was missing (IF); if it didn't work, you can EXCLUDE pernicious anemia.

Say this didn't work, then you:

2nd step: give 10 days worth of broad spectrum antibiotic; pt comes back and again you give them radioactive B12; see piles of radioactive B12 in the urine, what is dx? Bacterial overgrowth b/c knocked off the bugs eating B12

Say this didn't work, then you:

3rd step: pancreatic extract, swallow pills, then give radioactive B12; 24 hrs later, see what happens; if there is radioactivity in urine, pt has chronic pancreatitis.

If that didn't work, could be Crohn's, worm, etc.

Summary:
If B12 malabsorption was corrected by adding IF, pt has pernicious anemia
If B12 corrected by adding an antibiotic, pt has bacterial overgrowth
If B12 is corrected by adding pancreatic extract, pt has chronic pancreatitis.

IX. Normocytic anemias

When you do the corrections for the anemia and look for polychromasia; if correction is less than 2%, it is a bad response (BM not responding correctly). First two things you see: early IDA and ACDz – remember that you have to have a normocytic anemia first to become microcytic. Doesn't occur overnight. Therefore, with a decreased ret ct (ie less than 2%), must include microcytic anemia's in the differential, and you need to get a ferritin level.

IDA goes through diff stages: first thing that happens – decreased ferritin, then Fe decreases, TIBC increased, % sat decrease, and still won't have anemia. In other words, all Fe studies are ABNORMAL before you have anemia. Then you get mild normocytic anemia, and eventually microcytic anemia.

A. Causes:

1. Blood loss less than a week = normocytic anemia; no increase in ret response b/c nothing wrong with the BM, and not enough time (need 5-7 days for BM to get rev'd up) – so, after one week, would get an appropriate response.
2. Aplastic anemia – no marrow; if that is true, the peripheral blood will show pancytopenia (all hematopoetic cells are destroyed in the marrow); have normocytic anemia, thrombocytopenia, and neutropenia.

3. MC known C = drugs: chloramphenical – used in rocky mtn spotted fever, indomethacin, phenylbutazone, and thyroid related drugs
4. 2nd MCC = infections – esp. Hep C (wipes out everything); aplasia of RBC = parvovirus
5. Radiation and malignancy
6. Early IDA and ACDz (need to have serum ferritin levels)
7. Mechanism of normocytic anemia with less then 2% ret ct – renal failure, and decreased EPO (can be given exogenously) – decreased in hep B, C, and HIV. Athletes that 'dope' are given EPO, to increase RBC's to allow more O_2 delivery to body

B. Mechanisms of hemolysis – 2 ways to kill an RBC:

Normocytic anemias with corrective ret ct about 3%:

1. Extravascularly (outside of the BV).

They are killed by macrophages, usually in cords of bilroth in the spleen, sometimes in liver sinusoids. Every RBC must go to the cords of bilroth a few times per day and get examined by a macrophage – if the cell picked up an IgG or C3b, it is marked for destruction via phagocytosis b/c the macrophage has receptors for IgG and C3b. If you don't have IgG or C3b, can still die b/c the cell is in bad shape –abnormal shape: ie sphere will not be able to fit through a 2 micron hole to get to the sinusoids – it can't – therefore, spherocytes are removed extravascularly b/c they cannot get out; sickle cells cannot get out either b/c they have a bad shape. Another reason for their destruction is b/c they have something inside them that they shouldn't –a piece of nucleus; what is this called? Howell jolly body; macrophage will get rid of it.
There are autoimmune hemolytic anemias, and can be due to IgG or C3b on the surface of the RBC, or extravascular hemolytic anemias is where you have abnormal shape (ie sphere, Sickle cell – will not make it out of the spleen b/c removed by macrophages).

End product of phagocytosing an RBC: unconjugated bilirubin. When the RBC is broken down, you have hemoglobin, and there is an enzyme that splits heme from globin and the globin is broken into aa's and therefore goes to the aa pool. Then, takes the heme, splits it open, and saves the Fe. Now you have protoporphyrin, and spit it out; end result is unconjugated bilirubin in the macrophage within the spleen. Then, the macrophage spits out the unconjugated bilirubin into blood stream (which is insoluble b/c it's unconjugated). The unconjugated bilirubin then binds albumin and goes to the liver and is conjugated. So, what clinical finding will you see in pts with extravascular hemolytic anemia? Jaundice. Does that bilirubin get into the urine? No. Why? 2 reasons: (1) Lipid soluble and (2) Bound to albumin (albumin does not get into the urine) – so you are jaundiced, but doesn't get into the urine

2. Intravascular (within the BV)

Intravascular is less common – meaning that you die within the BV. How does that happen? You die within the vessel if you bump into something. Example: congenital bicuspid aortic valve with calcium there – if you bump into that, you would damage yourself and die. Example: if you have IgM on the surface of the RBC (IgM is the most potent activator of the complement system); this will go from 1-9, meaning that it will sit on the RBC, activate the complement and dies intravascularly; so, anything that is IgM mediated = intravascular hemolysis. So, what will you release into the bloodstream if you are killing the RBC? Hb. Don't want to lose all of it and need to retreat it – by getting back the aa's and retrieving the Fe. Specific protein that is made in the liver that is released when there is intravascular hemolysis – **haptoglobin** (aka suicide protein – b/c forms complex with Hb and is phagocytosed by the macrophage), therefore giving life to retrieve the Hb, therefore in pts with intravascular hemolysis, the haptoglobin levels decrease. Is it possible to get jaundice? Yes, but usually don't b/c macrophage is phagocytosing. Intravascular hemolysis: hemoglobinuria, and low haptoglobin levels

3. Summary:
   Extravascular = macrophages remove = unconj bilirubin is the end product = jaundice is the clinical manifestation
   Intravascular = Hb in urine, decreased haptoglobin

C. Intrinsic vs. Extrinsic Hemolytic anemia:

1. Intrinsic – something wrong with RBC, causing it to hemolyze: such as no spectrin, or not decay accelerating factor to neutralize complement, no G6PD enzyme in pentose phosphate shunt, or abnormal Hb (ie HbS). Therefore, something wrong inside the Hb molecule, causing it to hemolyze.

2. Extrinsic – nothing wrong with the RBC, just at the wrong place at the wrong time; ie it just happened to smash into the calcified valve (nothing was wrong with it, until it hit the valve). Then it will be dreading going to the cords of bilroth with destroy it b/c it has been marked with IgG and C3b for phagocytosis.

D. Something intrinsically wrong with the RBC causing it to hemolyze but there's nothing wrong with the BM (but something intrinsically wrong with the RBC), and the corrective ret ct is greater than 3%.

MAD – MC intrinsic probs
Membrane defect (spherocytosis, paroxysmal nocturnal hemoglobinuria), **A**bnormal Hb (SC trait Dz),
Deficiency of enzyme (G6PD def).

1. Membrane Defects:

(a) Spherocytosis: do no see a central area of pallor therefore must be a spherocyte and must be removed extravascularly. Clinically manifest with jaundice from unconjugated bilirubin. Spectrin defect and AD dz; splenomegaly always seen over a period of time. Gallbladder (GB) dz is common b/c there is a lot more unconjugated bilirubin presented to the liver and more conjugation is occurring and more bilirubin is in the bile than usual. So, whenever you supersaturate anything that is a liquid, you run the risk of forming a stone; if you supersaturate urine with Ca, you run the risk of getting a Ca stone; if you supersaturate bile with cholesterol, you will get a cholesterol

stone; if you supersaturate with bilirubin, you will get a Ca-bilirubinate stone. Therefore, pts have GB dz related to gallstone dz and then do a CBC with normocytic anemia and a corrected ret ct that is elevated, and see **congenital spherocytosis**. What's the diagnostic test? Osmotic fragility – they put these RBC's wall to wall in different tonicities of saline, and the RBC's will pop (therefore have an increased osmotic fragility).
Rx: splenectomy (need to remove organ that is removing them – they will still be spherocytes and will not be able to form a biconcave disk).

(b) Paroxysmal Nocturnal Hemoglobinuria = defect in decay accelerating factor. So when we sleep, we have a mild resp acidosis b/c we breathe slowly (if you have obstructive sleep apnea, the acidosis is worse). When you have acidosis that predisposes the complement that's sitting on ALL cells circulating in peripheral blood. RBCs, WBCs, and platelets all have complement sitting on it. There is no complement destruction of these cells b/c in our membranes we have delay accelerating factor. This factor causes increased degradation of the complement so it doesn't have an opp to drill a hole in our membrane, therefore we don't wake up in the morning with hemoglobinuria, neutropenia and thrombocytopenia. So, if you are missing decay accelerating factor, the complement will be activated and goes from C1-9, leading to intravascular hemolysis. Think about the name (paroxysmal nocturnal hemoglobinuria): occurs at night, and when you wake up in the morning, you pee out hemoglobin. So, when you do a CBC, not only have a severe anemia, but also a neutropenia and a thrombocytopenia: pancytopenia).

2. Abnormal Hb: Sickle Cell Trait/Dz

With sickle cell trait, there is NO anemia and NO sickled cells in the peripheral blood. You can have sickled cells in a certain part of your body – in the renal medulla within the peritubular capillaries (decreased O_2 tension), but not in the peripheral blood. This is b/c in SCDz, the amount of sickled Hb in the RBC determines whether it sickles or not. **Magic # = 60%**; if you have 60% or more, HbS can spontaneously sickle. Oxygen tension in the blood also determines whether a cell will sickle or not. At lower O_2 tensions, cells are more likely to sickle. This is an auto rec dz, meaning that both parents must have abnormal gene on their c'some (so its 2 traits); therefore, 25% complete normal, 50% heterozygous asymptomatic carrier, 25% complete dz (same with cystic fibrosis).

SC Trait vs. SCDz:

(a) In **sickle cell trait**, black individual with normal PE and normal CBC, but microscopic hematuria, the first step is sickle cell screen b/c microscopic hematuria is ALWAYS abnormal and must be worked up but in blacks = 1/8 people have the trait. So, SC trait is what you are thinking of; not renal stones, or IgA glomerulonephritis, but is SC trait normally.

(b) **SCDz** – 2 things are happening: Hemolytic anemia (usually extravascular) – can be very severe and commonly requires a transfusion and Occlusion of small BV's by the sickled cells (blockage of circulation) – lead to vasooclusive crisis, and this ischemia leads to pain. Therefore, they are painful crisis (occur anywhere in the body – lungs, liver, spleen, BM, hands/feet (bactulitis)). Over time, it leads to damage of organs – kidneys, spleen autoinfarcted (autosplenectomy) – in first 10 years of life, pt will have splenomegaly b/c trapped RBC's, and eventually autosplenectomy around age 19 (spleen will be the size of a thumb). After 2 years, it is nonfunctional – so even though you have a big/swollen spleen, it isn't working. How will you know what that has happened? Howell Jolly body (RBC with a piece of nucleus that should not be in the spleen – if the spleen were working, a fixed macrophage would have taken care of it). This occurs at about 2 yrs of age. This is fortunate b/c this is about the age where you can get pneumovax. With a nonfunctional spleen what infection is guaranteed? Strep pneumoniae sepsis.
MCC death in child with SCDz = strep pneumoniae sepsis.
They try to cover with antibiotics and pneumovax – pneumovax can be given at the age of 2 and that's about the time when the spleen stops working (start to see Howell jolly bodies). Slide with Howell jolly body and slide with sickled cells, then will ask, what's wrong with the spleen? It's dysfunctional; Howell jolly would have been removed if the spleen is functional.

When do they get their first sickle cell crisis? When little kids gets painful hands, and are swollen up (called bactulitis) – does not occur at birth, b/c HbF inhibits sickling and newborns in newborns, 70-80% of their RBC's are HbF. In SCDz, 60-70% RBC's have HbF, while the rest are HbS!
At this stage, there is enough HbF to inhibit the sickling; however, as the RBC's are broken down and replaced, the HbF decreases and HbS increases, and by 6-9 months of age, there is a high enough concentration to induce sickling and their first vasooclusive crisis, producing bactulitis. So, bactulitis doesn't come until 6-9 months b/c HbF inhibits the sickling.
Bone infarctions occur from sickling the BM.
Osteomyelitis – these pts are susceptible to osteomyelitis from salmonella due to a dysfunctional spleen. Salmonella is destroyed by macrophages. The spleen normally filters out salmonella, but is dysfunctional. MCC osteomyelitis is staph, but MCC in SCDz pt = salmonella.

What drug is used to decrease the incidence of vasooclusive crises? Hydroxyurea. How does it work? It increases HbF synthesis.

3. Deficiency of enzyme: G6PD deficiency

G6PD def is X-linked recessive.

Most enzyme def's are auto recessive ie PKU, albinism, homocystinuria). What are the two X-linked recessive enzyme def's? G6PD def and Lesch-Nyhan syndrome (involves purine metabolism with mental retardation, self mutilation, increased uric acid, def of HGPRT).

Glucose 6 phosphate has several functions: (1) to make glutathione, (2) to make ribose 5 carbon sugars for making DNA, and (3) to make glycogen from G6P (converted to G1P, UDP-glucose and glycogen).

Key: with this enzyme, we can make NADPH, which is the main factor for making anabolic types of biochemical rxn (ie steroid synthesis). NADPH will reduce oxidized glutathione to glutathione; its job is to neutralize peroxide to water. Which vitamin catalyzes this rxn? Riboflavin. Which enzyme helps glutathione neutralize peroxide? Glutathione peroxidase. Which trace metal is involved? Selenium. Every living cell makes peroxide as an end product, therefore every cell must a way to handle it. Catalase – present in all cells except RBC's and it can neutralize peroxide. It is stored in peroxisomes. Other way to neutralize peroxide is with glutathione (only thing available to RBC's b/c they don't have catalase). So, if you are deficient in this enzyme, there is a problem. So, peroxide increases to the point of hemolyzing RBC's why would that occur? B/c if you had an Infection, or if you took an oxidizing drug (ie sulfa drug, nitryl drug), which will lead to a lot more peroxide lying around. Peroxide will not be able to be neutralized if you are deficient in catalase. So, what will happen is the peroxide will affect the Hb. The peroxide will cause the Hb to clump and form Heinz bodies (Hb clumped up together). Will also affect the RBC membrane b/c it damages the membrane so much that the primary mechanism of destruction is intravascular. Little element is extravascular, but mostly intravascular. It is precipitated by infections and/or drugs. **2 MC drugs: 1) primaquine**– missionary got malaria, received a drug, and 2-3 days later the got hemoglobinuria, chills, and a hemolytic anemia (this is primaquine induced hemolysis). **2) Dapsone** is used in treating leprosy; every person with leprosy is given a screen for G6PD def b/c of the high incidence of producing hemolysis. See this dz in the same population as Beta thal – blacks, Greeks, Italians. Slide: smear with actively hemolyzing blood cells – **Heinz bodies** – when it goes into the cords of bilroth, the macrophage will take a big bite out of it and sometimes, is a small bite out of the membrane, and the cell goes to the peripheral circulation and is called a "**bite" cell** (RBC with little membrane). Need to do special stains to ID Heinz bodies. In Greeks or Italians with severe forms of G6PD def, they can eat fava beans which can precipitate an episode (aka favism).
Dx – when you have an acute hemolytic episode, the last thing you want to get a diagnosis is to get an enzyme assay. Why? B/c the only cells that are hemolyzed are the ones missing the enzymes. The ones that have the enzyme are still gonna be there, so you have a normal assay. So, NEVER use enzyme assays for active hemolysis. Need to special stain to ID the Heinz body. When the hemolytic episode is over that's when the dx is confirmed, this is done with a G6PD assay. **Will get a question on G6PD deficiency, either dapsone related or primaquine related.**

X. Autoimmune hemolytic anemias

Warm reacting antibodies are IgG and cold reacting is IgM
MC autoimmune hemolytic anemia = warm; MCC of it = Lupus

When you have autoimmune dz in your family, you have certain HLA types that predispose you to that autoimmune dz. Therefore, you should not be surprised if you have one autoimmune dz you're likely to have another. So, pts with lupus commonly also have autoimmune hemolytic anemia, autoimmune thrombocytopenia, autoimmune neutropenia, and autoimmune lymphopenia.

For example: the MCC of hypothyroidism = hashimoto's thyroiditis; these pts commonly have other autoimmune dz's – ie pernicious anemia, vitiligo, autoimmune destruction of melanocytes). So, if you have one autoimmune dz, you are likely to have others (ie if you have a hemolytic prob, it is prob autoimmune related).
This is b/c of the HLA relationship. Therefore, if you have a family that has an autoimmune dz, what would be the single best screening test to use? HLA (ie if they have the HLA type specific for lupus – there are specific HLA's for diff dz's). Therefore, HLA is the best way to see if pt is predisposed to something.

MCC autoimmune anemia = Lupus; it has IgG and C3b on the surface of the RBC, so it will be removed by the macrophage. This is an extravascular hemolytic anemia. How do we know that there are IgG or C3b Ab's on the surface? **Direct Coomb's test**: detect DIRECTLY the presence of IgG and/or C3b on the surface of RBC's. Indirect coombs is what the women get, when they are pregnant and they do an Ab screen on you (looking for any kind of Ab); so, when you look for Ab in the serum (NOT on RBC, on SERUM), this is an indirect Coombs. Therefore, another name for the indirect Coombs = Ab screen; with direct coombs, we are detecting IgG and/or C3b on the SURFACE of RBC's. you cannot do direct coomb's on platelets or neutrophils, but only RBC's.
So, the test of choice if you suspect an autoimmune hemolytic anemia is Coomb's test.

A. Drug induced autoimmune hemolytic anemias:

There are 3 types of drug induced hemolytic anemia (2nd MCC autoimmune hemolytic anemia = drug induced; MCC = lupus)

1. **PCN** – mechanism: the bpo group of PCN attaches to RBC (lil piece of PCN is attached on RBC membrane). This is bad if an IgG Ab develops against it b/c if it does, than the IgG attaches to the bpo group, goes to the spleen and is removed extravascularly; this is an ie of type II HPY
   Example: pt on PCN develops a rash – what type of HPY? Type I. Example: Pt on PCN develops a hemolytic anemia – what type of HPY? **Type II**

2. **Methyldopa** – aka aldomet. Use: anti-HTN for pregnant woman (other anti-HTN used in pregnancy = hydralazine). Methyldopa and hydralazine have complications – methyldopa can cause a hemolytic anemia; hydralazine can lead to drug-induced lupus (2nd to procainamide for drug induced lupus). Methyldopa works differently from PCN: methyldopa messes with Rh Ag on surface of RBC and alters them. They are altered so much that IgG Ab's are made against the Rh Ag (our OWN Rh Ag). So, the drug is not sitting on the membrane, it just causes formation of **IgG** Ab's and they

attach to RBC to have macrophage kill it – what type of HPY is this? **Type II**. Therefore, methyldopa and PCN are type II for hemolytic anemia.

3. Quinidine: this is the 'innocent bystander' b/c immune complexes are formed. Quinidine acts as the hapten, and the **IgM** Ab attaches; so, the drug and IgM are attached together, circulating in the bloodstream. This is a different **HPY – type III**, and will die a different way, b/c this is IgM. When IgM sees the immune complex, it will sit it, and activate the classical pathway 1-9, leading to intravascular hemolysis, and haptoglobin will be decreased, and in the urine, Hb will be present.

XI. Microangiopathic hemolytic anemia

RBC's all fragmented – schistocytes (schisto – means split). **MCC chronic intravascular hemolysis = aortic stenosis**, in this dz, the cells hit something; therefore have intravascular hemolysis, Hb in the urine and haptoglobin is down. This is a chronic intravascular hemolysis, and you will be losing a lot of Hb in the urine; what does Hb have attached to it? Fe; so what is another potential anemia you can get from these pts? Fe def anemia. Example: will describe aortic stenosis (systolic ejection murmur, 2nd ICS, radiates to the carotids, S4, increased on expiration, prominent PMI), and they have the following CBC findings: low MCV, and 'fragmented' RBC's (schistocytes) – this is a microangiopathic hemolytic anemia related to aortic stenosis.

Other causes of schistocytes: DIC (lil fibrin strands split RBCs right apart b/c RBC is very fragile); thrombotic thrombocytopenic purpura, HUS – see schistocytes. When you have platelet plugs everywhere in the body, the RBCs are banging into these things causing schistocytes and microangiopathic hemolytic anemia. Example: runner's anemia, esp. long distance you smash RBC's as you hit the pavement; very commonly, you go pee and see Hb in it; to prevent, use bathroom b4.

Another cause of hemolytic anemia: **malaria – falciparum** b/c you have multiple ring forms (gametocyte (comma shaped and ringed form). It produces a hemolytic anemia, which correlates with the fever. The fever occurs when the cells rupture (the hemolytic anemia).

CHAPTER 6. HEMATOLOGY: WBC

I. Non-neoplastic Lymphoid Proliferations:

A. Neutrophils – when you have acute inflammation = ie appendicitis, neutrophilic leukocytosis, left shift, toxic granulation, and leukamoid rxn. Leukamoid rxn means that it looks like leukemia but it isn't and it's benign. Usually involves any of cell lines. What causes leukamoid rxns? TB and sepsis. You see greater than 30-50,000 cells in the blood. Kids get these a lot (ie otitis media). Adult with otitis med = 12,000; kids with 30,000 (exaggerated). Example: **Pertussus – whooping cough – lymphocytosis** (60,000) – pediatricians are worried about ALL leukemia, but kid doesn't have anemia or thrombocytopenia; kid comes in pale, coughing. Lymphocytes are mature and are totally normal. Lymphocytosis w/ viral infection or with pertussus.

In **atypical lymphocytosis** – this is a lymphocyte that is doing what it's supposed to do when presented to and Ag. It's responding to the Ag by dividing and getting bigger, so basically it's an antigenic stimulated lymphocyte. When talking about atypical lymphocyte, the absolute first thing that pops into the mind is: **mononucleolosis – EBV**. Other dz that are seen with large, beautifully staining bluish cells: CMV, toxoplasmosis, any cause of viral hepatitis, phenytoin. EBV is called the kissing dz b/c the virus holds up in the salivary glands. EBV affects B cells and CD 21. Mono causes viremia, generalized painful lymphadenopathy, very commonly get exudative tonsillitis, jaundice (hardly ever seen), increased transaminases (off the chart), and spleen enlargement and can rupture. Therefore don't play sports b/c can ruptured spleen can occur, so avoid contact sports usually for 6-8 weeks. Also causes macrocytic anemia via inhibiting intestinal conjugase).

Audio Day 3: Hematology File 5

Example: the boards will give you a classic hx of mono, and ask which tests you run, but monospot test is not on the choices b/c that's the trade name, so pick heterophile antibodies (hetero = diff, phile = loving). Heterophile Ab's are anti-horse RBC Ab's (or anti-sheep); they are different, hence "hetero"phile Ab's. Once you have mono, you always have it and will have 3-4 recurrences over your lifetime – ie reactivation consists of swollen glands, very tired, etc. EBV lives in B cells; the atypical lymphs in mono are T cells reacting against the infected B cells.

B. Monocyte = king of chronic inflammation, therefore expect monocytosis in pts with chronic infections – ie rheumatoid arthritis, Crohn's, ulcerative colitis, lupus, malignancy

Side Note: creatine gives energy b/c it binds to phosphate, and that is the phosphate you get from making ATP – so what serum test is markedly elevated in someone taking creatine for their muscles? Creatinine! B/c the end product of creatine metabolism is Creatinine. The BUN is normal in this person. Worthy board question.

C. Eosinophilia

You would see eosinophilia in Hay fever, rash in pt with PCN, strongoloides

Protozoa infections DOES NOT produce eosinophilia, therefore it rules out amabiasis (pinworm), giardia, and malaria. Only invasive helminthes produces eosinophilia. Adult ascariasis does NOT cause eosinophilia b/c all they do is obstruct bowels, it's when the invasive larvae form crosses into the lungs that causes eosinophilia. So anything that is Type I HPY causes eosinophilia; protozoa do not cause eosinophilia; ascariasis, and pinworms do NOT cause eosinophilia (all others – ie whipworms do b/c they invade).

II. Myeloproliferative Dz: Polycythemia – increased RBC ct, increased Hb and Hct

Difference between serum Na and total body Na? yes. Serum Na is milliequavalents per liter of plasma; total body Na is milliliters per kg body wt (the total amount you have). Similarly: **RBC mass** = total # of RBC's in entire body in mL/kg in body wt

RBC ct = # of RBC's/microliter of blood, therefore its how many you have in a certain volume of blood. Why is this a big deal? Example: went running and vol depleted – RBC ct would be hemoconcentrated, therefore would look like more RBC's per microliter of blood (b/c you depleted the plasma volume), but what would the RBC mass be? Normal (not actually synthesizing RBC's). So, there are 2 types of RBC's: relative and absolute. **Relative** = decrease in plasma vol causing an increase in RBC ct, but the RBC mass is normal. **Absolute** increase – is appropriate or inappropriate?

When would it be appropriate? Syn of RBC's – tissue hypoxia, so, any source of tissue hypoxia would be an appropriate response. Example: if you have lung dz, hypoxemia, COPD, high altitude – these are ie's of appropriate polycythemias. What if we have normal blood gases, but didn't have tissue hypoxia? This would be an inappropriate polycythemia. So, there are two things to think about with **increased RBC mass: polycythemia rubivera**, which is an ie of a stem cell proliferative dz of the BM, meaning that the stem cells are dictators, and nothing keeps them in check – a neoplastic dz; they can become leukemias. So, it would be inappropriate to have normal blood gases and no evidence of tissue hypoxia and have an increase in RBC mass. 2) **Tumor or cyst with an excess production of EPO**: renal adenocarcinoma making EPO, causing an increase in RBC mass – this is inappropriate b/c a tumor is inappropriately making it.

In summary: polycythemia is relative or absolute. Relative means that you just lost plasma vol (ie from running) with RBC ct increased, and mass is normal. Absolute increase: is it appropriate or inappropriate? Appropriate – anything that is a hypoxic stimulus for EPO release. If there isn't a hypoxic condition causing the EPO production, then you are ectopically making EPO from a tumor or cyst or you have polycythemia rubivera (a myeloproliferative dz).

III. Myeloproliferative dz – neoplastic stem cell dz that has lost all regulation and nothing can inhibit it anymore. 4 dz's that fit under this definition:

1. Polycythemia rubivera
2. CML (only leukemia in this category)
3. Agnogenic myeloid metaplasia – BM is replaced by fibrous tissue
4. Essential thrombocythemia – where a stem cell that makes platelets goes crazy and make 1 million, 600 platelets for microliter,
5. Myelodysplastic syndrome

A. Polycythemia rubivera: 4 H's:

1. Hyperviscosity (remember Pouseau's law = TPR = viscosity/radius^4). With polycythemia, it will have an increased resistance and TPR will go up; it will predispose to thrombosis, which kills you – thrombosis of anything – ie dural sinuses; MCC Budd chiari = hepatic vein thrombosis; coronary artery, SMV, anything can be thrombosed b/c blood slugging around and this is why phlebotomy is done. Phlebotomy is performed to make you Fe def – they want to make you Fe def – why? If you make them Fe def, b/c then it will take longer to make RBC's, so you purposefully slow down the process.

2. Hypovolemia – only polycythemia that has an increase in plasma volume that matches the increase in RBC mass; none of the other causes have an increase in plasma vol (these are measured with radioactive techniques). So, it is very rare to see an increase in plasma vol with polycythemia, except for this case. Why? Myeloproliferative dz's take years and years to develop therefore plasma vol is able to keep up; therefore both increase together over time.

3. Histaminemia – all cells are increased: RBC's, WBC's, platelets, including mast cells and basophils. Example: Classic hx: pt takes a shower and gets itchy all over body – this is a tip off for polycythemia rubivera – why? Mast cells and basophils are located in the skin and temperature changes can degranulate mast cells, causing a release of histamine, leading to generalized itching (very few things cause generalized itching – bile salt deposition in the skin in pts with obstructive jaundice, and pts with mast cell degranulation), face is red looking, too b/c of histamine b/c vasodilatation, leading to migraine-like headaches.

4. Hyperuricema – b/c nucleated hematopoetic cells are elevated, they then die, and the nuclei have purines in them. The purines will go into purine metabolism and become uric acid. Example: pt on chemotherapy must also be put on allupurinol to prevent urate nephropathy and prevent renal failure from uric acid. (allupurinol blocks xanthane oxidase). When killing cells you're releasing millions of purines when the nucleated cells are killed and the tubules are filled with uric acid, leading to renal failure. Must put them on allupurinol. This called tumor lysis syndrome. The same thing occurs in polycythemia rubivera b/c there is an increase in number of cells that eventually die and you run the risk of hyperuricemia.

B. RBC mass/plasma vol/O2 sat/EPO

Polycythemia rubivera – h,h,N (inappropriate), low (have too much O2 b/c you have piles of RBCs and therefore suppress EPO (it's a hormone). The hint was O2 content=1.34 * Hb * O2 sat +pO2

COPD, tetralogy of fallot, high alt – H, N, L, H (appropriate polycythemia b/c it's responding to hypoxia)

Renal adenocarcinoma, hepatocellar carcinoma, any cyst (renal, esp. ie hydronephrosis, wilm's tumor) – H, N, N, H (even with normal gas studies b/c ectopically produced)

Relative Polycythemia – N, L, N, N

IV. Leukemias

They are a malignancy of the BM and mets anywhere it wants.

A. General characteristics of Leukemia; therefore, will always have:

1. Generalized lymphadenopathy, hepatosplenomegaly, etc…
2. Abnormal cells in the peripheral blood – BLASTS (myeloblasts, lymphoblasts, monoblasts, megakaryoblasts) – so some abnormal blasts are in the peripheral blood
3. B/c it is arising in the BM, will always crowd out the normal hematopoetic cells, and will ALWAYS have an anemia, usually normocytic
4. Thrombocytopenia b/c crowding out the normal megakaryocytes from making platelets
5. Usually an increase in WBCs ct with abnormal cells present
6. Acute vs. chronic – Do a bone marrow test and look at blasts – if blasts are <30%, this is chronic; if the % blasts is >30%, it is acute. Therefore the blast ct tells if its acute vs chronic

B. Age brackets: Know age brackets

0-14 = ALL
15-39 = AML – myeloblast with Auer rods in peripheral blood
40-59 AML, CML (separate with BM – AML with >30% and CML with <30%, 9, 22, Philly c'some)
60+ = CLL
MC overall leukemia regardless of age = CLL
MCC generalized nontender lymphadenopathy in pt 60+ = CLL; not b/c it's a lymphoma, but b/c it mets to lymph nodes).

C. Different Types of Leukemia:

Example: peripheral smear of 49 y/o, 150,000 WBC ct, 1% myeloblast in peripheral blood and BM, generalized nontender lymphadenopathy, hepatosplenomegaly, thrombocytopenia, and normal anemia – dx? CML (look at age bracket and % blasts). To prove, get 9, 22 study (abl protooncogene with nonreactor tyrosine kinase activity and goes from 9 to 22 and fuses with the cluster fusion gene). LAP – leukocyte alkaline phosphatase stain can also be used. Look at which neutrophils take it up – mature neutrophils all have LAP in them; neoplastic neutrophils do not – why? B/c they are neoplastic. So, if no stain, know its neoplastic (normal cells take up stain). Called a LAP score – always low in CML. So, the two tests: Philly c'some and LAP score, which is always low.

Example: tear drop cell b/c there was a dictator in BM, and cells have to move to the spleen, so there is a migration of hematopoetic cells from the BM to the spleen. When you take up hematopoesis anywhere other than the bone marrow, this is called extramedullary hematopoesis. So, the spleen in huge – esp. in atherogenic myeloid metaplasia. Some of the megakaryocytes go back to the marrow to lay down collagen; and megakaryocytes go back. Fibrosis of the BM occurs (used to be called myelofibrosis metaplasia). So, not everyone left the BM, and stay in the fibrotic marrow. For them to get to the spleen, they have to work their way through strands of fibrotic tissue, often times damaging their membrane, leading to tear drop cells (so, it gets passed the 'barbed wire' – fibrous tissue – and getting into the sinusoids, they are tear drop cells in the peripheral blood). So, pt with huge spleen, with tear drop cells – **atherogenic myeloid metaplasia**.

Example: too many platelets – **essential thrombocythemia** (makes too many platelets)

Example: 4 y/o pt that presents with sternal tenderness, fever, generalized nontender lymphadenopathy, hepatosplenomegaly, normocytic anemia, 50,000 WBC count many of which had an abnormal appearance cells. What is the dx? **ALL (acute lymphoblastic leukemia.** MC cancer in kids; the most common type is: common ALL Ag B cell leukemia. CD10+; calla+ Ag B-cell ALL, associated with down's syndrome

Example: 65 y/o, normal criteria, smudge cells and normocytic anemia. They also have hypogammaglobinemia b/c they are neoplastic B cells and cannot change to plasma cells to make Igs. Therefore, MCC death in CLL = infection related to hypogammaglobinemia. What is the Dx? **CLL**

Example: 62 y/o, normal criteria, special stain of TRAP (tartrate resistant acid phosphatase stain) – **hairy cell leukemia** (know the TRAP stain)

Example: 35 y/o pt, with normal criteria, with 50,000 abnormal WBCs and Auer rods (abnormal lysosomes), 70% blast cells in the BM. What is the Dx? **AML.** Know what Auer rods look like, know the leukemia that infiltrates gums (acute monocytic anemia – M5), and acute progranulocytic anemia (M3) – they always have DIC, has a translocation 15,17. Rx = retinoic acid (vit A – causes blasts to mature into b9 cells).

V. Lymph nodes

A. General Characteristics:

1. Painful vs painless: lymphadenopathy that is painful is not malignant; mean that you have inflammation causing it (does not always mean infection) – you are stretching the capsule, it's an inflammatory condition (lupus), and that produces pain. When you have non-tender, think malignant, either (1) mets or 2) primary lymphoma originating from it. Always tell if painful/less.

2. Localized vs. generalized lymphadenopathy: Localized (ie exudative tonsillitis goes to local nodes; breast cancer goes to local nodes. Generalized (systemic dz – ie HIV, EBV, Lupus).

3. Examples:
   (a) Bruton's agammaglobinemia – germinal follicle absent: B-cell
   (b) DiGeorge syndrome– paratrabeculae messed up: T-cell country

(c) Histiocytes (Han shculler Christian/letterman sieve dz) – involves sinuses
(d) SCID (adenine deaminase def) – B and T cell deficiency, therefore no germinal follicle and no paratrabeculae but will have sinuses.
(e) Reactive lymphadenopathy: Macrophage takes Ag, and presents to germinal follicles and they spit out a plasma cell, making Ab's

B. Non-Hodgkin's lymphoma

Follicular lymphoma = MC Non-Hodgkin's Lymphoma: B-cell; translocation 14,18; and apoptosis gene knocked off, so the cells are immortal.

What 2 tissues are resistant to invasion by cancer cells? Cartilage and elastic tissue

Example: **Burkitts**; caused EBV; Translocation 8,14, myc oncogenes, starry sky – normal macrophages looking like sky at night, #3 MCC cancer in kids; can cure; MC lymphoma in kids, usually in the abdomen (ie payers patches, paraortic lymph nodes, also but rarely in the jaw, or testes)

Example: plaque like lesions, no teeth, not a fungal infection – actually the inflammatory cells are really neoplastic; so the helper T cell in **mycosis fungoides** is neoplastic, therefore it's a T cell malignancy. Involves the skin and lymph nodes vs. **Sezary** cell syndrome which is seen in peripheral blood (malign helper T cell that is in peripheral blood, in mycosis fungoides)

Example: kid with EM of eczematous rash all over – generalized nontender hepatosplenomegaly, , EM of monomorphic cells which were CD 1+ cells – histiocytosis X (**letterman sieve dz**) (birbeck granules, look like tennis racket – clostridium tetani which has a spore also looks like a tennis racket)

Audio day 3: Hematology file 6

Painful lymphadenopathy = some type of inflammatory condition, not malignant

Painless lymphadenopathy = malignancy: MC malignancy of lymph node = metastasis
MC primary cancer of lymph node =
non Hodgkin's lymphoma: follicular B cell lymphoma (translocation: 14, 18. This knocks off apoptosis gene and the cell is immortal).

C. Hodgkin's Dz– four different types. In Hodgkin's the cardinal signs are: fever, night sweats, and wt loss (usually TB unless proven otherwise). It is usually localized, nontender lymphadenopathy. On micro: the malignant cell is Reid Steinberg cells, RS cells – owl eyes - common on boards (also giardia, CMV, ashoff nodule in rheumatic fever). Less # = better prognosis; more = worse

The most important one is **Nodular Sclerosis**: MC = nodular sclerosis, seen in women; it is nodular (hence the name), and has lots of sclerosis (collagen deposition, so it's hard and non-painful node). You would see it in a woman with lymph node involvement in 2 places: 1) anterior mediastinum and 2) somewhere above the diaphragm- ie the cervical nodes, superclavicular nodes, neck. This combination of mass in neck and anterior mediastinum = nodular sclerosis. You would see RS cells on micro.

2. Terms: poly and monoclonal (this will help to understand the diff from multiple myeloma and other things that increase gamma globulin p). On serum protein electrophoresis, albumin migrates the farthest b/c it has the most neg charge, whereas gamma globulin just sits there.

(a) Polyclonal: "poly" = many, "clonal" = plasma cells, therefore you have many clones of plasma cells b/c the gamma globulin region is where the gamma globulins are. Think "g-a-m" to know the order of most abundant/greatest number of globulin. Therefore, on electrophoresis, you see a little peak, this is an increase in IgG b/c it's the most abundant IgG – this makes sense b/c for chronic inflammation, the main Ig is IgG, and for acute inflammation the main Ig is IgM. So, in chronic inflammation (ie Crohn's, rheumatoid arthritis, UC) there is an increase in IgG – which will show a large diffuse elevation (a nice round mtn). This is called polyclonal gammopathy b/c many benign plasma cells are making IgG. Polyclonal gammopathy always means benign and chronic inflammation. Will not have polyclonal gammopathy with acute inflammation (ie acute appendicitis); this not any rise in the gamma gobulin region for acute inflammation – the main Ig is IgM for acute.

(b) Monoclonal = one clone of plasma cells are making Ig's; other plasma cells are not making Ig's b/c they are suppressed. So, when you see a monoclonal peak, this means it's a malignancy of plasma cells. Meanwhile, all other plasma cells are suppressed by immunologic mechanisms. The malignant clone makes its own Ig; most of the time it is an IgG malignancy. They are making many light chains and get into the urine – these are called Bence Jones proteins. Monoclonal usually means malignancy and always means multiple myeloma.

(c) Peaks (in order): albumin, alpha 1, alpha 2, beta, gamma – have

a pt 25 y/o, non-smoker, had emphysema of the lower lungs, no alpha 1 peak – what is Dx? Alpha 1 antitrypsin def.

VI. Plasma Cell Disorders:

A. Multiple Myeloma (MM)

MM is a very bad dz, incurable, and unless you get BM transplant, you will die. It's usually seen in people over 50, a little more common in women. The most common form is Ig kappa, which is abundant. Plasma cells have IL-1 (aka osteoclast activating factor); this is why you see lots of lytic lesions in the skull or bones. The lytic regions are round, and nicely cut (in contrast to Paget's dz, the lytic regions are fuzzy and not sharply cut). While in MM lesions have a fine, sharp (cookie cutter cut) border, b/c IL-1 activates osteoclasts, leading to the punched out lesions.

Example: if there was a lytic lesion in the ribs and pt coughed, what would potentially happen? Pathologic fractures and these are extremely common.

Example: elderly woman coughs and develops severe pain – you see lytic lesion of the rib, so what does the pt have? Multiple myeloma

Know what plasma cell looks like – has bright blue cytoplasm and nucleus is eccentrally located (around the nucleus are clear areas present). On EM, will see layer and layers of RER, b/c they are constantly making protein (ribo's are where ribosomal RNA sits on). Must know what plasma cell looks like on EM and giemsa stain. Summary of multiple myeloma – lytic lesions, Bence Jones proteins, and seen in elderly pts.

1. **Amyloidosis:** is a clinical characteristic of MM

Amyloid on EM is a non-branching, linear compound with a hole on the center of it. They always ask a question on amyloidosis b/c it ends up in the differential dx for multi-system dz (systemic amyloidosis). Amyloid is a protein, but what's interesting is that many other different proteins can be transformed/converted into this unique protein – ie pre-albumin,

calcitonin (tumor marker for medullary carcinoma of the thyroid),
light chains in MM, and

trisomy 21. In Trisomy 21 (Down's syndrome), the c'some 21 codes for beta amyloid, and if you have three of these, you will make more beta amyloid protein. And beta amyloid protein is toxic to neurons; so, if you have trisomy 21 are making more beta amyloid protein, then you will be losing more neurons b/c you are losing more of this protein that is toxic to neurons. This is why they always ask the question about a pt dying at forty and on autopsy, you see atrophy of the brain and it reveals senile plaques in frontal and temporal lobes, and will ask what pt had – Down's syndrome. All down's pts will get Alzheimer's. Down's pts die from 1 of 2 things: either from (1) endocardial cushion defects – which leads to heart defects and an ASD (in childhood) and a VSD or (2) Alzheimer's dz (death b/c chromosome 21 is making too much beta amyloid protein). Example: 40 y/o with Alzheimer's dz has downs syndrome. Beta amyloid is most important protein.

VII. Lysosomal storage dz's

Two different cells that they like to ask questions about.

1. Gaucher dz: there is a macrophage with a crinkled paper like appearance in the cytoplasm. There are lysosomes filled with glucocerebroside, therefore pt has Gaucher dz. It's an auto recessive dz with a missing glucocerebroside.

2. Niemann-Pick dz: bubbly cytoplasm, severe mental retardation, buildup of sphingomyelin in the lysosomes, therefore the pt has Niemann-Pick dz, missing sphingomyelinase.

3. Pompe's Dz: only glycogen storage dz that has lysosomal storage = Pompe's; only glycogen storage dz that is lysosomal b/c they are missing an enzyme to break glycogen down in the lysosomes. How does pt die? Die from cardiac failure b/c excess deposition of normal glycogen in the heart.

Summary: bubbly cytoplasm = Niemann-Pick dz; crinkled paper = guacher's, both are lysosomal storage dz

CHAPTER 6: HEMODYNAMIC DYSFUNCTION

I. Thrombogenesis: The Coagulation System

Hemostasis: things in our body that prevents clots from developing in BV's. If these clots were not prevented, the pt either has DIC, thrombotic thrombocytopenic purpura (TTP), or HUS, and all of them lead to death. So, why don't we form clots in our small BV's? [small blood vessels include arterioles, venules, and capillaries, while small airways include terminal bronchioles, resp bronchioles, alveolar duct, and alveolus].

A. So, why don't we form clots? B/c we have coagulation factors such as: heparin, PGI_2, Protein C and S, and tissue plasminogen activator. So all of these things are used to prevent little clots occurring in our small blood vessels.

1. Heparin (a GAG, a mucopolysaccharide). It is normally found in the body and helps prevent formation of clots. How does heparin work? It ENHANCES antithrombin III. Antithrombin III is made In the Liver (like all other proteins). Therefore, heparin gets the credit for anticoagulating you, but its antithrombin III does all the work. Antithrombin III neutralizes most of the coagulation factors. So, we have a little bit of heparin in our small vessels, which prevents clotting from occurring.
2. PGI_2, prostacyclin, made from endothelial cells, a vasodilator. When the vessel is vasodilated, and blood flows faster, it is more difficult for things to stick; therefore, it's more difficult for a thrombus to stick b/c it blows away so fast.

Therefore, vasodilatation is antagonistic to forming thrombi in anything b/c everything is moving too quickly. PGI_2 also prevents platelet aggregation.

3. Protein C and S are Vit K dependent factors (as are factors 2, 7, 9, 10). Functions of protein C and S: they INACTIVATE (ie neutralize or get rid of) two things – factors 5 and 8. They actually inhibit factors 5 and 8 in our body. This is interesting b/c antithrombin III cannot inhibit these. Antithrombin III can only inhibit serine proteases, and Factor 5 and 8 are not serine proteases.

4. t-PA (tissue plasminogen activator) – this is what we use to dissolve a clot in a pt with coronary thrombosis – it activates plasminogen, which produces plasmin. Plasmin basically eats everything in site.

B. Deficiency in any of the anticoagulants: So, if we are def in any of these things (heparin, PGI_2, protein C and S, and t-PA), clots would form. In other words pt will be thrombogenic.

Why are pts on birth control thrombogenic? B/c it increases the synthesis of 5 and 8, increases syn of fibrinogen, and inhibits antithrombin III. So, birth control pills are blocking heparin by inhibiting ATIII. Therefore, the estrogen of the pill is thrombogenic, thereby assisting in the formation of clots. Deadly duo: woman on birth control and smoking = bad; smoking is thrombogenic b/c it damages endothelial cells (so both are thrombogenic).

C. Formation of a stable clot

For example: a pt is shaving and cut himself. How do we stop bleeding when you cut a small BV (not talking about muscular arteries – need to plug that) – we're referring to an injury/cut/damage of a small vessel (ie arteriole, venule, capillary. What will stop the bleeding? To determine this we use bleeding time as ie: bleeding time is used to evaluate platelet function.

Example: If pt has hemophilia A and has no factor 8, the pt will still have a NORMAL bleeding time b/c bleeding time has NOTHING to do with coagulation factors.

Bleeding time is purely a PLATELET thing.

1. How do they perform the test?
Cut the pt (inflict wound), start stop watch, and dab wound every thirty sec; when the wound stops bleeding, this is the pt's bleeding time – normally it is 7-9 mins.

2. The pathway of bleeding time: When the vessel is cut, tissue thromboplastin is released (which activates the extrinsic coagulation system, but has nothing to do with bleeding time). The cut exposes collagen and of course Hageman factor (factor 12) is activated by the exposed collagen; hence the intrinsic pathway is activated, but this has nothing to do with bleeding time, either. Endothelial cells and megakaryocytes make an adhesion product (a type of glue) whose special purpose is to stick to platelets – vWF. vWF is part of the factor 8 molecule and is made in 2 places – megakaryocytes in the BM and endothelial cells. What's made from megakaryocytes? Platelets; which carry a little bit of glue with them in their granules. Also, platelets are made in the endothelial cells. So, when you damage the small BV's, vWF is exposed and platelets have receptors for vWF – which is basically an adhesion molecule (just like neutrophils had receptors for the endothelial cell made by the endothelial cell). If neutrophils cannot stick to venules, then they cannot get out to kill bugs. Same concept here – platelets have to stick to before they can do their thing – so vWF is the adhesion molecule that allows them to do that. So, now the platelet sticks – called platelet adhesion. When the platelet sticks, it causes the platelet to release chemicals – most imp chemical is ADP – this is a potent aggregating agent, and causes platelets to stick together. They start to help form a thrombus to begin to stop the bleeding. However this is not enough to complete the process. So, this is called the release rxn – when the platelet sticks, it causes the platelet to release chemicals, and the most imp chemical is ADP. When platelets come by, they will stick together (b/c of the ADP) and the bleeding will go down. But still not enough; needs another chemical. As soon as the platelet has the release rxn, it starts synthesizing its own unique substance – Thromboxane A_2; platelets make it b/c they are the only cell in the body that has thromboxane synthase. So, it can convert PgA_2 into TxA_2, potent vasoconstrictor. This is important in stopping bleeding, b/c if you slow rate of blood flow, it will make it easier for platelets to stick together and the platelets won't get washed away. As opposed to prostacyclin, which is a vasodilator the platelets cannot stick b/c the blood flow has increased. TxA_2 is the vasoconstrictor in Prinzmetal's angina. It's also a bronchoconstrictor, so it has affects in asthmatics b/c it helps LT C4, D4, and E4.
So, TxA_2 is a vasoconstrictor, a bronchoconstrictor, and a platelet aggregator. It puts the finishing touches on it and causes the platelets to really aggregate, and blocks the injured vessels, and bleeding time has just ended.

3. Integration: Platelets do two things (1) release rxn, where chemical were already made in it were released – so, preformed chemicals were released and (2) it makes its own chemical called TxA_2). This is analogous to MAST CELLS. For example: two IgE's bridged together, and pollen bridged the gap. This caused the mast cells to have a release rxn (release of preformed chemicals: histamine, serotonin, and eosinophil chemotactic factor). These chemicals then started the inflammatory rxn in a type I HPY rxn. The mast cell released arachidonic acid from its membrane and we ended up making PG's and leukotrienes. They were released 30 minutes to an hour later and furthered/enhanced type I HPY (inflammatory) rxns. So the mast cell had a release rxn of preformed elements and it made its own PG's/leukotrienes. That is what platelets did: released its preformed chemicals and made its own chemical: TxA_2.

Plug is temporary – it is a bunch of platelets stuck together and held together by fibrinogen, and is enough to prevent bleeding (to stop bleeding time), but if you scratch or try to open the wound, it would start bleeding again, so it's not a stable plug.

4. Conditions that arise with increased or decreased bleeding time: Lets screw up bleeding time:

(a) What would be an obvious mess up of bleeding time? Thrombocytopenia: decreased platelet count therefore if you have less than 90,000 platelets, you will have a prolonged bleeding time b/c you will not have enough to aggregate. Another dz that has a problem with adhesion molecule defect is vWB dz (MC genetic hereditary dz, AD)

(b) MCC prolonged bleeding time = taking aspirin; mechanism? Aspirin blocks platelet COX, not TxA_2 (blocked by Dipyrramidal). Endothelial cells have COX, too; so why didn't the endothelial cells inhibit COX from making PGI_2? The platelet COX vs the endothelial COX reacts differently to aspirin. Different compounds act differently to non-steroidal. It's a 9:1 ratio (aspirin block platelet COX more than endothelial COX); cannot neutralize both – would be bad. So, aspirin is irreversible and other NSAIDs are reversible for 48 hrs. So, if you took an aspirin, it prevents platelets from aggregating, and therefore they do not work, so if you cut yourself, the bleeding time will be increased. Aspirin inhibits platelets from aggregating; no TxA2, so it won't work and you will continue bleeding.

5. Continuation of Clotting: Recall that the release of t-PA which will activate extrinsic system and it also activates the Hageman factor 12 b/c of collagen being exposed therefore the intrinsic system is also activated. End product of coagulation is thrombin, and thrombin converts fibrinogen into fibrin. So, we have pile of platelets stuck together and they are bound with fibrinogen. What will happen right after the bleeding time ends? The activated thrombin (produced by the extrinsic and intrinsic pathways) will convert the fibrinogen (which is holding the platelets together loosely) into fibrin, making a more stable platelet plug that you are not able to dislodge. So, who will remove that platelet plug from the vessel? Plasmininogen, and when it is activated and plasmin are formed; plasmin will drill a hole through it and recanalize, so the vessel is normal again.

D. Platelet deficiency vs Coagulation deficiency

So, with bleeding time, the platelets (which are held together with fibrinogen) form a temporary hemostatic plug. This stops the bleeding time, but it's very unstable. When the Coagulation system makes thrombin, it converts fibrinogen into fibrin, making a strong platelet plug. This difference is very imp b/c it distinguishes a difference between a platelet abnormality vs coagulation factor deficiency

1. If you have a platelet problem, what will happen to bleeding time? Prolonged, b/c if the pt cuts a vessel, what will happen? It will continue to bleed (therefore a platelet prob). Therefore, in platelet abnormalities, you see bleeding from superficial scratches or cuts (pt continues to bleed b/c you can't form a temporary hemostatic plug). In addition, you mess up the integrity of small vessels when platelets are messed up, leading to petechia (hemorrhage only see in a platelet abnormality – pinpoint area of hemorrhage), echymoses (purpura), epistaxis (nose bleed, which is the MC manifestations in platelet problem).

NONE of these manifestations (petechia, echymoses, epistaxis, and bleeding from superficial scratches) occurs in Coagulation factor deficiency!!!

2. Coagulation deficiency: Example: pt w/ hemophilia A – def in factor 8; what is bleeding time? Normal. What type of problems do these pts run into? LATE re-bleeding. Example: appendectomy – everything went fine, pt woke up, starting moving around and blood started coming out (massive amounts of blood – came out of the wound and pt bled to death). B/c the only thing that was holding the blood in was sutures and temporary hemostatic plugs. If you have a Coagulation factor def, you cannot convert fibrinogen into fibrin, and the platelets will fall away, leading to late re-bleeding. Pt is able to handle superficial scratches/cuts. However, will not hold vessel closed for too long b/c late re-bleeding will take place. Best question to ask to see if they have a Coagulation def: have you had a molar tooth removed (ie a wisdom tooth)? Let's say she says yes; Then ask, did you have any problems with bleeding? NO, (therefore pt does NOT have Coag factor def.); why? Extraction of a wisdom tooth imposes the greatest hemostatic stress on the system that ever exists, its even worse after a thoraoctomy, and lots of surgical procedures. So if after extraction of a wisdom tooth no bleeding occurred, then they have normal Coag factors.

Example: If pt had a wisdom tooth extracted, and had hemophilia A, pt had no problems with bleeding; however, what is the ONLY thing holding the wound shut? Lil temporary platelet plugs that are held together by fibrinogen (not fibrin). Dentist tells you to wash mouth out (with salt or a little bit of peroxide) when you get home; bad b/c you will bleed to death and suffocate on your own blood (all hemostatic plugs are gone and pt bleeds to death). This is LATE rebleeding; not from superficial scratches. Other conditions of coagulation deficiency: Menorrhagia – more of Coag def, than a platelet problem, and the potential for Hemearthroses: where you bleed into closed spaces.

Summary: So, platelet problem (epistaxis, echymoses, petechia, bleeding from superficial scratches) vs coagulation problem (late re-bleed, Menorrhagia, GI bleeds, hemarthroses). This is all based on knowing what happens to small vessels.

E. Tests for platelet abnormalities

1. First do platelet count: if you took an aspirin you still have a normal # of platelets, but they don't work.

2. Secondly do Bleeding time – assesses platelet function

3. Test for vWF? Ristocedin cofactor assay - if missing vWF, ristocedin can't cause platelets to clump (most sensitive test for dx'ing vWF dz).

So, three tests that assess platelets: platelet count, bleeding time, ristocedin cofactor assay (for vWB Dz)

Example: older man with osteoarthritis – prostate was resection and massive bleeds: if have osteoarthritis, you have pain, and if you have pain, you will be on pain medication, an NSAIDS, and will give test results – PT/PTT/platelet count all

normal – bleeding time is longer. Rx – platelet pack transfusion – when you give from a donor, it WILL work (donor's platelets are normal). So, if your taking NSAIDs, platelets not working and if you have a prob during surgery, give pt platelets from donor.

Audio day 3: hematology file 7

F. Extrinsic vs. Intrinsic system:

1. Factors involved:
   Extrinsic = factor 7
   Intrinsic = factors 12, 11, 9, 8
   Both share the same final common pathway – factor 10. (What is another system that has a final common pathway? Complement–whether by the classical pathway, the alternate pathway, or by the MAC pathway, all includes C3)
   What do we have left? 10, 5, 2 (Prothrombin), 1 (fibrinogen) and then the clot.

2. Tests involved:

   a) Prothrombin time (PT):
   Evaluates the extrinsic system all the way down to the formation of a clot – so it only deals with 7, 10, 5, 2, and 1. End stage of the test is a clot in the test tube. INR = standardized way of doing it – standardization technique (same everywhere in world).

   b) Partial thromboplastin time (PTT):
   Evaluates the intrinsic system all the way down to a clot – so it deals with 12, 11, 9, 8, 10, 5, 2, and 1.

   Example: PT is prolonged, but PTT is normal, what is the factor def? 7
   B/c the prothrombin was prolonged; this includes 7, 10, 5, 2, or 1. And the PTT are normal, meaning that 12, 11, 9, 8, 10, 5, 2, 1 are all normal. So the only one responsible is 7.
   Example PTT is prolonged, but PT is normal, what is the factor def? Factor 8 (play odds). Why? If PTT is prolonged, it is 12, 11, 9, 8, 10, 5, 2, and 1 that is the problem. However the PT is normal, therefore 7, 10, 5, 2, and 1 are normal. Therefore, its one the PTT factors (12, 11, 9, 8). We know what hemophilia A (next to vWB Dz) is the MC factor def, therefore, if you play odds, it's a factor 8 def.

   Example: what did warfarin block? Epoxide reductase. So, that prevented the gamma carboxylation of Factors: 2, 7, 9, and 10. So, what do you follow with warfarin? PT. What is the only factor you are not evaluating to when you are doing a PT time for a person on warfarin? Factor 9 – b/c its part of the intrinsic system. What is the PTT in a person on warfarin? Prolonged b/c factors 2 and 10 are vit K dependent factors in the final common pathway. However, PT does a better job in evaluating warfarin b/c 3 out of the 4 things that it's involved in are in the prothrombin time. So, both PT and PTT are prolonged when you are on warfarin, but PT is better diagnostic tool.

   Example: what do you follow heparin therapy with? PTT (evaluates the intrinsic pathway). Factors that antithrombin III knocks off: 12, 11, 7, 10, 2, 1 are all neutralized by antithrombin III. So, with pt on heparin, PTT is prolonged, what is the PT? Prolonged. It's just that the PTT does a better job at evaluating heparin (many factors antithrombin III involved with)

   So, BOTH PT and PTT are prolonged if on warfarin or heparin; however, it turns out that PTT is better at evaluating heparin and PT is better for warfarin.

II. Fibrinolytic system: Plasmin

Plasmin – leaves crumbs – its breaks down things (fibrinogen, fibrin, coagulation factors) – think fibrinoLYTIC system. When it breaks down a clot, there are many pieces (ie fibrin) left around, which are fibrin degradation products.

What is the single best screening test for DIC? **D-dimers** (better answer) or fibrin split products. What plasmin does is breaks things apart, leaving crumbs behind and you have degradation products. D dimers are the absolute best test for DIC (di- means 2). When you form a fibrin clot, factor 13 (fibrin stabilizing factor) makes the clot stronger. How do you stabilize strands? Link them by putting connections between them to make them stronger (this is what factor 13 does). So, how do you make collagen stronger? By, linking them to increase the tensile strength (factor 13 will put a crossbridge in fibrin). What D-dimer is detecting are only those fibrin factors that have a link (ie when there are two of them held together, this what the test picks up). What does this absolutely prove? That there is a fibrin clot. Do you see this in DIC? Yes.

Example: Would you see it if you broke apart a platelet thrombus in a coronary artery? (Remember a platelet thrombus is a bunch of platelets held together by fibrin). So, what would the D dimer assay be if you broke apart that clot? Increased, you would see increased D dimers and would see the little fibrin strands held together by cross linking. They often do that to see if you have recanalized or if you got rid of your thrombus.

Example: it is often also seen with a pulmonary embolus, b/c if you have a pulmonary embolus, one test is a D dimer b/c you will form a clot that will activate the fibrinolytic system, and it will try to start breaking it down, and there will be a release of D dimers. Single best test for DIC. Good test for picking up pulmonary embolus, along with ventilation/perfusion scans. Excellent test to see if you have reperfusion after given t-PA b/c it proves that if D dimers were present, a fibrin clot must be present (fibrin was there so it proves it).

III. Vessel abnormalities

A. Senile purpura: Seen on the back of hands of an old person – they hit things and get senile purpura; vessels get unstable as you get older and subcutaneous tissue thins. When you hit yourself, BV's rupture and you get echymoses – called senile purpura, an age dependent finding. Only present in places that normally hit things, back of the hands and the shins. Example: Mom was put in old age home and the children were gonna sue the old age home for abuse. Do the children have a case? No, b/c it has nothing to do with abuse and is an age dependent finding. Example: now if they also saw echymoses on buttocks and back, this is not a normal place to get trauma related to just bumping into things – that would be abuse. Senile purpura is the cause of echymoses on the back of the elderly's hand. Everyone will get this, everyone, no one is exempt.

B. Osler Weber Rendu Dz aka hereditary telangiectasias: Many of these pts have chronic Fe def anemia, related to persistent GI bleeds. You can make the dx with PE of the pt. The pt will have small red dots called telangiectasias and if you look on the lips and tongue you will see telangiectasias, and if you do endoscopy, you will see the little red dots throughout the GI tract. What does this pt have? Osler Weber Rendu Dz aka hereditary telangiectasias. It is the MC genetic vascular dz. Therefore, you can see why you get chronic Fe def and bleeds b/c the telangiectasias will rupture. It is kind of like the angiodysplasia of the skin

So, these are the two vessel dz's: senile purpura and Osler Weber Rendu dz, and also scurvy.

IV. Platelet Abnormalities

Findings of platelet problems: all have a problem in making a hemostatic plug, epistaxis (MC), petechia, echymoses, and bleeding from superficial scratches/cuts.

Example: 12 y/o kid, with URI one week ago, presents with epistaxis. Perform PE, and you see lesions that do NOT blanch (need to know the difference between petechia and spider angiomas: petechias do not blanch b/c bleeding into the skin; spider angioma WILL blanch b/c it's an AV fistula). Platelet count is 20,000. What is your dx? Idiopathic thrombocytopenic purpura. Mechanism: IgG against the platelet. What type of HPY is this? Type II. Who is removing the platelet? Macrophages in the spleen (b/c IgG marked the platelet for destruction by the macrophage). This is similar to autoimmune hemolytic anemia, but this is autoimmune THROMBOcytopenia. Rx – if they are very symptomatic, give corticosteroids; if not, leave alone and it will go away.

Example: woman with "+" spearman Ab test, epistaxis, petechia, generalized tender lymphadenopathy, and splenomegaly. Pt has LUPUS, autoimmune thrombocytopenia, same mechanism: IgG auto-antibodies against platelets, a type II HPY rxn, with macrophage related removal.

A. TTP (thrombotic thrombocytopenic purpura) and **HUS** (hemolytic uremic syndrome)
Both have similar pathophysiology. These are NOT DIC, therefore you are not consuming coagulation factors; the PT and PTT are totally and unequally normal. What you see is a formation of a temporary hemostatic plug of small blood vessels (bleeding time) and the coagulation system converting fibrinogen to fibrin to form a strong platelet plug. So in TTP and HUS, something in the plasma damages small vessels throughout your body, so that platelets stick and platelets aggregate and eventually form firm platelet plugs in all the vessels of the entire body. Would you consume all the platelets with all that sticking going on? Yes. Will you bleed b/c of that? Yes. What will you see in your peripheral blood? RBC will be smashed, leading to schistocytes. Therefore you will have a microangiopathic hemolytic anemia. Pts will have thrombocytopenia, fever, renal failure (b/c glomerular capillaries will have these platelet plugs in them). Absolutely have to have schistocytes in the peripheral blood with hemolytic anemia to make the dx.

1. 2 causes of HUS:

   a) 0157:H7 E. coli (toxin producing E. coli that can be present in undercooked beef. The toxin damages the vessel, leading to the dz, and this is called HUS. One of the MC causes of acute renal failure in children = HUS.

   b) Shigella toxin (very potent) that leads to shigellosis and then HUS.
   In TTP/HUS will see low platelet count, prolonged bleeding time, and normal PT/PTT b/c you're not consuming coagulation factors, but only consuming platelets.

V. Coagulation deficiency

In Coagulation deficiency, you different sign's symptoms, such as: delayed bleeding ie go through operation with no prob, then the pt starts moving around that's when it's bad. When pt has an operation and they start bleeding out of the wound, the MCC is not a coagulation factor deficiency; the MCC is due to suture slipped or a bleed. When you have a coag deficiency, just have to tie it off.

Example: molar extraction with constant oozing of blood b/c nothing holding those small vessels together except a temp hemostatic plug – need a tight fibrin bond to plug it up.

Example: It is showing hemorrhage into the fascial compartment of the thigh. In the knee, there are repeated hemarthroses and the pt has hemophilia A. Will not see hemarthroses or bleeding into spaces with platelet abnormalities, but only coagulation factor deficiency.

A. Must know the difference between hemophilia A and vWB Dz (these are the key coagulation deficiencies)

1. **vWB Dz** – missing vWF, therefore there is a platelet adhesion defect, therefore, they have all the signs and symptoms of a PLATELET problem. However, they also have a factor 8 deficiency, but it is very mild and never severe. So, they have TWO abnormalities – they have a platelet defect AND a coagulation factor defect. This is why they can have menorrhagia and GI bleedings (this the coagulation part of it); will also see history of epistaxis and they bruise easy. There are 3 parts of the factor 8 molecule: vWF, factor 8 coagulate (part of intrinsic system), 8 Ag. The 8 Ag has a carrier function: it carries around vWF and factor 8 coagulant in the blood (so it's a chauffeur) - so it functions as a carrier protein. All 3 of these can be measured.

2. Differences in two dz's:
a) Genetics: In pts with hemophilia A it's an X linked recessive dz, therefore males get the dz. Whereas vWDz is Autosomal dominant, and only one of the parents have to have the abnormality and 50% of the kids will have the potential to get the dz.

b) Number of deficient factors: Hemophilia A only has one factor that is deficient: 8 anticoagulant; they have normal 8 Ag levels and normal vWF levels. vWDz has ALL 3 things decreased: 8 Ag, factor 8 anticoagulant (mildly decreased), and vWF.

B. What drug can increase the synthesis of all three of these factor 8 molecules? The drug comes from ADH and is called desmopressin (ddadp). This can increase the synthesis of all three factor 8 molecules. It will help treat mild hemophilia A, and is the DOC for vWDz.
In woman, if they have menorrhagia and normal everything else, you have vWDz. They put you on birth control and that took the bleeding away. In one of the cases, the Dr. ordered PT, PTT, and bleeding time tests. The tests for PT and PTT were normal and the bleed time was normal. The sensitivity for these tests is only 50%, so do not depend on these. The ristocedin cofactor assay is the test of choice for vWDz, and will be abnormal. Estrogen increases the synthesis of all factor 8 molecules.

So, 2 things increase the synthesis of all the factor 8 molecules: desmopressin and birth control pills (DOC for women).

C. USMLE Step 2: Anti-phospholipids syndrome (one of the causes of spontaneous abortion) includes: Lupus anticoagulant (not an anticoagulant, but the opposite: thrombogenic) and anti-cardiolipin antibodies. Both of these antibodies cause vessel thrombosis. Lupus anticoagulant is part of the syndrome that produces vessel thrombosis. Also seen in HIV pt. Anti-cardiolipin antibodies have a history of having a biological false + syphilis serology. So, here you are with VDRL and RPR being positive. To confirm, FT ABS would be negative (test Ag is beef cardiolipin). Therefore makes the VDRL and RPR false positive, b/c the confirmatory test was negative. So why was the RPR positive in the first place, b/c the test antigen is beef cardiolipin. Therefore syphilis antibodies react to against that beef cardiolipin, and producing a positive reaction. But so the anti-cardiolipin antibodies. Therefore you get a biological false "+" with a syphilis serology. If you have a woman with a biological false "+" syphilis serology, what is the very first test you should get? Serum anti ANA antibody b/c she can develop lupus. Anti-cardiolipin antibodies are a very common feature of LUPUS. Matter of fact, a biological false "+" with a syphilis serology is a criteria for diagnosing Lupus.

D. Disseminated Intravascular Coagulation (DIC)
Disseminated = all over the body
Intravascular = within the vessel
Coagulation = clotting (forming clots throughout the body)

What is consumed in a clot? Fibrinogen, 5, 8, prothrombin, platelets

In clot tube form a clot – on top is serum and the serum is missing what is consume in a clot (fibrinogen, 5, 8, prothrombin, platelets). This is what you have in DIC – consuming these coagulation factors, including platelets, in those clots throughout the body; therefore you have 2 dz's at once. You have (a) thrombi in vessels, and at the same time you are (b) anticoagulated b/c all you have circulating around is serum, you don't have plasma b/c you consumed the coagulation factors–called a hemorrhagic thrombosis syndrome. The syndrome is very unusual and two things are happening at the same time. What started all this off? The intravascular coagulation is responsible for consuming all these things.

So, what causes this? MCC = Septic shock (MCC septic shock = E. coli), snake bite (not the neurotoxin types, but the rattlesnakes), and ARDS.
Very simple to recognize – they bleed from every orifice or scratch, and even if there is a puncture wound.

Classic DIC = Dx is easy, b/c if you consuming all the Coagulation factors, PT and PTT prolonged and platelet count is decreased, d dimers "+". The test for Dx is D-dimer test.

Example: pt with abruptio placenta and had amniotic fluid embolism. Amniotic fluid gets into circulation of the mom, which contains thromboplastin, so, death is from DIC, not from the amniotic embolism. B/c the thromboplastin within the amniotic fluid precipitated DIC.

Example: hereditary thrombosis = young person w/ DVT, not normal and family hx

Example: factor 5 leiden – abnormal factor 5 that protein C and S cannot breakdown, therefore there is an increase in factor 5, which predisposing to thromboses

Example: Antithrombin III deficiency – MCC woman birth control (therefore, the MCC is acquired – can also be genetic – ie pt with DVT, put on warfarin and heparin, and do a PTT is normal after heparin, so you give more heparin, and the PTT is still

normal. So, pt with DVT, give heparin, PTT remains normal = AT III def. b/c heparin works on AT III. Normally, the heparin facilitates antithrombin III thereby increasing the PTT. In this case, no matter how much heparin is injected, there is no change in PTT, therefore there is no Antithrombin III for the heparin to work on (this is how dx is usually made – by mistake).

E. Coagulation disorders summary:
Platelet ct/bleeding time/PT/PTT (basic tests to evaluate Hemostasis)
Aspirin: N, H, N, N
Idiopathic thrombocytopenic purpura (MCC of thrombocytopenia in kids): L, H, N, N
TTP/HUS: L, H, N, N
Hemophilia A: N, N, N, H
vWDz: N, H, N, H (so, for lab tests, main diff from heme A is bleeding time)
warf/hep: N, N, H, H (INR PT = warfarin, , PTT = hep)

Disease	Platelet Count	Bleeding Time	PT	PTT
Aspirin	NL	HIGH	NL	NL
ITP	LOW	HIGH	NL	NL
TTP/HUS	LOW	HIGH	NL	NL
Hemophilia A	NL	NL	NL	HIGH
vWB Dz	NL	HIGH	NL	HIGH
Warfarin/Heparin	NL	NL	HIGH (W)	HIGH (H)
DIC	LOW	HIGH	HIGH	HIGH

VI. Blood Groups

A. Different blood groups and what is floating around in the serum: O is most common, A is 2nd most common, B is 3rd common, and AB is the rarest
O: have anti-A IgM, anti-B IgM, anti-AB IgG
A: anti B IgM
B: anti A IgM
AB: nothing
Newborn: nothing, why? They don't begin synthesizing IgM until after they are born and only after 2-3 months do they start synthesizing IgG.
Elderly: nothing – Example: an old person who is blood group A and by mistake received blood group B, but did not develop a hemolytic transfusion rxn – why? Their levels of Ab's are low when they get older that there wasn't anything around to attack those cells.

B. Associated Diseases:

Which is associated with g**a**stric cancer? A
Which is associated with du**o**denal ulcer? O
Universal donor? O (can give their blood to anyone b/c have NO anti-A or anti-B Ag).
What is the only blood group O can get? O
Universal recipient? AB b/c they have no Ab's to attack those cells

C. Other Antigens:
1. Rh + antigen means that you are "+" for D antigen

2. Duffy Ag is missing in black pop'n; therefore not as likely to get plasmodium vivax (malaria) b/c the Ag the P. vivax needs to parasitize the RBC's is the Duffy ag and if you don't have the Ag the P. vivax can't get it. (G6PD def, thalassemias, SCDz pts protected from falciparum – they are protected b/c they're RBC's have a shorter lifespan – so, the parasite cannot live out their cycle, and RBC's a shorter lifespan)

D. Major crossmatch: pt gonna get blood; their serum is in a test tube, with the blood of the donor unit and they mix the 2 together – so they mix the pt's serum with the donor's RBC's to see if they are compatible; looking for anything in the pts serum that will attack the antigens in the donor's RBC's. Another part of the workup for crossmatching is to do an antibody screen which is an indirect coomb's before mixing (remember that it detects the ANTIBODY). If this test is negative, the crossmatch is compatible (so, there is no Ab in the pts serum that will attack the donor's). This does not prevent a transfusion rxn, or that Ab's will develop later against the donor. What is the chance that anyone has the same Ag makeup as another? Zero. So, even if I get a blood group O when I'm group O, there is still an increase risk of ab attack. Moral of the story? Don't transfuse unless it's absolutely necessary

Audio Day 3: Hematology 8

VII. Side Notes
A. Questions asked during the break about hypersensitivity:
Lupus (not everything is type III)
Post strep (not everything is type III, either) – can cause type II if its post strep. rheumatic fever, however, if it is post strep glomerulonephritis, that is type III
Thrombocytopenia and Hemolytic anemia = type II
PCN rash = type I

PCN hemolytic anemia = type II (IgG Ab's against the PCN group attached to the RBC membrane)

Example: most common Ab in the USA is Anti-CMV (everyone has been exposed).

You are safest from getting HIV from blood transfusion than from all the other infections (1/625,000 per unit of blood chance of getting HIV– therefore uncommon get to get HIV from blood). This is due to all the screening tests that they perform. They do the Elisa test – which looks for anti-gp120 Ab's (remember, it's the gp-120 Ag that attaches to helper T cell (CD4) molecule). On western blot, looking for more (3 or 4) Ab's, making it more specific, so if you get this "+" on 3 or more, you are a true positive.

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What is the MC infection transmitted by blood transfusion? CMV, which is the MC overall infection. That is why this antibody is the most common.

What is MCC post transfusion hepatitis? Hep C (1/3000)

In newborn, want to prevent graft vs. host dz and CMV b/c no immune defenses, therefore, need to irradiate the blood. The irradiation kills off the lymphocytes and since the CMV lives in lymphocytes, we kill off the CMV virus also. This why we radiate blood before giving to newborns.

Accidental needle stick from a pt you know nothing about – what is the MC infection you can get? Hep B.

Accidental needle stick from HIV "+" pt; what is the chance of getting HIV+? 1/300. What do you do about it? You go on therapy as if you are HIV+. Go on to triple therapy (2 RTI's – AZT and a protease inhibitor) for six months and get constant checks – do PCR test looking for RNA in the virus (most sensitive), do Elisa test. In fact, the MC mechanism of a healthcare worker getting HIV = accidental needle stick

Do not transfuse anything into a person unless they are symptomatic in what they are deficient in. Example: If you have 10 grams of Hb, and have no symptoms in the pt, do not transfuse. You should transfuse the pt if they have COPD and are starting to have angina related to the 10 grams. Example: 50,000 platelet ct – no epistaxis = do not treat them; if they do have epistaxis, treat the pt.

Every blood product is dangerous b/c you can get infections from it.

B. Fresh frozen plasma – should never be used to expand a pts plasma volume to raise BP – use normal saline (it is too expensive and you run the risk of transmitting dz). Use fresh frozen plasma for multiple coagulation factor deficiencies – ie would be legitimate to give frozen plasma to replace consumed factors, as in DIC.
Example: pt with warfarin is over anticoagulation and bleeding to death – not to give IM vit K will take to long to work (takes 6-8 hrs to work), so the treatment of choice is fresh frozen plasma to immediately replace it. So, fresh frozen plasma is limited to use of multiple factor deficiencies (ie cirrhosis of the liver and you are bleeding – since most of the factors are made in the liver, they are deficient in all proteins).
DOC for heparin overdose is to give protamine sulfate.

C. Know the diff transfusion rxn's

1. MC transfusion rxn = **allergic rxn** (itching, hives, anaphylaxis) - this is an example of a type I HPY rxn – ie have unit of blood, and in their plasma you are allergic to something (ie PCN); Rx = benadryl, antihistamines

2. 2nd transfusion rxn = **febrile rxn**; it is due to HLA Ab's; pt has HLA Ab's against leukocytes of donor Ag. So, when the unit of blood is transfused into me, and there are some leukocytes with HLA Ab on them, my Ab will react against it, destroy the cell and release the pyogenes from neutrophil, leading to fever.

If I've never been transfused, should I have HLA Ab's against anything? No! Continuing question: Who is most at risk for having a febrile rxn with transfusion? Woman – b/c she is has been pregnant – every woman that has had a baby has had a fetal maternal bleed, so some of the babies leukocytes got into the bloodstream, and the woman developed an anti HLA Ab (the HLA's are from the husband, that have been passed on to the woman). So, the more pregnancies a woman has had, the more anti HLA Ab's she will develop b/c of her previous pregnancies. This is also true for spontaneous abortions – you can still get HLA Ab's. So, women are more likely to have transfusion induced febrile rxns b/c they are more likely to have anti-HLA Ab's (we should not have human being's HLA's in our blood stream b/c we haven't been exposed to human's blood).

Example: Who has the greatest risk in developing febrile rxn? The answer choices for this question would be a newborn, 12 y/o without transfusion, woman with one pregnancy, woman with spontaneous abortion, and man. The answer is woman with spontaneous abortion b/c that is a pregnancy and there is a potential for HLA ab's to leak out of the fetus into the mother.
Febrile rxn is a type II HPY rxn against the HLA Ab (allergic rxn is type I)

3. **Hemolytic transfusion rxns** are very rare. Example: If you are blood group A, and given group B by stupidity b/c the pt has anti-B IgM (remember that IgM is the most potent complement activator and that cell will not last only about 1 msec) This is b/c the IgM will attack it, C1-C9: MAC, anaphylatoxins are released, and shock will ensue – very serious – aka clerical error).

Example: pt has Ab against Ag on RBC's in the unit – you would think that this shouldn't happen b/c the crossmatch said it is compatible; and did an Ab screen that was negative (Indirect Coombs). However, some Ab's are not present, and you have memory B cells. Suppose if I got blood transfusion 30 years ago, there are no Ab titers now b/c they would've gone away – however, there are memory B cells; these ab's will be way below the sensitivity of an Ab screen, come out compatible from a crossmatch, and will have neg indirect coomb; however, after transfusion, memory B cells would detect the foreign Ag. After the B cell detects the Ag, it will start dividing in the germinal follicle and start dividing and become a plasma cell, which would make anti-calla Ab. This can occur in a few hrs or may occur in a week – depending on the Ab. That's the one they like on the boards – **delayed hemolytic transfusion rxn**.

Example: woman postpartum, difficult delivery (abruptio placenta) was transfused 3 units of blood. When she left the hospital, she had an Hb of ten. One week later, she is jaundice and week, and has an unconjugated hyperbilirubinemia and has an Hb of 8. What is the dx? Hb was less than what she left the hospital, and they will not mention the coombs test) – What is most likely cause? Halothane (no b/c that takes over a week to develop), hepatitis (no, which takes 6-8 weeks to develop). Answer: delayed hemolytic transfusion rxn – so, they might ask what test would you get? Indirect coombs test to prove it b/c you will see the Ab Coating the RBC. Moral of the story? **Transfused with certain level of Hb, 1 week later have jaundice and less Hb = delayed hemolytic transfusion rxn = type II HPY**

VIII. ABO/Rh incompatibility

A. ABO incompatibility:

If blood group O woman have a baby, the mom will have a problem with ABO incompatibility b/c mom already have an Ab that can cross the placenta (blood group O people have anti A IgM, anti B IgM and anti AB IgG, normally). Normally, there is an anti AB IgG Ab which can cross the placenta, and attack an A or B RBC. So, there could be a problem in the very first pregnancy.

Example: mom is blood group O negative and baby is blood group A negative. Is there an incompatibility of blood groups? Yes. Is there an incompatibility in Rh groups? No. Just the blood groups, since the mom is O while baby is A. The mom is O, she has anti AB IgG, which will cross the placenta; the A part of the Ab will attach to the A part of the A cells of the baby's. The baby's macrophages of the spleen will destroy it, which is Type II HPY, mild anemia, and unconjugated bilirubin which is handled by the mom's liver; no kernicterus, no probs with jaundice in the baby b/c in utero, the mom's liver will take care of it. When the baby is born the baby, it will have a mild anemia and jaundice. MCC jaundice in the first 24 hrs for a newborn = ABO incompatibility (not physiologic jaundice of the newborn – that starts on day 3). Why did the baby develop jaundice? B/c the baby's liver cannot conjugate bilirubin yet and must handle unconjugated bilirubin on its own now, so it builds up. This is an exchange transfusion rxn for ABO incompatibility – most of the time is b9, and put under UV B light. How does UV B light work? It converts the bilirubin in the skin into di-pyrol, which is water soluble and they pee it out (Rx for jaundice in newborn). Anemia is mild b/c it is not a strong Ag and doesn't holster a brisk hemolytic anemia. If you do a coomb's test, it will be positive b/c IgG's on the RBC's. So always an O mom with a blood group A or AB baby. This can occur from the first pregnancy (not like Rh sensitization where the first pregnancy is not a problem). In any pregnancy, if mom is blood group O, and she has a baby with blood group A or B, there will be a problem (blood group O = no problem).

B. Rh incompatibility

Mom is Rh negative and baby is Rh positive. Example: mom is O negative and baby is O positive (not ABO incompatible, but Rh incompatible). In the first pregnancy: deliver baby without going to a Dr, and there is a fetal maternal bleed, some of the babies O positive Ab's got into my bloodstream, which is not good. So, mom will develop an anti B Ab against it. So, mom is sensitized which means that there is an Ab against that D Ag and now mom is anti D. 1 year later, mom is pregnant again, and still O negative, and have anti D and the baby again is O positive. This is a problem b/c it is an IgG Ab, which will cross the placenta, attach to the babies D Ag positive cells (of all the Ags, the D Ag hosts the worst hemolytic anemia). So, the baby will be severely anemic with Rh than will ABO incompatibility. The same thing happens though – baby's macrophages phagocytose and mom's liver will work harder. When the baby is born, the bilirubin levels are very high, a severe anemia occurs, and there is an excellent chance that an exchange transfusion will be necessary (99% chance), so take all the blood out (gets rid of all the bilirubin and sensitized RBC's and transfuse b/c baby is anemic). So, they will usually always have a exchange transfusion.

Therefore, for the first pregnancy, the baby is not affected, and this is when the mother gets sensitized. In future pregnancies, the baby will a lot worse.

How do we prevent? Mom will do an Ab screen test and she is Rh negative. Around the 28th week, give her Rh Ig, which is prophylactic. This is anti D, which comes from woman; it has been sensitized and heat treated and cannot cross the placenta. Why do they give at 28 weeks? Pt may get fetal maternal bleeds before the pregnancy or a car accident or fall can cause babies blood to get into mom's circulation. So, mom has anti D Ab's to sit on the D positive cells and destroy them, so mom won't get sensitized. Then, mom gives birth to baby (lets say it is Rh pos). Do a Plyhowabenti test and takes mom's blood to ID (if any) fetal RBC's in the circulation and count them; they can say how much is in there. Depending on that, that will determine how many viles of allergen Ig you give the mom to protect her further (anti D only last three months, and need to give more at birth, especially if the baby is Rh positive).

Example: Mom: O negative; Baby: A positive→ 2 problems: ABO incompatible and Rh incompatible. But, there is not going to be a prob with sensitization. No Why? After delivery of baby, some of the babies cells (which are A cells) get into the mom's blood (which mom has anti A IgM) ; those cells will be destroyed so fast, that in most cases the mom cannot generate Ab against those cells b/c they have been destroyed. So, ABO incompatibility protects against Rh sensitization. You still would give Rh Immunoglobulin. So if you are ABO and Rh incompatible, Rh sensitization will be protected against.

Kid with erythroblastosis fetalis will have Rh incompatibility – what do they die of? Heart failure – severe anemias will decrease viscosity of blood, so they get a high output failure: LHF, then RHF, huge livers b/c extramedullary hematopoesis b/c they are so severe anemic.

Example: cross section of brainstem from kid – what is the cause of color change? Its yellowish – due to kernicterus – prob from a baby that had Rh incompatibility. Remember, it's an unconjugated hyperbilirubinemia b/c it's a hemolytic anemia and lipid soluble; liver cannot syn it; goes to brain and is very toxic leading to severe debilitating dz or death.

Cardiology audios- 4 hours total

III. Rxn to Injury Theory

Cells involved- platelets, monocytes, macrophages, cytotoxic t cells with cytokines
(neutrophils not involved)

Atherosclerosis in an aorta – rxn to injury theory = injury to endothelial cells lining the elastic arteries and muscular arteries – what is injuring it? Ammonia in cig smoke, CO in cig smoke; so, poisons damage the endothelial cells; LDL damages it, and if its oxidized, it damages it worse; viral infections damage it, too**. Chlamydia pneumoniae (2nd MCC atypical pneumoniae); pts with MI – most had Ab's against Chlamydia pneumonia, homocysteine – all these things damage endothelial cells**

What happens when you damage endothelial cells? Platelets stick to it and PDGF is released into the artery and PDGF causes smooth muscle cells within the media to proliferate and they undergo hyperplasia and then, they chemotactically migrate to the subintimal level. They have all these smooth muscle cells migrating to the intima of the vessel. Monocytes have access into the vessel b/c it has been injured and monocytes also have GFs. As the LDL increases, the macrophages phagocytose them. Macrophages and smooth cells have LDL w/in them; the LDL becomes oxidized and a fatty streak is produced. Over time, a fibrofatty plaque develops, which is pathognomonic of atherosclerosis. It can be complicated by dystrophic calcification, fissuring, thrombosis and a complicated atherosclerosis.

IV. Arterial Disorders:

A. Atherosclerosis is a primary factor for certain dz's –
CAD; atherosclerotic stroke relates to plaques; abdominal aneurysm due to weakening of the vessel; nontraumatic amputation of lower extremity (peripheral vascular dz); mesenteric angina, small bowel infarction, renovascular atherosclerosis of the renal arteries. **Atherosclerosis only involves muscular arteries and elastic arteries**. Can small vessel, such as arterioles get hardened? Yes. Example: look at the spleen – hyaline arteriolar sclerosis and hyperplastic arteriolar sclerosis (onion skinning).

1. Hyaline arteriosclerosis is a small vessel dz; lumen is narrow; whenever there is a lot of pink staining stuff, this is hyaline. Example: small vessel dz of diabetes and HTN – two major dz's that produces a small vessel dz with different mechanisms:

a. Diabetes: nonenzymatic glycoslyzation – aka HbA1c; glycoslyzation is glucose attaching to aa and protein. For HbA, its glucose attaching to aa and HbA, and the HbA is glycosylated. HbA1c levels correlate with the blood glucose levels of the last 6-8 weeks, so this is the best way of looking at long term glucose levels. All the damage seen in diabetes is due to glucose. For a diabetic, you should be under 6%, meaning that you are in a normal glucose range. There is nothing unique about diabetes except for a large glucose level, you keep that normal, and it's as if you don't have diabetes. The **only two pathologic processes are this: nonenzymatic glycosylation** of small BV's including capillaries in the kidney, and **osmotic damage**. Those tissues that contain aldose reductase – lens, pericytes in the retina, schwann cells – all have aldose reductase and can convert glucose into sorbitol and sorbitol is osmotically active sucks water into it and those cells die, leading to cataracts, microaneurysms in the eye b/c the pericytes are destroyed and weakened and the retinal vessels get aneurysms, and you get peripheral neuropathy b/c schwann cells are destroyed. They all related to excess glucose. So, tight glucose control = normal life.

What does nonenzymatic glycosylation to do the basement membrane of small vessels? Its renders them permeable to protein, so the protein in the plasma leaks through the BM and goes into the vessel wall, produces a hyaline change and narrows the lumen. What if there is nonenzymatic glycosylation of the GBM? It will render it permeable to protein – called microalbuminuria. This is the first change to be seen in diabetic nephropathy. So, what is the mechanism? Nonenzymatic glycosylation.

b. Hypertension
Does not use nonenzymatic glycosylation. It just uses bruit force and drives (b/c of increase in diastolic pressure) the proteins through the BM and produces the effect. When we look at a kidney in HTN, it is shrunken, has a cobblestone appearance – this is b/c there is hyaline arteriolosclerosis of the arterioles in the cortex, ischemia, and is wasting away with fibrosis and atrophy of tissue. Lacunaer strokes (tiny areas of infarction that occur in the internal capsule) are a hyaline arteriosclerosis problem related to HTN.

2. Hyperplastic arteriosclerosis
Seen in malignant HTN; more common in blacks then whites, mainly b/c HTN is more common in blacks than whites. Mainly see this vessel dz in malignant HTN (ie when pt has BP of 240/160).

B. Aneurysm
1. Definition: area of outpouching of a vessel due to weakening of the vessel wall. Atherosclerosis can cause weakening of the abdominal aorta leading to an aneurysm.

What would be the analogous lesion in the lungs with weakening and outpouching? Bronchiectasis – due to cystic fibrosis with infection, destruction of elastic tissue leading to outpouching and dilatation of the bronchi. Example: what is the GI aneurysm? Diverticular dz – have a weakening and outpouching of mucosa and submucosa

2. Law of Laplace – the wall stress increases as radius increases. In terms of this, once you start dilating it, it doesn't stop b/c as you dilate something, you increase the wall stress and eventually it ruptures. So, in other words, all aneurysms will rupture – it's just a matter of when.

3. Abdominal Aorta Aneurysm: Why is the abdominal aorta the MC area of aneurysm? B/c there is no vasa vasorum or blood supply to the aorta below the renal arteries. So, the only way abd. aorta gets O2 and nutrients is from the blood that's in the lumen. So, part furthest from it mgets screwed. Therefore, apart from the part that is not getting much O2 and nutrients, it will be more susceptible to injury, therefore atherosclerosis leads to weakening of the wall and aneurysm/injury occurs.
a. MC complication abdominal aortic aneurysm = rupture. The **triad of s/s are**: a sudden onset of severe left flank pain b/c the aorta is retroperitoneal organ and so it does not bleed into the peritoneal cavity, but into the peritoneal tissue. So, **severe left flank pain, HypoTN, and pulsatile mass on PE.** These are three things that always occur when there is a ruptured aortic abdominal aneurysm. **MC complication of any aneurysm = rupture**

4. Aneurysm of the arch of the aorta – MCC = tertiary syphilis. Pathology of syphilis is vasculitis of arterioles. Chancre, too. Its painless b/c if you section it, you will see little arterioles surrounded by plasma cells and the lumen of the vessel is completely shut, so it is ischemic necrosis. In other words, it is ischemia of the overlying tissue undergoing necrosis. B/c nerves are next to vessels, they are knocked off, too, and it is painless. **All of syphilis is a vasculitis**. That is what the *Treponema* infects – small vessels and arterioles. What are they affecting in the arch of the aorta? The vasa vasorum; the richest supply of vasa vasorum is in the arch, so its logical that the *Treponema* will pick it – leads to endarteritis obliterans (they are obliterating the lumen), ischemia, weakening under systolic pressures, leads to depression in the arch of the aorta (looks like a catcher's mitt). What will that do to the aortic valve ring? It will stretch it – which murmur will this lead to? Aortic regurg. Murmurs can occur b/c there is valvular damage or b/c the valvular ring is stretched. So, there can be stretching of the ring and nothing wrong with the valves, and have a murmur, or you can have damage to the valves and have a murmur. Syphilis is an example of stretching of the aortic valve ring leading to a murmur and aortic regurg.

Aorta should be closing during diastole – as you pump the blood out, and the SV goes down, and b/c the aortic cannot close properly, only some of the blood will drip back in. So you will have more volume of blood in the left ventricle in someone with aortic regurg. Frank-starling forces will be working. As you stretch cardiac muscle, you increase the force of contraction. Normally, you have a 120 ml's of blood and get out 80, so the EF is 80/120 =66%. Lets say you have 200 mls of blood in the LV b/c blood is dripping back in, and frank-starling force gets out 100 mls of blood, which has an EF of 50%. So this isn't as efficient. Therefore, frank-starling occurs in a pathologic condition. If you have 100 mls of blood coming out of your aorta, that's not good b/c their head is wobbling, and when they open their mouth you can see uvula pulsating, can take their nail and lift it up and see pulsations of the vessels under the nail, Water-hammer pulse, and when listening with the stethoscope of the femoral artery you can hear Durasane's sign. This is all due to the increase in SV coming out related to the fact that there is more blood in the LV. syphilitic aneurysms of the abdominal aorta is the classic example of this. Anatomy correlation: the Left Recurrent Laryngeal Nerve wraps around the arch and therefore can get hoarseness. Again the MC complication is rupture.

5. Dissecting aortic aneurysm:
a. Key factor that causes a tear in the aorta is HTN b/c it imposes stress on the wall of the vessel. There must be weakening the elastic artery and is caused by elastic tissue fragmentation. **Cystic medial necrosis**: that's where the GAG's mix together and there's mucinous material w/in, and walls of aorta rub upon itself, and when adding a little bit of HTN leads to a tear. Wherever the area of weakness in the elastic artery is where the blood will dissect and tear – blood can go to the pericardial sac, leading to cardiac tamponade. This is called the proximal dissection (MC). Most of the tears up in the arch; therefore you would think the pt may have an absent pulse; this is very common in pts with tears that are proximal. When it dissects, it closes lumen to subclavian artery and it usually dissects on the left and causes an absent pulse on left.

b. Chest pain in MI is diff than the chest pain in a dissecting aneurysm. MI has chest tightness radiating to left arm and jaw; in aortic dissection, there is a tearing pain radiates to the back; and is a retrosternal pain. Pulse on left is diminished vs. the one on the right. On chest x-ray, widening of the aortic knob. With blood there, diameter of aorta will be enlarged, as seen on x-ray, and this test is 85% sensitive in detecting it, therefore it is the screening test of choice; see widening of the **proximal aortic knob**. To prove, do transesophageal ultrasound or angiography to confirm dx.

c. Many dz's can predispose to aortic dissections:
(1) **Marfan syndrome** (eunochoid proportions – ht of pelvic brim to feet is greater than from pelvic brim to the head. Also, another definition is that arm span is greater than the height. AD inheritance, c'some 15, defect in fibrillin, which is a component in elastic tissue. Due to the defect in fibrillin, the elastic tissue is weak – this is why they have dislocated lenses and have dissected aortic aneurysms (MCC death in marfans is MVP).

(2) **Ehler Danlos** has a collagen defect, MCC of death

(3) **Pregnant women** are susceptible to dissecting aortic aneurysms b/c in pregnancy they have twice the amount of plasma vol vs. a non-pregnant woman. There is an increase of plasma vol by 2 and RBC mass by 1, so it's a 2:1 ratio of increasing plasma vol to RBC mass; which decreases the Hb concentration. That's why all pregnant women have decreased hemoglobin; usually around 11.5 is their cutoff for anemia and the cutoff is 12.5 for normal women. This is b/c of dilutional effect with excess in plasma vol. Apparently in some women, the excess plasma volume for 9 months can cause weakening of the aorta and thereby causing an aneurysm.

V. Venous Disorders:

A. Superior vena cava lung syndrome in a smoker with primary lung cancer, now complaining of headache and blurry vision – look at his retina and see retinal vein engorgement, and congested – dx? **Superior vena cava lung syndrome** – usually due to primary lung cancer knocking off the sup vena cava, leading to backup of venous blood into the jugular venous system and to the dural sinuses; this is a very bad dz, and will lead to death. Usually treat with radiation to shrink the tumor to get normal blood flow. Don't confuse with **Pancoast Tumor** – associated with Horner's syndrome. So, SVC syndrome has nothing to do with Horner's, as opposed to Pancoast.
B. Varicose Veins

VI. Tumors of Blood Vessels:

A. Sturge Weber syndrome – "web… looks like a mini map on their face"
it's a vascular malformation in the face and notice it's in the trigeminal nerve distribution (making it easy to dz). However, on the same side of the brain there's an AV malformation, predisposing to bleeding. So, not only a vascular malformation of the face, but also an AV malformation in the same side of the brain, which predisposes to bleeding. Also, these pts are a little mentally retarded. (some pts show it on the entire side of the face)

B. Osler Weber Rendu aka Hereditary hemorrhagic telangiectasia – small telangiectasia in GI. AD inheritance characterized by localized telangiectases of the skin and mucous membranes and by recurrent hemorrhage from these lesions.

C. Spider angioma/spider telangiectasia: If you press down on this, the little tentacles will go away (therefore it blanches) – called spider angioma. It is due to hyperestrinism. This is normal in pregnancy. If a male has spider angioma, he has cirrhosis (MCC cirrhosis = alcohol). Why would a male have a spider angioma? B/c if you have cirrhosis, you cannot metabolize estrogen – so it builds up, leading to gynecomastia, warm skin, palmer erythema, and spider angioma related to hyperestrinism. Another reason would be b/c they cannot metabolize 17 ketosteroids either, therefore they will be aromatized those in the adipose tissue into estrogen. So, they are 2 ways of getting hyperestrinism in cirrhosis. So, how is this different from petechia? It looks diff; also, it will blanch when you press it in b/c it's an AV fistula – in other words, the blood goes directly from arteriole to a venule and is bypassing the capillaries.

D. Capillary Hemangioma: pic of child with red lesion (not bilateral wide eye lesion – so its not retinoblastoma); what do you do? **Leave it alone**; do not surgically remove b/c by 8 y/o, it will be gone – so, leave capillary angiomas alone b/c they will go away.

E. Bacillary angiomatosis:
Kaposi sarcoma is caused by the HHV 8 organism. If there was a lesion seen only in AIDs pts that looks like Kaposi sarcoma, but it's not; what is it due to? It's due to bacteria – **bacillary angiomatosis** – **due to bartenella hensilai** – seen with silver stain. Rx? Sulfa drug. This organism also causes Cat Scratch Dz.

F. Angiosarcoma of the liver – common causes "VAT" = Vinyl chloride (people who work with plastics and rubber), Arsenic (part of pesticides, contaminated water), and Thorotrast (a radioactive diagnostic agent thorium dioxide).

VII. Vasculitis Syndromes

A. Concept of Vasculitis: Vasculitis of small vessels (arterioles, venules, capillaries), muscular arteries, and elastic arteries. All of these vasculitis present with different signs and symptoms (ie like coagulation disorders vs. platelet disorders).

1. Small vessel vasculitis – 99% of the time it is due to a type III HPY, meaning it is involves immune complex deposition, that will deposit in the small vessel, activate complement and attract neutrophils (C5a), and will get fibrinoid necrosis and damage to the small vessel and **PALPABLE PURPURA**; (remember the old person with purpura on the back of the hand – that was not palpable and was due to hemorrhage into the skin, there was no inflammatory problem – it just ruptured into the skin) but if it was palpable, it would be considered a SMALL VESSEL vasculitis not a platelet problem.
Example:
Leukocytoclastic vasculitis (hypersensitivity vasculitis);
nuclear dust = fibrinoid necrosis and immune complex dz's; and
Henoch-Schonlein purpura. **So, SMALL VESSEL vasculitis = PALPABLE purpura (always told in the stem of the question).**

2. Muscular artery vasculitis – Polyarteritis Nodosa and Wegener granulomatosis. These will get THROMBOSIS of the vessel, not palpable purpura. Will have **INFARCTION**. Example: Kawasaki's Dz in children "crims" coronary artery vasculitis ,rash,infarction,mi, swelling
– get coronary artery vasculitis – MCC MI in children = Kawasaki's dz – b/c part of the syndrome, in addition to mucocutaneous inflammation, desquamation of skin, and lymphadenopathy, there is a coronary artery vasculitis – thrombosis occurs and little child will have an infarction. **So, infarction is what you see with a muscular artery vasculitis.** Examples: Polyarteritis Nodosa, Wegener granulomatosis, Kawasaki's dz in kids.

3. Elastic artery vasculitis – When you knock off an elastic artery, then you deal with arch vessels, and they will get pulseless dz=Takayasu's arteritis – the vasculitis will block off the lumen of one of the arch vessels, leading to **STROKES** and can knock off the internal carotid. Example: Takayasu's – young, far eastern lady with absent pulse.

So, palpable purpura = small vessel vasculitis
Infarction = muscular vasculitis
Involves pulse/stroke = elastic artery vasculitis

B. Temporal Arteritis – unilateral headache, aches and pains all over body, loss of vision of same side of headache, hurts when pt chews in temporal area. This is a granulomatous (have multinucleated giant cell) vasculitis of the temporal artery, a type of giant cell arteritides. It can involve other portions of the artery including the ophthalmic branch and produce blindness. That's why the sedimentation rate is the ONLY screen discreet for temporal arteritis. Why? Not that it is specific, but b/c this is an arteritis, (an inflammation) the sed rate should be elevated. If the sed rate is NOT elevated, it could be a transient ischemic attack. This is good screen b/c it takes time to take a biopsy and look at it, and the pt could go blind. So, you must put the pt on corticosteroids immediately (right there and then) just based on hx alone. The pt will be on corticosteroids for one year. It's associated with polymyalgia rheumatica – muscle aches and pains. They want you to say it is polymyositis, but it isn't. Polymyalgia rheumatica does not have an elevation of serum CK, and have aches and pains of muscles and joints. In polymyositis, it's an inflammation of muscle.

C. Buerger dz (aka thromboangiitis obliterans – smokers dz); "ew boogers and smoke make me so sick my fingers and toes curl"
males, young, digital vessel thrombosis, leading to autoinfarction of their fingers, AND toes. It's an acute inflammation involving small to medium-sized arteries.

Henoch-Schonlein purpura: (butt, joints, git, renal,skin) (palpable purpura on butt, n legs, joint probs, and kidney probs)
14 y/o, URI one week ago, presents with polyarthritis, joint pains, hematuria, with RBC casts and palpable purpura of buttocks and lower extremity – dx? Henoch-Schonlein purpura = MC vasculitis in children – immune complex (as is all small vessel vasculitis)– anti IgA immune complex, and the RBC casts are due to glomerulonephritis. Do not confuse with IgA glomerulonephritis – Berger's dz

E. Wegener granulomatosis
-if u had to go listen to wagner in concert, you would pretend u had to use the bathroom or get pneumonia
"infarc'n, lung, urt, renal , saddle nose ,canca—cyclophosamine rx"
pt with saddle nose deformity (not congenital syphilis) – also probs with sinus infections, URI's, lung probs with nodular masses, and glomerular dz – dx? Wegener granulomatosis (MCC of saddle nose deformity). This is a granulomatous inflammation AND vasculitis. Therefore, it involves the upper airways, lungs, and kidneys; also, there is an Ab that is highly specific for it – **c-ANCA (anti-neutrophil cytoplasmic Ab). Rx - Cyclophosphamide** (which can lead to hemorrhagic cystitis and bladder cancer and how can you prevent the hemorrhagic cystitis? Mesna).

F. Polyarteritis Nodosa –
" panca, hbsag, kidney, heart problems, infarc'n"
male dominant dz that involves muscular arteries, therefore infarction is a part of it. Has **p-ANCA Ab and a high association with Hep B surface Ag'emia**. Example: have IVDA with chronic Hep B who has a nodular inflamed mass on the lower extremity and hematuria (due to kidney infarct); what does the pt have? Polyarteritis Nodosa b/c the pt has a chronic hep B infection therefore has hep B surface antigens. So, remember **p-ANCA and Hep B surface Ag.**

G. Bacterial infections: vessel in **RMSF**. The rickettsial organisms infect endothelial cells; the spots are petechia; unlike other rickettsial dz's with rash, this starts on the extremities and goes to the trunk (whereas others start on the trunk and to the extremities). Also have to remember the vector: tick. Other tick born dz's: Lyme dz (borrelia burgdorferi – b. recurentis is relapsing fever, and has antigenic shifts; it is a spirochete (Leptospira and syphilis are also spirochetes). So, 3 spirochetes – Leptospira, Treponema, Borrelia ("BLT")

F. Fungus that is wide angle, nonseptate , pt has DKA, and cerebral abscesses related to fungus – **mucormycosis** (know relationship of this fungus and DKA);
Diabetics commonly have mucor in their frontal sinuses; so when they go into ketoacidosis and start proliferating, they go through the cribiform plate into the frontal lobes where they infarct it and infect it with the dz.

VIII. Functional Vascular Disorders: Raynaud Dz
There are many causes this; some involve cold reacting Ab's and cold reacting globulins. People who go outside in the cold weather will get Raynaud's and cyanosis in the nose and ears (that comes and goes away); so, it is due to IgM cold agglutinin dz or cryoglobinemia in old man with Hep C.

However, we have other dz's that are **collagen vascular dz** and first manifestation is Raynaud's; this involves a digital vasculitis and eventually a fibrosis – progressive systemic sclerosis (aka scleroderma), and its counterpart CREST syndrome.
Vasculitis of fingers and leads to fibrosis – will eventually auto-amputate finger (like Berger's).

CREST syndrome – Calcinosis (dystrophic calcification) and Centromere Ab (specific for crest syndrome), Raynaud's, Esophageal dysmotility, Sclerodactyly (finger that is very narrow), Telangiectasia (very similar to the pin point hemorrhages – also seen in Osler Weber Rendu).**********

Other causes due to vasoconstriction – common in pts that take drugs for migraine – drugs for migraines cause vasoconstriction of vessels. So, Raynaud's can occur after taking Ergot derivatives; Buerger dz, too.

Therefore, general causes of Raynaud's: vasoconstriction, vasculitis of the digits (ie CREST and scleroderma), and cold reacting Ab's and globulins .

IX. Hypertension (HTN)

MCC death with HTN = MI (2nd = stroke, 3rd = renal failure)
Essential HTN= MC

A. Multifactorial Inheritance: What racial group has highest incidence of HTN? Blacks. Why? Multifactorial inheritance (aka polygenic inheritance; other dz's include: gout, CAD, Type II diabetes, affective disorders, congenital pyloric stenosis, essential HTN). This means that you have a tendency to FOR the dz, but don't necessarily get the dz. Why? B/c it's MULTIfactorial!

Example: I am black, what should I do to prevent from getting it? I cannot get rid of genetics, and my genetics are that I **cannot get rid of salt in my urine** - retaining too much salt **(which is the basic mechanism of essential HTN in blacks and elderly**). So, cannot control genetics, but I can control 3 things: (1) weight has a direct correlation with HTN; (2) reduce salt intake; and (3) exercise. Example: family hx of gout, what can I do so I avoid gout? Avoid red meet, no alcohol (which will decrease purine metabolism). Example: If you had a family hx of DM type II – be skinny (lean and mean)– as you lose adipose, upregulate insulin receptor synthesis and that alone could prevent you from having the dz.

B. Mechanism of HTN – b/c you **retain salt** (it's not the only mechanism, but the MC one). When you retain salt, what compartment will the salt be retained in? ECF – if that is true, what will be the plasma volume if you have excess salt in your vascular and interstitial compartment? Increased – if your plasma vol is increased, your stroke volume will be increased – which is your **systolic HTN (b/c increase in PLASMA vol)**. When you have excess salt, salt wants to go into smooth muscle cells (into peripheral resistance arterioles). When sodium enters muscle, it opens certain channels for Ca to go in; Ca goes in and smooth muscle will contract, so the peripheral resistance arterioles are vasoconstricting. TPR = viscosity/radius^4; we are decreasing radius, increasing resistance, and **retaining more blood in the arteriole system (that registers as an increase in diastolic pressure).** This is why the Rx of choice for essential HTN in blacks and elderly = hydrochlorothiazide – b/c you rid salt and water to decrease BP; however, do not use if pt has hyperlipidemia, so use ACE inhibitors.

Is this a high or low renin type of HTN? Low renin b/c increased plasma volume = increased blood flow to the renal artery = decreased renin. So that's the basic mechanism of HTN.

C. Complications: HTN is a major risk factor for CAD, leading to **MI (MCC death**). Stroke = #2. Blood is located in globus pallidus and/or putamen – this is where almost all of the HTN'ive bleeds occur in the brain. This is b/c the lenticulostriate vessels (which are small vessels of the middle cerebral artery) under increased pressure form aneurysms called **Charcot Bouchard aneurysms**, and they rupture. This is not a good place to rupture. Therefore, this is not an infarct – it is a hematoma – it's a blood clot right there. Neurosurgeons can suck these out. Therefore the **2nd MCC death is HTN'ved bleed**. Example: kidney that is too small with a pebbly surface due to hyaline arteriolosclerosis – a small vessel dz is causing ischemia of the kidney, atrophy of tubules, destruction of glomeruli, shrinkage of kidney, and leads to kidney failure. This is the **3rd MCC death in HTN.** MC overall abnormality in HTN = LVH (mech: afterload prob b/c the heart has to contract against increased resistance and if it remains over a period of time it will eventually lead to heart failure.

Audio Cardiovascular 2

CHAPTER 7: CARDIOVASCULAR

THE HEART

I. Hypertrophy of the Heart:

Concentric (thick) HPY'd heart vs. Dilated HPY heart: 2 different etiologies, and they involve work. It requires a lot of work to contract and push blood thru a stenotic aortic valve, or increased TPR from HTN. These will cause an **increased afterload = concentric HPY.**
If you have a valvular problem, and have excess volume of blood in the ventricles – increased preload = increased work. Therefore, the frank starling goes into effect b/c stretching and increasing preload in there, and you have to work harder to increase the force of contraction – this produces dilated HPY. Therefore, **concentric HPY = afterload problem; dilated HPY = volume overload = preload problem (increased volume)**

II. Heart sounds –

S1 heart sound = beginning of Systole = mitral and tricuspids close (mitral closes before the tricuspid b/c higher pressures)

S2 heart sound = beginning of Diastole = pulmonic and aortic close (variation with respiration – as diaphragm goes down they increase the intrathoracic pressure. Blood is being sucked into the right side of the heart, and the pulmonic valve will close later than the aortic valve. So, the second heart sound has a variation with inspiration – the P2 separates away from A2 b/c more blood coming into the right heart, so the valve closes a little bit later.

S3 heart sound = normal under 35 y/o's. After that, it is pathologic. S1 = beginning of systole and S2 = beginning of diastole; obviously, S3 = early diastole. S3 is due to blood, in early diastole, going into a chamber that is volume overloaded. So, blood from the left atrium is going into overloaded chamber, causing turbulence, which is the S3 heart sound. Only hear **S3 heart sound in volume overloaded chamber**. It could be from LHF (left ventricle overloaded) or RHF (right vent overloaded), so there are left sided S3's and right sided S3's – it means volume overload in the chamber. Analogy: rivers going into ocean – leads to turbulence (ocean is the ventricle with a lot of fluid in it and the river is the blood coming in during diastole; the river hits this large mass of fluid in the ventricle, causing turbulence and an S3 heart sound).

S4 heart sound = late diastole – this is when the atrium is contracting and you get the last bit of blood out of the atrium into the ventricles, leading to S4 sound. S4's occur if there is a problem with compliance. Compliance is a filling term.

So, when talking about compliance, referring it's ability to fill the ventricle. The left atrium is contracting, trying to get blood into a thick ventricle; the ventricle is noncompliant, and therefore resistance will occur. This will create a vibration, leading to an S4 heart sound. An **S4 heart sound is due to a problem with compliance**. The left atrium is encountering a problem in putting blood in late diastole into the left ventricle and it doesn't want to fill up anymore. This could be due to 2 reasons: (1) b/c it's hypertrophied (it doesn't want to fill anymore–restricting filling up) or (2) it's already filled up and has to put more blood in an already overfilled chamber.

Summary: Slides:
Vol overloaded? No S3. So can it have an S4? Yes.

If you have HTN, which type of heart will you have? Concentric HPY. So, in HTN, which type of heart sound will you have? S4.

Vol overloaded? Yes. So can it have an S3? Yes; can it also have an S4? Yes. Why can it also have an S4? B/c it can't fill up anymore. Analogy: turkey dinner – all filled up, but always room for desert – lil vibration that occurs when it fills is an S4 heart sound. So you have both S3 and S4 heart sound = gallop rhythm (they have S1, 2, 3, and 4).

How do you know if its from the left or right? It is breathing. When you breath in, you are sucking blood to the right side of the heart. **All right sided heart murmurs and abnormal heart sounds (ie S3, S4) increase in intensity on inspiration** – this is more obvious b/c there is more blood in there, and it emphasizes those abnormal sounds. Prob get them on **expiration with positive intrathoracic pressures** that are helping the left ventricle push blood out of the heart – this is when abnormal heart sounds and abnormal murmurs will increase in intensity on expiration. So, all you have to do is figure out that there is an S3 heart sound. *****Then, you have to figure out which side it is coming from. Louder on expiration, therefore its from the right side.
Example: essential HTN = left;
Mitral regurg = right;
and Mitral stenosis = middle.

III. Murmurs

Stenosis = prob in **opening**, that is when the valve is opening, and that is when the murmur occurs.
Regurgitation = prob in **closing** the valve, that is when the valve is closing, and that is when the murmur occurs.

Need to know where valves are heard best – right 2nd ICS (aortic valve), left 2nd ICS (pulmonic), left parasternal border (tricuspid), apex (mitral) – this isn't necessarily where the valve is, but where the noise is heard the best.
A. Stenosis:

1. Systolic Murmurs:
Who is **opening in systole = aortic and pulmonic valves** = therefore, murmurs of aortic stenosis and pulmonic stenosis are occurring in systole. This is when they are opening; they have to push the blood through a narrow stenotic valve.

a. Aortic Stenosis – LV contracts and it is encountering resistance - intensity of the murmur goes up; as it is pushing and pushing, it gets to a peak and this is diamond shape configuration – this is why it is called an **ejection murmur.** So, they often have diagrams of the configurations on these murmurs. With an ejection murmur (aortic stenosis), it will have a crescendo-decrescendo (hence, diamond shaped configuration). So, with aortic stenosis, there is an ejection murmur in systole, heard best at the right 2nd ICS, which radiates to the carotids, and the murmur intensity increases on expiration, and will probably hear an S4

b. Pulmonic Stenosis – heard best on left 2nd ICS, ejection murmur, and increases on expiration.

2. Diastolic murmurs: In diastole, mitral and tricuspid valves are opening.

a. Mitral Stenosis (problem in opening the valve) – who has the problem? Left atrium. Here's the problem, the mitral valve doesn't want to open but it has to in order to get blood into the left ventricle. So, the left atrium will get strong b/c it has an afterload to deal with – it becomes dilated and hypertrophied (the atrium) – which predisposes to atrial fib, thrombosis, and stasis of blood. So, the atrium is dreading diastole b/c it has to get the buildup of blood into the left ventricle. With the build up of pressure, the mitral valve "snaps" open, and that is the opening snap. All the blood that was built up in the atrium comes gushing out into the ventricle, causing a mid-diastolic rumble. So, you have an **opening snap followed by a rumbling sound** (due to excess blood gushing into LV). With mitral stenosis, there is a problem with opening the valve, and therefore you are under filling the left ventricle, and therefore will be no HPY b/c you are under filling it. If you are having trouble getting blood into it, you are not overworking the ventricle; the left atrium has to do most of the work. Heard best at the apex and will increase in intensity on expiration. **(same concept with tricuspid stenosis, just a different valve).**

B. Regurgitation – problem in closing the valve.

1. Systolic Murmurs: mitral and tricuspid are closing in systole.

a) Mitral Regurg: If they are incompetent and mitral valve cannot close properly. Example: 80 mls of blood = normal stroke volume; lets say 30 mls into the left atrium and only 50 mls leaves the aorta. So, an extra 30 mls of blood in the left atrium, plus trying to fill up and have excess blood there – way more blood ends up in the left ventricle and it becomes **volume overloaded**. So, how would the murmur characteristics be if there is a problem in closing the valve? It will not be an ejection murmur; will just sound like "whoooosh" all the way through, as blood all the way through systole is going through the incompetent mitral valve, back into the left atrium – therefore it is pansystolic or almost pansystolic – so it's a 'straight line' effect. Sometimes, it will obliterate S1

and S2. **So, is an apical murmur, pansystolic, S3 and S4 (b/c a problem with compliance and volume overload, increased in intensity on expiration.**

b. Tricuspid Regurg: it will be pansystolic, S3 and S4, left parasternal border, and increases on intensity on inspiration). Example: IVDA with fever, pansystolic murmur along parasternal border, S3 and S4 heart sound, accentuation of the neck veins, what is the most likely dx? Infective endocarditis of tricuspid valve, which is the MC infection. So, it was extremely imp to know if the murmur increased on inspiration (which is right sided). If the question said that the murmur had increased on expiration, it would be Infective endocarditis of the mitral valve (which is left sided).

2. Diastolic Murmurs: want the aortic and pulmonic valves to close (what you just pumped out doesn't want to come back in).

Aortic Regurg (as seen in syphilis aneurysm but this is due to the stretching of the ring). In systole the blood goes out and the valve should be closing properly , but it doesn't, so some blood will trickle back in. Example: 80 cc went out initially and 30 cc is dripped back in. As blood keeps dripping back in, you will get a **volume overloaded** chamber. Eventually you will have and EDV of 200 mls (instead of 120). So, for aortic regurg, when you hear the murmur? After the 2nd heart sound b/c it isn't closing and blood is dripping back in – that makes the sound of a high pitched blowing diastolic murmur into the right second ICS, increases in intensity on expiration, S3 and S4 heart sounds, vol overloaded, and bounding pulses. What valve leaflet is dripping blood? Anterior leaflet of mitral valve. This is one side of the outflow tract out of the aorta. What murmur does that create? **Austin flint murmur**. If you have aortic regurg with an Austin flint murmur, you need to call the cardiac surgeon. Need to replace the valve b/c you are significantly dripping blood. Therefore, this murmur is imp b/c when it is there, you have to perform surgery.

IV. Heart Failure: Left or Right Heart Failure

Left HF = lungs and Paroxysmal nocturnal dyspnea/pillow orthopnea

Right = Liver

A. Left heart failure=forward failure, cant get blood out of the heart b/c the LV fails
Therefore your left ventricle has to push against an afterload and fails; or it has to deal with excess volume and fails; or you've had so many infarcts that the left ventricle is no longer muscle but now fibrous tissue and this reduces contractility and it fails. It's a forward failure b/c you are having problems getting blood outside of the heart. This means that EDV will increase b/c you cannot get all the blood out b/c you cannot push it out. The pressure and volume will go back in to the left atrium, back into the pulmonary vessels, increase the hydrostatic pressure, and then pulmonary edema. With chronic left heart failure, this will lead to hemorrhage and alveolar macrophages will phagocytose RBC's, leading to rusty colored sputum. On cytology, you will see heart failure cells, which are alveolar macrophages that has phagocytosed RBC's and is broken down to hemosiderin. **Pulmonary edema is always left heart failure**. **Left heart failure is a diagnosis of symptoms, b/c the main symptom in LHF is dyspnea (SOB), have trouble breathing b/c fluid in there.**

B. Right Heart Failure: Diagnosis of signs: Backward Failure; cant get blood into the heart.
RHF is a problem of the right heart getting blood through the pulmonary vessels to the left heart. So, if it fails, blood builds up behind it, and it is a backward failure. B/c if it cannot get blood through pulmonary vessels into the heart, blood will build up behind it, and hydrostatic pressures will build in the venous circuit. This leads to neck vein distension; also, will get hepatomegaly (which is painful), and a nutmeg liver b/c of the increased pressures in the vena cava are transmitted to the hepatic vein, which empties into it, then back into the liver and the central vein, then will get red dots all over liver, which looks like a nutmeg. **MCC congested hepatomegaly = RHF**. What caused the increased in hydrostatic pressure also going to produce pitting edema and possibly ascites – therefore its more signs than it is symptoms. So, **neck vein distension, pitting edema, hepatomegaly, nut meg liver, ascites**.

C. Examples of LHF:
When you lie down to go to sleep, you can reabsorb up to 1 liter of fluid b/c it will go from the interstium to the venous side b/c there's no effective gravity. Therefore, there is extra blood going back to the right heart and into the left heart. However, what if you had left HF? There will be excess blood coming back (that wasn't there when you were standing up) and the left heart is having trouble getting blood out, with even more blood coming back in. Then the heart cannot handle it and goes back to the lungs, leading to dyspnea and continues for the next 30 minutes– this is **paroxysmal nocturnal dyspnea**. Eventually it settles down, you go back to sleep, wake up again, and it occurs again. Pt realizes that after you stand up, then it eventually goes away – therefore they put a pillow under them to decrease the dyspnea when they wake. This is called **pillow orthopnea**. If its one pillow orthopnea, its not that bad; however, if you have to sit up, you have serious left heart failure b/c you are imposing gravity. Just by putting head on one pillow will decrease venous return back to the heart. If you put 2 pillows under, it will decrease the dyspnea even more b/c of effective gravity. So, **pillow orthopnea and paroxysmal nocturnal dyspnea are signs of LEFT heart failure.**

D. Treatment:
If you have heart failure (right or left), what is the best nonpharmacologic treatment? Restrict water and salt.

What the king of Rx of HF? ACE inhibitor b/c it decreases afterload AND preload at the same time. ACE inhibitors increase longevity by (1) decreased aldosterone, therefore decreased salt and water reabsorption which decreases preload and (2) by blocking Angiotensin II, will lead to a decrease in vasoconstrictor effect on peripheral resistance arterioles, which will decrease afterload.

Pts with **spironolactone + ACE inhibitor** did better b/c aldosterone will eventually break through and become elevated again, therefore ACE inhibitor acting against aldosterone is not a permanent suppression. So spironolactone which specifically block

aldosterone, plus the ACE inhibitor is an increase in prognosis. Therefore, now it's normal to put the pt on spironolactone and ACE inhibitor b/c it will increase longevity.

E. High output failure
One cause is **endotoxic shock** – peripheral resistance arterioles are dilated, therefore an increase in C3a, C5a, NO, leading to increased venous return to the heart and the heart eventually gives up. There are also many other causes, and they relate to Pouseau's law – viscosity/radius to the fourth power. So, if you vasodilate the peripheral resistance arterioles, and you decrease TPR, more blood returns to the right heart, the left heart has to deal with it, too, and pt runs the risk of high output failure. So, one cause of the vasodilatation is **septic shock**, while the other is **thiamine deficiency**. Problem in thiamine def: ATP depletion: smooth muscle cells and peripheral resistance arterioles need ATP, therefore they do not work as well, and there is vasodilatation of the peripheral arterioles, leading to high output failure. So, thiamine def can produce high out put failure b/c vasodilatation of those vessels.

Graves's dz – hyperthyroidism – thyroid hormone increases the synthesis of beta receptors in the heart. Get an increase in force of contraction, and more blood. Systolic pressures are higher, and go into high output failure.

AV fistulas – ie get stabled in the leg; and develop an AV malformation, where there is arteriole blood bypassing the microcirculation going directly to the venous circulation and the blood comes back faster to the heart than normal; a bruit can be heard over the mass and it will be pulsatile; if you press the proximal portion of it, heart rate would slow (Brenham's sign) – these are all signs of AV fistula, leading to high output failure.

So, 3 examples of high output failure are endotoxic shock, graves, and AV fistulas

V. Congenital heart dz

A. Know fetal circulation (which vessels have the least/most O_2); remember that the baby is NOT exchanging blood with O_2 in the lungs. Pulmonary vessels in the fetus look like they have pulmonary HTN – they are so thick that it is extremely hard to get blood through the pulmonary artery into the LV b/c very little blood can go there – this is why baby needs a patent ductus to get blood out. Where is O_2 coming from? Coming from chorionic villus dipping into lake of blood, which derives from mom's spiral arterioles. Have chorionic villi dipping into blood and extracting O_2 from it. Obviously, this is not as good an O_2 source as the lungs; therefore, you want a high affinity Hb to be able to get what little O_2 is down in the area – this is why babies have HbF, b/c of its high affinity to grab O_2 from the blood. Bad news is that it gets the O_2, but doesn't want to give it up (says mine) – it left shifts the curve. What is compensatory response? This left shift causes tissue hypoxia, which will cause EPO to be released and the kid will have an 18 gram Hb – b/c of this, all newborns (in a sense) have polycythemia. This is the way around HbF's high affinity for O_2 – more RBC's made, more Hb, and baby gets more O_2.

Order of O_2 passing: O_2 goes through syncytiotrophoblast of chorionic villus, into the cytotrophoblast, then through the myxomatous stroma of the chorionic villus, then into the blood vessel. The blood vessels of the chorionic villis all coalesce to form the **umbilical vein**. This has the **highest O_2 content**. It goes to the liver and it can go two ways: 1) into the hepatic sinusoids and recollects into the hepatic vein and gets dumped into the IVC; and 2) ductus venosis and straight into the IVC. Then it goes up the right side of the heart; the foramen ovale is open in all fetuses (its not closed) – so all this blood is coming up the IVC – will it go straight across, through the foramen ovale and into the left atrium, or will it go into the IVC into the right atrium, down to through the tricuspid valve, and into the right ventricle? It will go through the foramen ovale. So, all this oxygenated blood will go directly from the right atrium of the foramen ovale into the left atrium, then the left ventricle and out the aorta. What about SVC blood valve? It is coming from the superior part of the right atrium (its not gonna make a left turn and go through the foramen ovale). It will go straight down, through the tricuspid valve into the right ventricle. Now, it will go out the pulmonary artery. This is a PROBLEM b/c the pulmonary vessels are too thick and it's encountering this tremendous amount of pressure. To counter this problem, kept the patent ductus open (which is kept open by the PGE2, a vasodilator, made by the placenta) – so, there is a right to left shunt and blood can get out of the pulmonary artery and dumped back into the aorta. Then, when the baby is born and takes its first breath, the pulmonary vessels (that were all shut), all open within a millisecond, and blood is going through those pulmonary arteries and gas exchange is occurring through the lungs in literally seconds. Also, the patent ductus closes and forms the ligamentum arteriosum. This is normal fetal circulation. Vessels with the least O_2 are the 2 umbilical arteries, and the one with the most amount of O_2 is the umbilical vein.

B. Shunts:
Look at O_2 saturations (this is how they dx them – they catheterize, measure O_2 saturations in different chambers, and know which direction the shunts are going.

Need to get used to two terms – step up and step down.
If you have a **left to right shunt**, and have oxygenated blood going into unO_2'd blood, what is happening to O_2 saturation on the right side? **Step up b/c mixing O_2'd with unO_2'd blood.**

If you have a **right to left shunt** with **unO_2'd blood going into the O_2'd blood**? **Step down**.
The O_2 saturation on the right side of the heart in blood returning from the body is 75%. The O_2 saturation on the left side is 95%.

C. VSD (MC)
Who's stronger - left or right ventricle? Left, therefore the direction of the shunt is left to right. So, oxygenated blood will be dumped into the right ventricle, leading to step up. Also, it will pump it out of the pulmonary artery, leading to step up. So, you have a step up of O_2 in right vent and pul artery. What if this is not corrected? With this mech, you are volume overloading the right side of the heart b/c of all that blood coming over. The outcome of this will be **pulmonary HTN** (the pulmonary artery has to deal with more blood and must contract more – leading to pul HTN) – Once pul HTN occurs, right ventricle will have a problem contracting

and it will get hypertrophied. Suddenly, you run the risk of reversing a shunt b/c then right ventricle could eventually be stronger than the left. So, it will be a right to left shunt – this is called **Eisenmenger's syndrome**. So, an uncorrected left to right shunt has the potential for producing Eisenmenger's syndrome. After reversal of the shunt occurs, pt will have **cyanosis** (aka cyanosis tardive). Most VSD's close spontaneously and some need to be patched.

D. ASD
Normal for a fetus to have a patent foramen ovale; it is not normal once they are born. Which direction will blood go through the foramen ovale? Left to right (b/c the left side is always stronger than the right). Therefore, what will happen to the right atrium? **Step up** – so it will go from 75 to 80%. What will happen to the right ventricle and pulmonary artery? **Step up**. So, **what is the main diff in O2 saturations in VSD vs ASD? ASD is step up of O2 also in the right atrium**. Are you volume overloading the right heart? Yes. So do you run a **risk for Eisenmenger's**? Yes. What else are at increased risk for? Paradoxical embolization. What if you weren't lucky enough to have a DVT in the leg, and it embolize up and the pressures of the right side of the heart are increasing, and you have a patent foramen ovale – will there be an embolus that can go from the right atrium to the left atrium and will have a venous clot in arterial circulation? Yes – this occurs in pts with ASD. **MC teratogen that has ASD associated with it? Fetal alcohol syndrome (1/5000)**

E. PDA
It's normal in a fetus but not when they are born. Connection between the aorta and pulmonary artery – which is stronger? Aorta. So, oxygenated blood goes from left and get dumped in the pulmonary artery before going into the lungs. So, what happens in the pulmonary artery? Step up. So, now its 80% O2 saturation – **the pulmonary artery is the only thing that has a step up of O2**. Then will go under the lungs and the pulmonary vein will have the normal 95% O2 sat. B/c there is an opening between these, there is blood going back and forth during systole and diastole – **machinery murmur** – where is it heard best? Between shoulder blades. Can you vol. overload the right heart? Yes. Pulmonary HTN? Yes. Now which way will the shunt go? Will go the same way when it was a fetus; you will have unO2'd blood dumping into the aorta. Where does the ductus empty? Distal to the subclavian artery – so, the baby will have pink on top and blue on bottom b/c dumping unO2'd blood below the subclavian artery, therefore will have **differential cyanosis – pink on top, cyanotic on bottom**. What is the teratogen assoc with PDA? Congenital Rubella. If you had a PDA, can you close it off without surgery? Yes. How? **Indomethacin - this is a potent NSAID, which would inhibit PGE2**, and therefore would start constricting and close on its own.

F. Tetralogy of Fallot
MC cyanotic congenital dz: "tetra" = four – overriding aorta: its straddling the septum; pulmonic stenosis below the valve, RVH, membranous septal defect (VSD). What determines whether you get cyanosis or not? Degree of pulmonic stenosis; not all babies have cyanosis and are acyanotic – called **acyanotic tetralogy**; why does this occur? Lets say the degree of pulmonic stenosis is not that bad – when the right vent contracts, a lot of the blood goes up the pulmonary artery to get O2'd and less blood gets into the left ventricle, and therefore probably will not have cyanosis at birth. What if it was a severe stenosis and when the right vent contracts, very lil blood got up there? Most will be shunted right to left and there will be a step DOWN in O2 in the left vent and baby will be cyanotic. So, **it is the degree of pulmonic stenosis that determines whether you have cyanosis or not.** Which of the groups of shunts is cardio-protective in a pt with tetralogy of fallot? PDA, ASD – good – lets say there is an ASD, therefore blood will go left to right b/c we get O2'd blood emptying into the right atrium. This would cause a step up of blood into the right atrium (this is good). How about a PDA? Lets make believe this occurs – so, unO2'd blood pushed from left from the aorta down to the pul artery to get O2; some of the unO2'd blood put back into the pul artery, where it gets O2'd and more gets out – **good to have PDA and ASD (foramen of ovale) with tetralogy of fallot.**

Right to left leads to polycythemia and a real risk for infective endocarditis b/c shunts going into left side, therefore can get vegetations going into the brain and other systemic organs. **All congenital heart defects lead to infective endocarditis.**

G. Transposition of Great vessels
Example: in Kartagener's syndrome with syndrome with sinus inversus – this not the case with transposition of great vessels – have a normal heart that is on the right side (everything isn't reversed the way it is in sinus inversus). What's transposed? Not the right atrium – it is still getting unoxygenated blood. Its not the left atrium – it is still getting 95% O2 saturated blood from the pulmonary vein. **The problem is in the ventricles** – the right ventricle is being emptied by the aorta; and the left is being emptied by the pulmonary artery. So, the thing that is transposed are the ventricles (the atria are fine). This is incompatible with life unless you have shunts: VSD, ASD, and PDA can work. How's does this work?

Start at the atrial side – have 95% O2 coming into left atrium and it is going from the left to right; there will be a step up of O2 in the right atrium and therefore also a step up of O2 in the right ventricle. Some will go out the aorta and rest will go to the left ventricle. This is good b/c the left ventricle is being emptied by the pulmonary artery, so the blood will be taken to the lungs to be oxygenated. So, these shunts are necessary. Otherwise, the right vent being emptied by the aorta would be all oxygenated blood and the left ventricle being emptied with the pulmonary artery would not be okay. So, by having the shunts, can get around these defects. An ASD is necessary so you can get O2'd blood into the right atrium, and from the right atrium there will be a step up of O2 in the right ventricle, which is being emptied by the aorta; obviously this blood isn't 95% saturated (maybe 80%), and this is why there is cyanosis in these patients. At least some blood can get out of the aorta and have some O2 to the pt and they can survive for a little while. B/c of the right to left shunt, that blood is being emptied by the pulmonary artery and that is going to the lungs and being oxygenated. So, the shunts are necessary for life. So, with Kartagener's, there is NOT a complete transposition of vessels, but a normal heart on the right side (called sinus inversus).

H. Coarctation – have preductal and postductal
Pre = before patent ductus; post = after patent ductus (after the ligamentum arteriosum)
Preductal occur in Turner syndrome and go straight into failure, therefore must be corrected immediately. **Postductal** are not present at birth and can occur at any time during the pt's adult life. Important to recognize b/c they are a surgically correctable cause of HTN.

Stenosis in aorta – what is happening proximal? There is trouble getting blood through that, therefore there will be a murmur heard best between the shoulder blades – a systolic murmur. There is a lot of pressure built up proximally, so the prox aorta will be dilated and there will be a lot of pressure going into the vessels – the subclavian, internal carotids – therefore the **BP in the upper extremities will be higher than it is in the lower extremities.** Also, with increased blood flow into the brain, at the junction where the communicating branches hit the main cerebral branches, we have no internal elastic lamina and no smooth muscle there, therefore it is a weak area (for ALL people); therefore, **everybody has the potential to develop berry aneurysms**. What would exacerbate, or make the berry aneurysm a realistic thing? **HTN** (any cause of HTN can cause berry aneurysms – ie ADPKD, essential HTN, the bottom line is HTN, and **ALL hypertensive pts run the risk of berry aneurysms** – we all have the same defect at the junction form any cause of HTN – its not unique to ADPKD, its in all cases of HTN – other relations to HTN = subarachnoid bleeds, stretch/dilatation of aortic valve ring and therefore a murmur of aortic regurg. All the pressure on the wall of the proximal aorta **can also predispose to dissecting aortic aneurysm**. What is distal to this? Decreased blood flow, **claudication** (angina of peripheral vessels – so when they walk, they will get calf pain, buttock pain, then they stop and it goes away, they walk it hurts) – this is all due to ischemia, and the muscle development to the lower extremities will not be too good, either. Muscle mass will be decreased, BP difference between upper and lower extremities, and the blood flow to the renal arteries is decreased, leading to activation of the RAA will lead to HTN. So the **HTN in pts with Coarctation is due to activation of RAA** – so it is a high renin HTN. So, if you can correct it the HTN will go away. When there is a problem (ie a roadblock), we have to go around it – ie need collaterals. However, the aorta is not a good place to have a roadblock b/c only have two ways to get around the block: 1)(rarest) superficial epigastric artery, with the internal mammary artery can get around this; this is at the lateral border of hasselbach (the superficial epigastric artery). So, when you stick your finger in the canal and have an indirect inguinal hernia. Right through the medial side will feel a pulsation (where the sup epigastric artery is). 2) intercostals – on the undersurface of the ribs and getting extra blood through them – leading to **notching of ribs** (visualized on x-ray).

VI. Major risk factors for coronary artery dz: Know the risk factors!
Age is the most imp risk factor (cannot control) -45 for males; 55 for women – why? Higher estrogen levels, which affect HDL levels. Risk factor for CAD is not LDL, its HDL. HDL visits fatty streaks, sucks LDL out, takes it to the liver to be metabolized. 55 in women b/c that is the age of menopause; not taking estrogens and that is the age when estrogens go down; HDL levels go down and risk goes up. Family history of premature artery dz, cig smoking, HP, HDL<35, diabetes, LDL (cholesterol is not a risk factor, LDL is) b/c all therapeutic decisions are based on LDL levels, not cholesterol levels. HDL is a negative risk factor: if your HDL is greater than 60, you can subtract one from your major risk factor - ie 58 y/o, but HDL is above 60, can subtract the age risk factor and will have no risk factors.

VII. Ischemic Heart Disease:
4 types: Angina, Myocardial Infarct, Sudden Cardiac Death Syndrome, Chronic Ischemic Heart Disease

A. Sudden cardiac death syndrome = death within the last hr – what will you see at autopsy? Will NOT see a coronary thrombus, will see severe coronary artery atherosclerosis. So, usually these pts do not have a thrombus, but do have severe coronary artery dz, leading to ischemia, PVC's, ventricular fibrillation (die of ventricular arrhythmia just like in MI); die so fast that there are no changes in the heart (ie pallor/Coagulation necrosis); see severe coronary artery dz and dx sudden cardiac death. Very high risk in smokers.

B. Chronic ischemia heart dz –It's a lot of our parents, uncles and aunts who have coronary artery dz with little infarcts, or had a small heart attack, basically talking about subendocardial infarctions. What happens is that the muscle gets replaced by fibrous tissue and eventually the poor LV is all fibrous tissue, with no muscle therefore the ejection fraction is very low. Its 0.2 instead of the normal 0.66 and they die from heart failure. Fibrous tissue does not have contractility; this dz is the 2nd MC indication for a heart transplant.

C. Angina (MC type of heart dz)
3 types – exertional, prinzmetal, unstable (resting) angina

1. **Exertional** – chest pain on exertion, goes away within 5-10 minutes of resting; ST depression on EKG (1-2 mm depression) – therefore a candidate for coronary angiogram to see what's going on.

2. **Prinzmetal's** – seen in women, occurs in morning; due to vasospasm of the coronary arteries, NOT atherosclerosis. In some people, TxA2 is implicated for the vasospasm. **ST depression means subendocardial ischemia**. Coronary arteries penetrate the outside of the heart and go in, so the subendocardial tissue get screwed b/c its furtherest from the blood supply. Therefore, with coronary artery atherosclerosis, and decreased blood flow, who gets screwed? Subendocardium and it reacts to it with pain and ST depression. With vasospasm of coronary artery, get transmural ischemia – therefore there is ischemia throughout the entire thickness of the muscle – this produces ST elevation. So, Prinzmetal's angina has ST elevation b/c transmural ischemia.

3. **Unstable** – aka pre-infarction angina – get angina on resting. Classic hx: initially had stable angina, now pt just get it when they are sitting. This means that they will need angioplasty and put into the hospital. Do not put on treadmill, they will die. What veins do they use? Saphenous vein – over 10 years will become arterialized (it will look exactly like an artery). If you take a vein, and put arterial pressures into it, it will change its histology and look exactly like an artery. They have a high tendency for fibrosing off after 10 years b/c they are veins.
Internal mammary is an artery, therefore won't have the same problem b/c it is used to those pressures. They will remain patent, but cannot do four vessel bypass with one internal mammary artery. So, they use the saphenous vein, which has the tendency to undergo fibrosis over time b/c they are arterialized under pressure. They can also use the internal mammary.

D. Acute MI
Thrombus composed of group of platelet cells bound together with fibrin. TPA doesn't have a problem with this b/c it just breaks the fibrin bonds to destroy the clot. It has a much bigger problem with the breakdown of a venous clot b/c those have more fibrin. The thromboses/clots in the heart do not have that much fibrin. Another factor to deal with is reperfusion injury – O2'd blood goes into

injured tissue, superoxide free radicals form, Ca form, and a few of the injured myocardial cells will die. Once those die, it will still improve longevity.

1. Complications of MI:
a) LAD coronary artery is MC vessel thrombosed, and supplies entire anterior part of your heart and the anterior 2/3's of the interventricular septum. So, there will be paleness, with the ant 2/3's knocked off. Where are most of the conduction bundles? Anterior 2/3's. So, if you have complete heart block that requires ectopic pacemaker, what is the most likely vessel thrombosed? LAD. When you have LAD occlusion, you have **classical signs – pain radiating the jaw, pain down the left arm, substernal chest pain.**

b) RCA = 2nd MC thrombosed artery – which supplies the entire posterior part of the heart and the posterior 1/3 of the ventricular septum and the entire right ventricle. So, it supplies the post heart, post 1/3 of the septum and the entire right ventricle. The mitral valve has two valves with papillary muscles – posteromedial papillary muscle and posteromedio papillary muscle. So, what supplies the posterior? RCA. Also have the SA node and AV node. The SA node has an equal distribution between left and right. However, the **AV node has a 95% supply from the branches of the RCA** – this brings up interesting complications. Example: pt with mitral regurg murmur, which is related to posteromedial papillary muscle dysfunction, or may break – what is the problem? Thrombosis of the RCA b/c the RCA supplies that papillary muscle. So, mitral regurg murmur that occurs during MI would be due to RCA. **If you knock off the AV node, this is sinus bradycardia, and atypical chest pain**. The RCA is dangerous b/c sometimes pt will get **epigastric pain**, which is an atypical pain. This simulates GERD; ie pt sent home with pepto bismol, and ends up dying at home (b/c of missed dx). They should have been sent to hospital. Therefore, elderly pt with **epigastric pain could be GERD or coronary artery thrombosis of the RCA.**
2. Gross/microscopic features
Need to know when the heart is softest and has a chance for rupturing – this is between 3-7 days. When do you see gross manifestation of being a pale infarct? 24 hrs – begin seeing paleness. Coagulation necrosis in 4-6 hrs.

Example: LAD thrombosis b/c see pale anterior 2/3 of heart. Rupture – pericardium filled with blood (hemopericardium) – most are interior, and therefore is from the LAD thrombosis – how does this manifest itself? Day 3 or day 4 complain of chest pain, have muffled heart sounds, neck vein distension, and know they have ruptured.

Example: rupture of post medial papillary muscle – and it was infracted, therefore the RCA is the cause
of the rupture – so, what would the murmur be? Mitral regurg –On day 3 pt goes into heart failure, have a pansystolic murmur, increases on expiration, and S3 and S4 heart sound. It wasn't there a day before – meaning the posterior medial papillary muscle was dysfunctional b/c it was infracted or it ruptured. So, it's something that wasn't there before and suddenly arise between days 3-7. Will go into heart failure b/c massive volume overload and go right back to the lungs.

Example: rupture of ant wall
Example: rupture of papillary muscle, and the posteromedial one is MC
Example: Coag necrosis
Example: interventricular septum ruptures, therefore a left to right shunt and a step up. Most interventricular ruptures are LAD thromboses.

Example: **mural thrombus** (mural = wall) – in this case, mural is a thrombus, on the wall. They are almost always LAD thrombi b/c need a place to stick. With anterior MI, always give aspirin and put pt on warfarin/heparin – why do they do that? To prevent mural thrombus from forming. So, when you have an anterior prob, they will anticoagulate you. **Mural thrombi are mixed clots** – they are not a pure venous like clot or a platelet like clot, they are mixed. Here's how it works: you have a transmural infarction and therefore injury to endothelial cells of the heart, therefore platelets will stick – so platelets are the first things that stick and then b/c the muscle is not contracting that well (b/c infracted muscle does not contract), there is stasis, and so on top of the platelets is a venous like clot, which Coagulation factor 5,8, and RBC's, so its mixed (platelets with fibrin and venous clot from stasis). With **aspirin**, you not only preventing a coronary thrombus with decreasing platelet aggregation, but also preventing a mural thrombus from initially forming b/c it inhibits the platelets from aggregating. Also, **by putting on warfarin and heparin**, you prevent the other part of the clot from forming. Don't want these b/c it can embolize and therefore are very dangerous.

3. Fibrinous pericarditis – can occur 2 times in a person with MI: 1) 1st week – get a friction rub, chest pain (relieved when leaning forward and worse when leaning back - a 3 component friction rub). That's due to transmural infarction and increased vessel permeability. And 2) hx of transmural infarct, comes in 6 weeks later with fever, muscle aches and pains, and a 3 component friction rub in the chest = **Dresslers's syndrome , which is an autoimmune pericarditis**. When had infarct, damage of the pericardial surface led to autoAb's against pericardial tissue. This took 6 weeks to build up, and they start attacking the pericardium leading to systemic symptoms related to immunologic rxn = Dresslers's. Therefore, **2 types are 1st week, not autoimmune, and 6 weeks, autoimmune.** Basically treat with NSAIDS.

4. Later complications – ventricular aneurysm
Example: pt 3 weeks out of MI – chest bulges – what under there? Massive pectoralis major – ie **systolic bulge of pericardium is ventricular aneurysm**. Blood is collecting in the aneurysm and making the chest bulge out. This is a late manifestation – know it's a vent aneurysm; the MC complication is NOT rupture, this aneurysm is lined by scar tissue and therefore will not rupture**. MCC death in a vent aneurysm = heart failure.** Most of heart has scar tissue, which leads to decreased ejection fraction, therefore, **die of HEART FAILURE not rupture**.

Example:Acute MI – wasn't – it is **fibrous tissue, which is whiter and more patchy.** Fibrous tissue (scar) can be anywhere from 3 weeks to 10 years

Must look at EF (ejection fraction) before leaving hospital; if you don't have a good EF, probably will die. If you have a low EF, you had a big infarct, with a lot of muscle that was destroyed. Therefore, EF is the biggest prognostic factor. If its close to 0.66, that's good. But if your 0.4, ie its very bad.

5. How do we dx MI? CK-MB is dx of choice
Not an EKG b/c it has only an 80% sensitivity showing a new q wave, ST elevation. They have great specificity: Troponin I; CK-MB is an isoenzyme of creatinine kinase – have CK-MM, MB, and BB.

CK – MB is primarily in cardiac muscle. Therefore, when you infarct the muscle, you will see a primary increase in cardiac muscle, and when the muscle is infracted, will see an increase in that enzyme. Starts to go up at 6 hrs. Peaks in 24 hrs, and gone in 3 days b/c if CK MB is present after 3 days defines REinfarction. So, the reappearance of CK-MB = REinfarction.

Troponin I elevates a few hrs earlier than CK MB – its goes up at about 4 hrs, and peaks in about 24 hrs, too. It lasts 7 days, which is good. However, cannot dx reinfarction. So, after day 3 Troponin will still be there and therefore, you cannot dx reinfarction. CK-MB replaces LDH isoenzymes.

LDH isoenzyme: Normally, LDH2 is higher than LDH1. However, **LDH1 is in cardiac muscle**. So, when you have an infarct, you release LDH1, and 1 becomes higher than 2 – which is called the flip. When you infarct through the muscle, 1 will be higher than 2, and that is the flip. This occurs in about 18 hours and peaks in about 3 days and last for a week. Most of the time, we use LDH enzymes if the pt came in 2-3 days after symptoms and CK-MB will have been gone by then. Then, look at LDH isoenzymes, and recognize that there is a flip and realize that there was an MI few days ago. This will be replaced by Troponin 1 b/c its elevated during this time period.

VIII. Valvular Heart Disease
A. Mitral Valve Prolapse – MC mitral valve lesion – more common in women; too much valve and looks like a parachute (air goes under a parachute and fills it up – same with blood) – blood will prolapse into left atrium, and when it stops, it causes a click. Prolapse means that something is coming out – ie rectal prolapse.

So, with mitral valve prolapse, it is extending into the left atrium. When it stops, and cannot go in anymore, it stops and causes a click, and it followed by a short mitral regurg murmur. So, it goes "click murmur, click murmur" (not "snap murmur" – opening snaps occur in mitral and tricuspid stenosis). What is the pathology? Myxomatous degeneration. What GAG makes up the valve? Dermatan sulfate, therefore its an excess of dermatan sulfate in the mitral valve, and it becomes redundant (too much of it), blood goes under it and causes a click and murmur. Is it closer to S1 or S2? It deals with preload. If we increased vol of blood in the left ventricle, then the click and murmur will come closer to S2 b/c it takes longer for all the events to get blood out. If we decrease the amount of blood coming into the left ventricle (decrease preload), the click and murmur come closer to S1. So, when standing and have MVP, what is preload vs. lying down? It is less. Less preload = less blood in the ventricle = click and murmur closer to S1. Now, let's say pt lies down – click and murmur closer to S2 b/c increasing preload. They will ask: what will happen to click and murmur with anxiety? What will happen to heart rate with anxiety? Increase. Therefore, will have less time to fill ventricles, therefore will come closer to S1.

Queston on examinations " American tourist came back with diarrhea… answer is giardisis"
B. Aortic Stenosis
MC valvular cause of syncope with exercise
MCC angina with exercise.
MCC microangiopathic hemolytic anemia

This will an ejection murmur, right 2nd ICS, radiation into the neck, systolic, increases in intensity on expiration. Intensity of murmur with different positions: what will increase the intensity of the murmur (what will make it worse and therefore louder)? Increasing preload in the ventricle. With decreased blood in the ventricle, it will decrease the intensity of the ejection murmur b/c it has to go out the stenotic valve.
If you are putting more blood into the LV and need to get it out, it will increase the intensity - this is imp b/c it differentiates it from hypertrophic cardiomyopathy.

Why do they get angina with exercise? Pulse is diminished and therefore the stroke volume will decrease. So, when do the coronary arteries fill up? Diastole. With less blood there (b/c couldn't get it out and had to get it through the valve), there is thickened muscle and less blood going to the heart, leading to angina. So, this is the MC valvular lesion leading to angina. Also, with syncope with exercise, b/c you have decreased cardiac output, you will faint.

C. Mitral stenosis
Slide: Thrombi, left atrium is dilated; **murmur in diastole** (stenosis prob in opening and this valve opens in diastole, leading to snap and rumble), heard at apex and increases in intensity on expiration.
MCC mitral stenosis – rheumatic fever (acute). Rheumatic fever -vegetations; due to group A beta hemolytic streptococcal infection. Usually occurs as post-pharyngitis. As opposed to post streptococcal glomerulonephritis, this can be pharyngitis or a skin infection. Most of time rheumatic fever is from a previous tonsillitis. When you culture blood in pts with rheumatic fever, it will be negative. Will not be able to grow the organisms b/c its not an infective endocarditis. It is an immunologic mechanism. **With strep, M protein is the pathogenic factor for group A strep**. Certain strains have Ag's similar to the heart and joints. So, when we make Ab's against the group A strep, we are also making Ag's against the heart (our own tissue) – therefore we attack our own heart, joints, basal ganglia and elsewhere. This is called **mimicry** b/c we are developing Ab's against our own tissue, b/c there are similar Ag's in the M protein of the bacteria, **so its is all immunologic**! MC valve involved is the mitral valve. The vegetations are sterile and line along the closure of the valve. The vegetations usually do not embolize. **Know Jones criteria for dx of acute rheumatic fever** – ie young person, few weeks ago had an exudative tonsillitis, now presents with joint pain and swelling and

dyspnea, rales in the lung, pansystolic murmur, apex, and increases in intensity on expiration, S3 and S4 heart sound – due to acute rheumatic fever. Dx is rheumatic fever. **MC symptom is polyarthritis**. They like this question b/c in children, there is a limited **d/d for polyarthritis – it includes juvenile rheumatic arthritis, Henoch Schonlein purpura, rubella, acute rheumatic fever. However, none of these have symptoms of heart failure and mitral insufficiency except for acute rheumatic fever.** So, if they ask you the MC valvular lesion in acute rheumatic fever, it is NOT mitral stenosis. It takes 10 years to have a stenotic valve (mitral stenosis). So, the murmur that you hear is mitral REGURG, b/c all parts of the heart are inflamed, leading to friction rub, myocarditis (inflamed myocardium), and endocarditis (these are the valves with the vegetations). So, will get mitral regurg murmur with acute rheumatic fever. Other features of Jones criteria: joints, cardiac abnormalities, erythema marginatum (skin zit), subcutaneous nodules (like rheumatic nodules on the extensor surfaces – they are exactly the same). Rh nodules and nodules associated with acute rheumatic fever are exactly the same. They are both immunologic dz's. Late manifestation of Jones' criteria is abnormal movements – called Syndham's chorea. Example: pt with acute rheumatic fever (grade 3, pansystolic, apex, rales, S3 and S4, nodules, erythema marginatum) - 6 weeks later have Syndham's chorea. **ASO titer is imp, too – b/c it's a group A strep infection and its elevated.** Aschoff nodules – reactive histiocytes in the myocardium; only find with bx on death.
Summary: immunologic dz, will not culture out group A strep in the blood, Jones criteria (polyarthritis, MC carditis, subcutaneous nodules, erythema marginatum, Syndham's chorea.
Ie mitral stenosis, looking from left atrium, down to the ventricle – looks like a fishmouth (fishmouth appearance).

Example: what is the most posteriorly located chamber of you heart? Left atrium. Seen best on transesophageal ultrasound. B/c it is posteriorly located, and enlarged when dilated, it can press on the esophagus, leading to dsyphagia with solids (not liquids). Also, it can stretch the left recurrent laryngeal nerve and cause hoarseness. This is called **Orner's syndrome**.

Example: if they have an irregular irregular pulse, what does that mean? **Atrial fibrillation**. Does it surprise you that they get thrombus in the left atrium? No. B/c there is a lot of stasis b/c blood is having trouble getting through, leading to stasis and thromboses. So, have to anticoagulate the pts, which is a bad combo.
Atrial fib + thrombus = bad combo. When you picture A fib, its like a vibrator and lil chips can come off and embolize – this is very common in patients with MITRAL STENOSIS.

MVP – valve is being prolapsed into atrium, b/c it is so redundant, and, chordae tendinae will rupture, leading to acute mitral insufficiency. This is not common in MVP – most of the time it is asymptomatic. MC symptomatic thing = palpitations.
2 genetic dz's with MVP assoc: Marfan's and Ehler Danlos syndrome. Marfan pt and pt died suddenly, why? NOT dissecting aortic aneurysm (do not die immediately with dissections – get pain, radiation and cardiac tamponade) – answer is MVP and conduction defects. So, **pt with marfan and dies suddenly, this is due to MVP and conduction defects (not dissecting aortic aneurysm).**

Tricuspid regurg – know about IVDA with infective endocarditis.

Carcinoid syndrome – in order to have carcinoid syndrome, must have metassis to liver of carcinoid tumor. Serotonin and the tumor nodules gets into hepatic vein tributaries and gets into the venous blood and bathes the right side of the heart, and serotonin produces a fibrous tissue response of the valves. So, will get tricuspid insuff and pulmonic stenosis. These are the 2 valvular lesions assoc with carcinoid syndrome. (TIPS)

IX. Infective endocarditis
Mitral valve with vegetations and rupture chordae tendinae; vegetations are big and bulky and destroying the valve (hence, infective).
What is **MCC? Strep viridians; 2nd MCC = Staph**
While brushing teeth, have a transient strep viridians infection. If you have an underlying cardiac dz, then you run the risk of developing a bacterial endocarditis b/c just brushing your teeth can cause it to get into the bloodstream; with damaged valves, it can seed into it and produce vegetations.
Staph aureus can affect a NORMAL valve OR a damaged valve.
MC valve involved in infective endocarditis = mitral valve; 2nd MC valve = aortic valve
If you are an IVDA (who inject into veins), MC valve involved = Tricuspid valve, 2nd MC is aortic
Tricuspid involved = Murmur of tricuspid regurg, pansystolic, increased on inspiration
Aortic valve involved: aortic regurg, high pitched diastolic after S2
Staph is #1 (MCC) for IVDA
If you have **colon cancer/ulcerative colitis** (any type of ulceration of the colonic mucosa), there is a unique type of infective endocarditis – this is **strep bovis** = **group D strep – commonly involved with dz's that produce ulceration of the colonic mucosa – ie UC or colon cancer. History of colon cancer and have infective endo – organism is strep bovis (not staph).**
Aortic valve – close relationship of membranous portion of the septum with the aortic valve. So, why did pt get vegetations of the aortic valve? B/c they got VSD that was not picked up. If you have congenital heart dz, you have an increased risk for infective endocarditis. VSD that someone did not pick up caused aortic valve to get infective and cause aortic regurg. Therefore, on the test, will be mitral valve infective endo, or aortic infective endo with a VSD.
Splinter hemorrhages; Painful = osler's nodes; painless = janeway lesion; in eye – Roth spot (red with white center – just like Koplik spots in measles, which are red with a white center). This is why it is called the Koplik spot of the eye. What do they all have in common (aside from the fact that they are seen in infective endocarditis)? Splinter hemorrhages, Osler's nodes, janeway lesions, Roth spots, and glomerulonephritis? **All are type III HPY**. All these lesions are immune complex vasculitis.
Vegetations all over surface of the valve and pt has a "+" serum ANA – dx? **Libman sacs endocarditis – pt has Lupus** (Libman sacs is not the MC lesion of the heart with Lupus – pericarditis is); Libman sacs is the 2nd MCC, which is fibrinoid necrosis like rheumatic fever.
Marantic vegetations in mucous secreting colon cancer = Paraneoplastic syndrome (it is marantic endocarditis in a pt with colon cancer). Acute rheumatic fever looks like it.
X. Myocarditis vs. Pericarditis

On the test, if you have an infection question, it is **Coxsackie virus.**
MCC of myocarditis and pericarditis;
MCC viral meningitis = Coxsackie virus.
Cause of hand, foot and mouth dz? Coxsackie virus
Herpangina is due to Coxsackie's virus.
Example: Pt with heart failure did an endomyocardial bx and it had lymphocytic infiltrate in there, and it was due to Coxsackie's myocarditis. To dx, need to do a bx of subendocardial tissue, and will see lymphocytic infiltrate (as expected with ANY virus). Therefore, ie, pt in heart failure, bx of myocardium has lymphocytes = Coxsackie's virus myocarditis

Chest x-ray – see water bottle config – this pt as muffled heart sounds (cannot hear anything), when the pt breaths in, neck veins distend (shouldn't happen b/c when you breath in and increase neg intrathoracic pressure, the neck veins should collapse on inspiration), radial pulse is decreased on inspiration, when you take BP there is a drop of 10mmHg during inspiration. Dx? **Pericardial effusion**
What the name of the triad? Beck's triad. What is the name of the sign? **Kussmaul's sign**. What is the drop of 10 mm Hb on inspiration? **Pulsus paradoxus.** How does all this occur? B/c there is an effusion of the pericardial sac, meaning that that heart cannot fill up (b/c there is fluid around it) – leading to muffled heart sounds. So, when you breath in and blood is supposed to get into the right side of your heart, it cannot expand. So, the neck veins distend instead of collapse, which is called Kussmaul's sign. What ever happens to right side of the heart affects the left side of the heart b/c the left side receive blood from the right side. So, there is no blood going into the right heart, and therefore, no blood is going out of the left heart, either. So, on inspiration, blood cannot get out of left side (b/c blood is not coming out of the right heart), leading to a drop in pulse – **hence pulsus paradoxus**. Always see these things together: neck vein distension, drop in pulse magnitude, and drop in BP, Kussmaul's sign, pulsus paradoxus = **pericardial effusion**. However, this is not what they will ask you – they will ask what **is first step in management? Echocardiogram** – shows that they have fluid (proves it – b/c need to call surgeon to do pericardiocentesis).
What **is it MC due to? Pericarditis. What is the MCC pericarditis? Coxsackie.**

What if woman has this and a "+" serum ANA? Lupus.
Any young woman that has an unexplained pericardial or pleural effusion is lupus until proven otherwise. Why? Serositis = inflame serosal membranes – its gonna leak fluid, leading to effusions. And is a feature of Lupus.

E. Constrictive pericarditis
In third world countries, TB is MC. In USA, due to previous cardiac surgery b/c have to go through pericardium. Slide of a heart and thickened pericardium, no fluid, so when you breathe in blood goes to right heart, fills up and hits wall – called **pericardial knock** – therefore **to differentiate pericardial effusion from constrictive pericarditis, have muffled heart sounds in effusion with no knock in pericardial effusion, and in have some filling up with a pericardial knock in constrictive pericarditis.** White stuff in pericardium is dystrophic calcification, and can see it on x-ray. Pt goes to Russia and gets diarrhea = giardiasis)

XI. Cardiomyopathies
Large left ventricle and right ventricle

A. Congestive cardiomyopathy (aka dilated cardiomyopathy) – Example: woman 6 weeks postpartum, and do a chest x-ray and she has a generalized cardiomegaly – heart is huge, has effusions at both lung bases – dx? Congestive cardiomyopathy; this is a dz of the cardiac muscle and has many causes. Pt has both left and right heart failure. Causes: 6 weeks postpartum (don't know why), Coxsackie's myocarditis, alcohol, drugs; MCC transplants is due to congestive cardiomyopathy. Cardiotoxic drugs – daunorubicin, tricyclics = drug induced cardiomyopathies = congestive cardiomyopathy. Alcoholic with big heart due to thiamine def = congestive cardiomyopathy.

B. Hypertrophic cardiomyopathy
MCC sudden death in a young athlete = **hypertrophic cardiomyopathy.** Thickness of septum very thick with an asymmetric HPY; why? B/c the interventricular septum is thicker. Blood flow of left vent – goes through narrow opening (ant leaflet of mitral valve – so, if you have aortic regurg, blood will hit anterior leaflet of mitral valve and produce Austin flint murmur). Why is this a narrow opening? B/c it is too thick. If we took a laser to burn it off, could open it up; so, where is the obstruction in hypertrophic cardiomyopathy? Its not at the level of the aortic valve, but below it. Why does it obstruct? Venturi phenomenon – things go through a narrow opening quickly and there is a negative pressure behind it. When blood, under increased force of contraction is forced through, the negative pressure behind it sucks the anterior leaflet behind the septum and stops the blood, leading to obstruction of blood flow. What can we do to make this better (what can we do to reduce the intensity of the murmur and have the pt have better CO)? Put more blood into the ventricle – increase preload and decrease obstruction b/c it would pull it away b/c there is more blood in it. All these things that increase preload will make the intensity of the murmur less and improve the pt. So, if you are standing up, will that improve the dz? No, b/c would decrease preload, leading to a harsh systolic murmur. However, if lying down, there is increased venous return to the right heart, and increased blood in the vent, this would decrease intensity of murmur. Digitalis would be contraindicated b/c it would increase force of contraction, make it go faster and make it obstruct quicker. A beta blocker would be good; Ca channel blocker would also be good b/c it would decrease force of contraction, slow the heart rate, and increase preload. This is MCC sudden death in a young athlete. If you took a section of the septum, its not a normal septum – its disorganized, and the conduction bundles are messed up, leading to conduction defects - with conduction defects, run the risk of V. tach and death at any time. This abnormal conduction system and asymmetric septum is responsible. Ie 16 y/o bball player that died suddenly – what do you see at autopsy? Hypertrophic cardiomyopathy. Mech? Abnormal conduction

C. Endocardial Fibroelastosis (ie of restricted cardiomyopathy)
If it is restrictive, something is preventing the ventricle from filling up. This is the MC dz causing restrictive cardiomyopathy in children, and is called endocardial Fibroelastosis. This dz is the MC reason why a child needs a heart transplant. If the child does not get a transplant, they will die. Other causes of restrictive cardiomyopathy – Pompe's, Fe overload, amyloid.

D. Cardiac myxoma

85% in the left atrium, 15% in right
B9, movable – can move over and block orifice of mitral valve, leading to syncope. They can embolize (they are very soft and have bits and pieces inside them). Have a lot of junk inside them, which leaks out. It can lead to fever, and other signs and symptoms. Syncope cannot figure it out; then get a transesophageal ultrasound and see it. So, this is the **MC primary b9 tumor of the heart in adults**.

They **describe tumor in heart of kid** – this is **rhabdomyoma** (b9 tumor of cardiac muscle) – they are assoc with auto dom. dz, which one? **Tuberous sclerosis**. So, if they talk about a tumor in the heart of a CHILD, do not pic myxoma (seen in adults); it's a rhabdomyoma and is more likely in a child with tuberous sclerosis.

CHAPTER 8: RESPIRATORY

I. A-a gradient – know how to calculate:

Alveolar O2 and arterial pO2 are never the same. The difference between the two is called alveolar arterial gradient. Reasons for it: (1) Ventilation and perfusion are not evenly matched in the lungs. When standing up the ventilation is better than perfusion in the apex, whereas perfusion is better than ventilation at lower lobes. This explains why almost all pulmonary infarctions are in the lower lobes – perfusion is greater there. Also, this explains why reactivation TB is in the apex – TB is a strict aerobe and needs as more O2, and there is more ventilation in the upper lobes (higher O2 content). Normally, alveolar O2 is 100 and the arterial pO2 is 95. So, normally, the gradient is 5 mmHg. As you get older, the gradient expands, but not that much. Most people use their upper limit of normal – in other words, have a very very high specificity of 30 mmHg. If you have an **A-a gradient of 30 mmHg or higher there is a problem**. It is very high specificity (aka PPV – truly have something wrong). The concept is easy – you would expect the gradient btwn the alveolar O2 and the arterial O2 to be greater if you have **primary lung dz**. What will do this? Ventilation defects (produces hypoxemia, and therefore prolongs the gradient – dropping the PO2 and subtracting, and therefore a greater difference btwn the two), perfusion defect (ie pul embolus), and diffusion defect. But the depression of the medullary resp center by barbiturates does not cause a difference in A-a gradient. So, **prolonged A-a gradient tells you the hypoxemia is due to a problem in the lungs (vent perfusion/diffusion defect). A normal A-a gradient tells you that something outside the lungs that is causing hypoxemia (resp acidosis – in resp acidosis, PO2 will go down).** Causes of resp acidosis: pulmonary probs (COPD), depression of resp center (obstruct upper airway from epiglottitis, larygiotracheobronchitis, café coronary (paralyzed muscles of resp), Guillain Barre syndrome, amyotrophic lateral sclerosis, and paralysis of diaphragm. These all produce resp acidosis and hypoxemia, but the A-a gradient will be NORMAL). So, prolonged A-a gradient, something is wrong with the lungs. If A-a gradient is normal, there is something OUTSIDE of the lungs that is causing a resp problem.

Few things must always be calculated: anion gap (with electrolytes) and A-a gradient for blood gases – all you need to do is calc alveolar O2. We can **calculate the A-a gradient** = 0.21 x 713 = 150 (0.21 is the atmospheric O2; and 760 minus the water vapor=713). So, **150 minus the pCO2** (given in the blood gas) **divided by 0.8** (resp quotient). So, normal pCO2 = 40, and 40/.8=50 and 150-50 = 100; so, now that I have calc the alveolar O2, just subtract the measured arterial pO2 and you have the A-a gradient. This is very simple and gives a lot of info when working up hypoxemia.

II. Upper Respiratory Disease:

A. Nasal Polyps:

3 diff types of nasal polyps – MC is an allergic polyp. Never think of a polyp in the nose of kid that is allergic as an allergic polyp. Allergic polyps develop in adults after a long term allergies such as allergic rhinitis – Example: 5 y/o child with nasal polyp and resp defects, what is the first step in management? Sweat test – b/c if you have a polyp in the nose of the kid, you have cystic fibrosis; it's not an allergic polyp.

B. Triad Asthma

– take an aspirin or NSAID, have nasal polyps and of course have asthma. They don't tell you the pt took aspirin and that the pt has a polyp. The aspirin or NSAID is the answer but this is how they will ask the question: 35 y/o woman with chronic headaches or fibromyalgia. Pt has some type of chronic pain syndrome and will not tell you that the pt is on medication, and she develops occasional bouts of asthma – what is the mech of the pt's asthma? B/c she is taking an NSAID. What they won't tell you that she has a polyp and that she is on an NSAID; however, if a pt is in pain or has chronic pain, it is safe to assume the pt is on pain medication (ie an NSAID, Motrin or aspirin). Mech of asthma from pain medication: what do aspirin/NSAIDs block? COX, therefore arachidonic acid cannot forms PGs but the Lipoxygenase pathway is left open. Some people are very sensitive to this and LT C4, D4, and E4 are formed, which are potent bronchoconstrictors, leading to asthma. It is NOT a type I HPY rxn. It is a chemical mediated non type I HPY rxn. **So, chronic pain can lead to asthma b/c of aspirin sensitivity.**

Another assumption you have to make: any well built male on anabolic steroids (ie football player, wrestler) with intraperitoneal hemorrhage – produce benign liver cell adenomas which have the tendency of rupturing.

C. Laryngeal carcinoma (a squamous cell carcinoma)

Concept of synergism: MCC = Smoking; 2nd MCC = alcohol
Alcohol and smoking have a SYNERGISTIC effect which leads to laryngeal carcinoma. Example: lesion in this slide is a laryngeal specimen – which of the following have the greatest risk factor? Answer – **alcohol AND smoking** (this is true for any squamous cancer from the esophagus to the mouth to the larynx). Smoking = MCC cancer in mouth, upper esophagus and larynx. Alcohol can do the same thing, so if you are smoker and alcohol consumer, you can double your risk. MC symptom assoc = hoarseness of the throat.

Example: epiglottis; what can infect it? H. influenza – what is the symptom? Inspiratory strider. Example: 3 month old child died with inspiratory strider – dx? Croup – parainfluenza; this is a TRACHEAL inflammation. Whereas epiglottitis is elsewhere. Both produce upper airway obstruction.

III. Respiratory Distress Syndromes:

A. Hyaline membrane dz (Neonatal Resp distress syndrome)

If something has a lot of pink in it, what is it? Hyaline
Key to understanding this dz is massive atelectasis

1. What is atelectasis? Collapse of airways. Why did these airway collapse? No surfactant (aka lecithin/phosphotidyl choline/phosphotidyl glycerol – they are all surfactant). So, deficient of surfactant causes atelectasis b/c:
Collapsing pressure in the airways = surface tension/radius of airway. So, on expiration, normally the airway will be smaller b/c there is a pos intrathoracic pressure. If you decrease the radius, you will increase the collapsing pressure in the airways. Therefore, on expiration (in all of us), we have to decrease surface tension (which is what surfactant does) – by doing this, it keeps the airways open on expiration, preventing atelectasis.

2. Three causes of RDS:

a. Prematurity: surfactant begins syn early, but it peaks at 32-35 week, so if you are born prematurely, you will not have enough surfactant, and baby will develop increased risk of developing RDS. Sometimes mother has no choice and must deliver baby, or else it will die, and there is something you can do to the mom so the baby has more surfactant: give mother glucocorticoids b/c they stimulate surfactant synthesis. Example: what can you do to increase surfactant (but glucocorticoids wasn't one of the answer choices) – thyroxine (thyroid hormone) (as does prolactin); does that mean you give thyroxine b4 delivering the baby? No, will give mom and baby hyperthyroidism.

b. Diabetes: gestational diabetes = woman who wasn't pregnant, becomes pregnant, and then obtains glucose intolerance after delivery – so if a diabetic gets pregnant, this is not called gestational diabetes, but a diabetic that got pregnant. Its imp that a woman in pregnancy has good glucose control b/c if she is hyperglycemic, baby will be, too. B/c baby is hyperglycemic, it will stimulate insulin synthesis, and insulin has a negative effect on surfactant syn and will decrease its synthesis.

c. C section – b/c the baby is not delivered vaginally, there is no stress. B/c the baby has not been stressed, the ACTH and cortisol are not released, and surfactant is not made. Whereas a child that is delivered vaginally has a lot of stress and therefore a lot of ACTH and cortisol is being released, which stimulates surfactant release. So, C section predisposes to RDS.

So, these are the three main causes (prematurity, diabetes, and C section).

3. Complications and associated conditions:

a. Example: why are the babies of poor glycemic control big (macrosomial)? The baby's insulin is increased to keep the glucose down. Insulin will increase storage of triglyceride in adipose (it increases fat storage). Where is most of the adipose located? Centrally. So, one of the reasons why they have macrosomia is b/c insulin stimulates synthesis of TG and deposition of fat. Also, insulin increases uptake of aa's in muscle (like growth hormone). So, it will increase muscle mass. So, **the reason for macrosomia is increased adipose and muscle mass, both due to insulin.** This also explains why they get hypoglycemia when they are born. The mother's hyperglycemia is coming into the baby, causing the baby to release insulin; the moment insulin is made and the cord is cut, and no more increase in glucose, glucose goes down, and leads to hypoglycemia.

b. Superoxide free radical damage seen in retinopathy of prematurity and blindness and bronchopulmonary dysplasia.

c. Why do babies with RDS commonly have PDA? B/c they have hypoxemia. When a normal baby takes a breath, it starts the process of functional closure of the ductus. However, with hypoxemia after they are born, it remains open, and they have a machinery murmur.

d. Hyaline membranes are due to degeneration of type II pneumocytes and leakage of fibrinogen, and it congeals to form the membrane. So, they will give a classic history for RDS, and then will ask for the pathogenesis of hypoxemia in the baby. This is a massive ventilation defect b/c everything is collapsing. This is a SHUNT problem, which leads to a massive interpulmonary shunt. Rx=PEEP therapy – positive end exp pressure b/c these airways are collapsed and you need to get O2 into them and surfactant. So, give O2 and at the end of expiration, pump in pressure, which keeps airways open on expiration, so you can keep O2 in them.

Example: pic with type II pneumocyte (with lamellar bodies – look like onion, and hyperplastic arteriolosclerosis b/c they are concentrically shaped). These lamellar bodies contain surfactant. This would ID it as a type II pneumocyte. They commonly give EMs of the lung with an alveolar macrophage. Macrophage has 'junk' in the cytoplasm. The type II pneumocyte is the repair cell of the lung and synthesizes surfactant.

B. Adult Respiratory Distress Syndrome (ARDS)

In terms of ARDS, essentially it is the same as RDS in pathophys, but is NEUTROPHIL related injury. In RDS you're not making surfactant b/c you are too premature or have too much insulin and just have collapsed alveoli. BUT in ARDS its b/c you have too much inflammation; there is no inflammation in RDS.

MCC ARDS = septic shock (MCC septic shock = E coli from sepsis from an indwelling catheter; MCC DIC = septic shock). Example: In the ICU – if a pt come in with dyspnea and its within 24 hrs of having septic shock, pt has ARDS. If pt is in septic shock and within 48 hrs of admission and is bleeding from every orifice, he has DIC. **So, first day = septic shock, second day = ARDS, third day = DIC.**

Pathogenesis: Neutrophils get into the lung in septic shock and start destroying all the cells of the lung (type I and II pneumocytes). So surfactant production decreases and result is massive atelectasis (collapse). However, this is neutrophil related (the neutrophils are destroying the type II pneumocyte. The reason why they get hyaline membranes in the ARDS is b/c the neutrophils have to get in the lungs by going through the pulmonary capillaries, so they put holes in them as they get out of the bloodstream and into the lungs (this is why it is called leaky capillary syndrome). All the protein and fibrinogen get in and produce hyaline membranes. Therefore, you can actually see hyaline membranes in ARDS. So, there is massive collapse and the pathophys is intrapulmonary shunting. This is the same in RDS, but ARDS is neutrophil related, which is a bad prognosis.

IV. Pneumothorax

Spontaneous pneumothorax and tension pneumothorax

A. Spontaneous pneumothorax

MCC spontaneous = ruptured subpleural bleb – have pleura and right underneath is a bleb (air pocket). The bleb (air pocket) ruptures causing a hole in the pleura, so that part of the lung collapses. B/c what's keeping it expanded is neg intrathoracic pressure, which keeps the lungs expanded. So, if you put a hole in the pleura, then the atmospheric pressure is not negative, but is the same as the air you are breathing. So, there is nothing to hold it open and therefore it collapses. When parts of the lung collapse, there are things that will take up the slack. One of those is the diaphragm. If you collapse part of the lung, the diaphragm will go up on that side to take up the open space on that has been left. Not only that, if there is a collapse on one side, the trachea will go to the side that there is space. So, will have **tracheal deviation to the side of the collapse, and the diaphragm is up, leading to spontaneous pneumothorax**. Usually seen in tall male – they have blebs that rupture and lead to spontaneous pneumothorax. Can also get in scuba divers b/c they come up too quickly, which leads to rupture of the blebs.

B. Tension pneumothorax

Diff from spontaneous pneumothorax. MC due to knife injuries into the lung. There's tear of pleura (flap), sp when you breathe in the flap goes up and on expiration it closes. So, the air stays in the pleural cavity. So, every time you breathe, the flap goes up, air stays in, and on expiration it closes. So, for every breath you take, it keeps increasing and the pressure in the lung. The lung hasn't collapsed yet. **The increase in pressure starts pushing the lung and the mediastinum to the opposite side**. When it pushes it, it compresses the lung and it leads to compression atelectasis (it is not deflated b/c of a hole – there isn't a hole – it's a tear that when the air went in it went up and it shut on expiration, and that pos pleural pressure is pushing everything over to the opposite side). This compression will push on the SVC, right vent, and left atrium on the opposite side. This will compromise blood return and breathing, leading to a medical emergency. So, it's like filling tire up with air, but cannot get out. Air is filling pleural cavity and cannot get out. It keeps building up and starts pushing everything to the opp side. With a pos intrathoracic pressure, the diaphragm will go down (goes up in spontaneous pneumothorax).

V. Pulmonary Infection

A. Pneumonia

1. 2 kinds – Typical and Atypical

Typical – wake feeling normal, then suddenly develop a fever, productive cough
Atypical – slow, insidious onset (feel bad over few days)

2. Community vs. Nosocomial (hospital acquired)

If you get pneumonia in the **community** and it's typical, it is Strep pneumoniae. If you get pneumonia in the community and it is atypical, it's mycoplasma pneumoniae.
Organisms in the hospital (**nosocomial**) = E coli, Pseudomonas, Staph aureus (will not get strep pneumoniae in the hospital).

3. Productive cough in Typical pneumonia

Reason for productive cough in typical pneumonia: have exudate (pus) and signs of consolidation in the lung – Slide: yellow areas with microabcesses which are consolidation in the lung. Ie lobar pneumonia = see consolidation in lung, within alveoli, causing consolidation. Therefore, with typical, see consolidation and pus in the lung. Physical dx'tic tools of lung consolidation: decreased percussion, increased TVF (when the person talks, feel vibrations in chest – if have consolidation in ie the upper left lobe, will have increased TVF b/c it is a consolidation, compared to the other side – so, **increased TVF indicates consolidation**), having an "E to A" (egophony) sign (pt says E and you hear A), whispered pectoriloquy (pt whispers "1, 2, 3" and I will hear it very loud with the stethoscope). Therefore, **decreased percussion, increased TVF, egophony, and pectoriloquy = consolidation.**

What if there is a pleural effusion overlying the lung? Only thing you would have is decreased percussion (this separates pleural effusion from pneumonia).

4. Atypical pneumonias

They do not have a high temp and do not have productive cough b/c they are interstitial pneumonias. They have inflammation of the interstitium – there is no exudate in the alveoli – which is why you are not coughing up a lot, and therefore do not have signs of consolidation. So, will not have increase TVF, "E to A", with an atypical. Atypical pneumonia has an insidious onset, relatively nonproductive cough, no signs of consolidation.

MCC typical pneumonia = strep pneumoniae (know the pic) – gram "+" diplococcus (aka diplococcus) – Rx = PCN G

MCC atypical pneumonia = mycoplasma pneumoniae; 2nd MCC = Chlamydia pneumoniae; which are all interstitial pneumonias.

Bronchopneumonia: MC due to strep pneumonia, and community acquired. Lobar pneumonia. Slide: lobar consolidation on chest x-ray – strep. Pneumonia.

a) Viral pneumonias

1) Rhinovirus = MCC common cold; they are acid labile – meaning that it won't lead to gastroenteritis in the stomach b/c is destroyed by the acid in the stomach. Never will have a vaccine b/c 100 serotype.

2) RSV – MCC bronchiolitis – whenever you inflame small airways, its leads to wheezing. This is a **small airway dz and bronchiolitis is MC due to RSV and pneumonia**. So, **pneumonia and bronchiolitis is MC due to RSV in children**.

3) Influenza – drift and shift – have hemagglutinins, which help attach the virus to the mucosa. Have neuraminidase bore a hole through the mucosa. **Antigenic drift = minor change/mut'n** in either hemagglutinins or neuraminidase; do not need a new vaccine; **antigenic shift= major change/mut'n** in either hemagglutinins or neuraminidase need a vaccine. **The vaccine is against A Ag.**

b) Bacterial pneumonias

1) Chlamydia psittacosis – from birds (ie parrots, turkeys).
2) Chlamydia trachomatis – a little kid was born and a week later he was wheezing (big time), pneumonia, increased AP diameter, tympanic percussion sounds, no fever, eyes are crusty (both sides), weird cough – **staccato cough (short coughs). He got it from his mom's infected cervix. (MCC conjunctivitis in 2nd week = Chlamydia trachomatis). (MC overall of conjunctivitis is inflammation of erythromycin drops).**

c) Hospital-acquired gram-negative pneumonias

1) Pseudomonas – water loving bacteria, therefore see in pt in ICU when on a RESPIRATOR. pt water unit with green productive cough with.

2) Klebsiella – famous in the alcoholic; however, alcoholic can also get strep pneumonia. So, how will you know strep vs. Klebsiella? Alcoholic with high spiking fevers, productive cough of MUCOID appearing sputum – the capsule of Klebsiella is very thick. Lives in the upper lobes and can cavitate, therefore can confuse with TB.

3) Legionella – atypical cough, nonproductive cough, very sick can kill you, from water coolers (water loving bacteria), seen in mists in groceries or at restaurants. Example: classic atypical pneumonia, then pt had hyponatremia – this is Legionella. Legionella just doesn't affect the lungs, also affects the other organs such as liver dz, **interstial nephritis** and knocks off the juxtaglomerlur cells, and kills the renin levels, low aldosterone and therefore lose salt in the urine, **leads to hyponatremia** (low renin levels with low aldosterone). Rx = erythromycin

B. Fungal Infections
The two systemic fungus are Candida and Histo

1. Candida – seen in indwelling catheters (usually those in the subclavian). And get Candida sepsis

2. Histoplasmosis = **Midwest** (Ohio/Tennessee valley) carried by dung of starlings and bats – often seen in cave explorers, or spelunkers. They develop non-productive cough. Histo is the only systemic fungus that has yeasts phagocytosed by alveolar macrophages.

3. Cryptococcus = **Pigeons**– looks like mickey mouse – yeast forms are narrow based buds. Example: NY exec with pigeons roosting in air conditioner and developed non productive cough. Example: painter developed resp infection worked on Brooklyn bridge with pigeons, how do you treat? **Amphotericin B**.

4. Blastomycosis = SE USA = skin and lung infections; broad based bud

5. Coccidioidomycosis: SW USA (new Mexico, Arizona, southern Cal. = coccidiomycose – has spherule endospores (know the pic). Example: in LA earthquake, a # of people had nonproductive cough–the arthrospore (the infectious form) is in dust. With the earthquake, dust comes up, breathe it in. Example: man that is an Indian artifact explorer in the sonaran desert, which is in Arizona, and is a CAVE explorer that developed nonproductive cough – this is **COCCIOMYCOSIS** (not Histo b/c not the Midwest).

6. Aspergillus – 3 different manifestations/dz's:

1) loves to inhabit abandoned TB fungus cavities – **fungus ball** (aspergilloma, a very common cause of massive hemoptysis). Example: left upper lobe cavitary lesion and asp love to live in there = fungus ball
2) vessel invader; therefore will invade the vessels in lung, leading to **thrombosis and infarction**
3) allergies the mold, leading to extrinsic **asthma** and type I HPY

So, three manifestations: fungus ball, invasive vascular dz producing hemorrhagic infarctions of the lung, and asthma. Example: pic of corona – component of Aspergillus (looks like a crown) – septate is very characteristic (mucormycosis is nonseptate and has wide angles, while Aspergillus has narrow angles in its budding and corona's).

7. PCP (Pneumocystitis carinii pneumonia

Fungus (used to be a protozoa) – b/c more things in the cell wall that look like a fungus. It's associated with HIV, MC AIDs defining lesion (as soon as the helper T cell ct is 200, it usually shows up). Used to be MCC death in AIDs pt, but now has gone down, b/c as soon as your CD4 ct is 200, dr. will put pt on prophylactic therapy with TMP-SMX.

When taking **TMP-SMX and protecting against PCP,** would other organism is the pt protected from? **Toxoplasmosis**. (so, you get 2 for 1). MCC space occupying lesion within the brain in a pt with AIDs= Toxoplasmosis

Seen with silver stain: cysts of PCP can be seen – look like ping pong balls, seen in alveoli, leading to alveolar infiltrate, leading to dyspnea, tachypnea, foamy bubbly infiltrate, on chest x-ray, looks all white out b/c of the involvement of the lung – however, not only seen in lungs, can be seen in any part of the body– also seen in lymph nodes of HIV "+".

Other organisms that are only seen with silver stain: bartenella henselae (bacillary angiomatosis), Legionella (not visualized with gram stain, therefore use butuly??? silver stain)

8. TB

Organism in upper lobe of lungs – (play odds) – TB – see cavitary lesion, which is reactivation TB (not primary). Primary TB is the lower part of the upper lobe or the upper part of the lower lobe and close to the pleura (kind of in the middle of the lobe). Primary TB has a Ghon focus and a Ghon complex. Most people recover; when pt is immunocompromised, it leads to reactivation and goes into the apex and produces a cavitary lesion. **There is no Ghon focus or complex in reactivation TB, only primary TB.**

Other things that cavitate in upper lobes:

Which systemic fungus is the "TB" of the lungs? Histoplasmosis
Which cancer can cavitate in the lung? Squamous Cell carcinoma of the lung
Which bacteria (that has a big mucous wall around it) can also produce cavitations in the upper lobe? Klebsiella pneumoniae.
What is acid fast stain staining? Mycolic acids.
So, just b/c something is cavitating the upper lobe, it is not necessarily TB.

C. Foreign Bodies

If you are **standing or sitting up**, foreign bodies will go to **posterobasal segment of the right lower lobe**. This is the most posterior segment of the right lower lobe.

If you are lying down (MC way to aspirate things), foreign body will go to superior segment of the right lower lobe.
If you are lying on the right side, can go to 2 places – 1) middle lobe 2) posterior segment of right upper lobe (this is the ONLY one that is in the upper lobe.
If you are lying down on your left, and aspirate, it will go to the lingula.

Summary:

Sitting/standing = posterobasal segment of right lower lobe
Back: superior segment of right lower lobe
Right: middle or sup segment of right lower lobe
Left: lingula

D. Abscess

MCC abscess = aspiration of oropharyngeal material

Seen commonly in street people that do not have good dentition, may be drunk and fall and oropharyngeal material will be aspirated. Aspirate consists of aerobes and anaerobes, leading to putrid/stanch smell. The aspirate is a mixture of all these organisms: Mixed aerobes and anaerobes, fusobacterium, bacteroides. Can get absecces in the lung from pneumonia: staph aureus, Klebsiella (however, MCC is aspiration), see fluid cavities in lung on x-ray.

VI. Pulmonary Vascular Disease:

A. Pulmonary Embolus

2 types of emboli – tiny ones that produce wedge shaped hemorrhagic emboli or can chip off large ones. Where do most Pul emboli embolize from? MC SITE for thrombosis is the deep veins of the lower leg. This is NOT the most common site for embolization; it is the femoral vein (this is the MC site for embolization). Makes sense b/c venous clots propagate toward the heart (deep veins to the femoral vein, and the femoral vein is a larger vessel, therefore it is more likely to chip off). So, the femoral vein is the MC site for embolization to the lung. The deep veins are the MC site where deep venous thrombosis begins. (when it get to the femoral vein, it is dangerous for embolization). So, small ones produces hemorrhagic infarct that is only if you have an underlying lung dz. If I have a small embolus, prob won't infarct b/c don't have abnormal lungs. However, if you have preexisting lung dz you will infarct. 85% of the time embolus will not produce infarct. However, in the 15%, most of the pts with infarcts have preexisting lung dz (ie they are smokers). The other type of embolus is a saddle embolus (it is huge) and blocks off the orifices of the pulmonary vessels and pulmonary arteries. If you knock off at least 3 out of the 5 orifices, you are dead in a millisecond, so there is no infarction b/c you don't have time to infarct. It produces acute right heart strain and immediate death. **Screening test of choice: Ventilation perfusion scan – will have ventilation, no perfusion; confirmatory test is pulmonary angiogram.**

VII. Restrictive Pulmonary Disease

Restrictive – something is restricting it from filling. Example: restricted filling of the heart = restrictive cardiomyopathy. Or restriction in filling up of the lungs with air. Have 2 terms: **compliance (filling term, inspiration term) and elasticity (recoil, expiration term);**

For restrictive lung dz, picture a hot rubber bottle for restrictive lung dz. The hot rubber bottle is difficult to 'blow up', therefore **compliance is decreased** and it is hard to fill the lung up with air. So, what's preventing it from blowing up? Fibrosis (interstial fibrosis, MC'ly). If you get the hot water rubber bottle filled with air and let the air out, what happens to the elasticity? Increases. So, compliance is decreased and cannot fill it up, but once you do fill the lung up, it comes out quickly (**elasticity increases**).

Example: pt with sarcoid – diff to fill lungs, but get it out fast (due to fibrosis). So, all TLC, RV, TV (all lung capacities have all equally decreased). FEV1/FVC on spirometer – take a deep breath (ie pt with sarcoid) – FEV1 (amount you get out in one sec – normally it is 4 liters) is decreased, FVC (total that got out after deep inspiration) is decreased (b/c increased elasticity) – this is the same as FEV1, so the ratio is often 1. Normally, the FVC is 5 liters, and the FEV1 is normally 4 liters – so, the normal FEV1/FVC ratio is 4/5 =80%. B/c the elasticity is increased, the FVC is the same as FEV1, and therefore the **ratio is increased** to 1 instead of 0.8.

Examples of restrictive lung dz's:

1. **Pneumoconiosis** – airborne/dustborne dz's – famous in big cities (LA, NY). Cole worker pneumoconiosis – esp. in west Virginia/Penn, have an anthrocotic pigment that causes a fibrous rxn in the lung, leading to restrictive lung dz. Have an increased incidence of TB, but not cancer.

2. **Silicosis** – Sandblasters get graffiti off things, or work in foundries and deal with rocks (ie quartz), and break them down, and breathe in dust, leading to silicoses). Have nodules in the lung that are hard has rock (literally) b/c there is quartz in them and it looks like metastatic dz in the lung (silica dioxide – which is sand in the lung) – again, increased of TB, not cancer. If pt happens to have rheumatoid arthritis, and also has one of these pneumoconiosis (ie Cole workers), have a potential for a syndrome, which is called caplan syndrome. **Caplan syndrome** consists of rheumatoid nodules in the lung (same as extensor surfaces in the arm). Rheumatoid arthritis commonly involves the lung with fibrosis. And rheumatoid nodules can form in the lung. **The combo of rheumatoid arthritis (rheumatoid nodules) in the lung, plus pneumoconiosis (silicosis/asbestosis/Cole workers) = caplan syndrome.**

3. **Asbestos** – asbestos fibers look like dumbbells (therefore ez to recognize). These are called ferruginous bodies. Asbestos fibers coated with iron, therefore can call them either asbestos bodies or ferruginous bodies. MC pulmonary lesion assoc with asbestos is not cancer – it is a fibrous plaque with a pleura, which is b9 (not a precursor for mesothelioma). **MC cancer assoc with asbestos = primary lung cancer, 2nd MCC = mesothelioma, which is a malignancy of the serosal lining of the lungs.** If you are a smoker and have asbestos exposure, you have an increased chance of getting primary lung cancer. This is a good example of synergism (other causes of lung cancer (SCC) include smoking, alcohol). Asbestos + smoker = will get cancer. There is no increased incidence of mesothelioma with smoking (not synergistic). Example: Roofer for 25 years, nonsmoker (do tell you, but you had to know that 25 years ago, all the roofing material had asbestos in it; in other parts of NY, many buildings were torn down, and there was asbestos in the roofing of those buildings, which was inhaled by many people, and 10-30 years later they developed primary lung cancer or another complication of asbestosis). What would he most likely get? Primary lung cancer (primary pleural plaque was not there). If he was a smoker? Primary lung cancer. Mesothelioma takes 25-30 years to develop. Lung cancers take about 10 years to develop. Lung cancers are more common, and you die earlier. What is the main cause of asbestos exposure? Roofers or people working in a naval shipyard (b/c all the pipes in the ship are insulated with asbestos), also in brake lining of cars and headgear.

4. **Sarcoidosis =2nd MCC restrictive lung dz.**
   Example: classic x-ray – lymph nodes (hilar lymph nodes are big), haziness seen, too, which is interstial fibrosis. **Sarcoid is a granulomatous dz** that has NO relationship to infection (**cause = unknown**). **Causes a noncaseating granuloma** (not caseating b/c no relationship to TB and systemic fungal infections). The lungs are ALWAYS involved (lungs are the primary target organ), and more common in blacks. Example: black person, 35 y/o, with dyspnea, see hilar nodes on x-ray, uviitis (blurry vision – this is inflammation of the uveal tract – this dz always affects something in the face, and the face the 2nd MC site a lesion will occur with this dz, can also involve salivary glands or lacrimal glands – something in the head/neck/face area (behind the lungs). This dz is a dx of exclusion, therefore must rule out

anything that causes granuloma (TB, Histo), along with the correct physical presentation = Sarcoidosis. **Rx = steroids**. ACE enzymes are very high in these pts b/c granulomas in kidney; **hypercalcemia** – macrophages (epitheloid cells) make 1-alpha-hydroxylase. If they are making 1-alpha-hydroxylase, what is the mech of hypercalcemia? Hypervitaminosis D. you are second hydroxylation more vit D and therefore have excess vit D, and vit D promotes reabsorption of calcium and phosphorus, leading to hypercalcemia. **This is the MC noninfectious cause of granulomatous hepatitis (TB is the MCC of infectious hepatitis, 2nd MC = pneumoconiosis).**

5. **Hypersensitivity pneumonitis (farmer's lung, silofillers dz, bysinosis**)

These are restrictive lung dz's. Don't confuse farmer's lung and silofillers dz – they are BOTH seen in farmers. So, remember one, the other is the other!

Silofillers dz – put things in silos, which is a closed space, and fermentation of gas occurs, the gas is nitrogen dioxide – Example: farmer went into a room in his barn and suddenly developed wheezing and dyspnea, why? B/c he took in nitrogen dioxide, which is a fermenting problem. (silo can explode b/c gas from fermentation).

Farmer's lung – thermophilic actinomyces (a mold).
Example: on tractor, dust being blown up in the air and thermophilic actinomyces (which is a mold) is inhaled; leading to hypersensitivity and HPY pneumonitis and they end up with a restrictive lung dz.

Bysinosis – worker in textile industry, and they get dyspnea. These are the HPY and restrictive lung dz's.

Goodpasture syndrome
Begins in the lungs with a restrictive lung dz (with coughing up blood – hemoptysis), and ends up very shortly with renal dz (therefore, it starts in the lung and ends in the kidneys). This is a restrictive lung dz.

VIII. Obstructive lung Dz

A. Deals with compliance/elasticity concept

In obstructive lung dz, no prob getting air in, but have a problem in getting the air out. Why don't you have a problem getting it in? B/c the elastic tissue support is destroyed, so it is very ez to fill up the lungs. However, b/c the elastic tissue support is destroyed, it is very difficult hard to get it out b/c it collapses on expiration, so you can get air in, but cannot get air out. In a pt with obstructive air dz, they breathe in with no problem, but have trouble getting it out. So, something is left over in the lung – cannot get all the air out, therefore the residual volume is increased (whenever something is left over, it is called the 'residual'). So, if you cannot get air out, then the residual volume increases, which means that the TLC will increase, which means that the diaphragm will go down b/c as the lungs are over inflated, and the AP diameter will go out. So, with obstructive lung dz, you have increased AP diameter and diaphragms go down (depressed). There is only a certain amount of expansion your chest can go. Eventually, the chest starts to compress other volumes (as you trap air and residual volumes go up). So, tidal volume starts decreasing, vital capacity goes down b/c the residual vol is increasing and you are compressing other volumes. **So, TLC and RV increases, everything else decreases.** On spirometer, FEV1 is very low (usually 1 – normally it is 4). In other words, you have a better FEV1 with restrictive lung dz b/c you can get air in. The FVC (total amt they can get out) is 3 liters (vs. 5 liters). **When you do a ratio of FEV1/FVC, the ratio has decreased, hence distinguishing restrictive from obstructive dz's.**

Classic COPD x-ray: hard to see the heart, with depressed diaphragms (at level of umbilicus), increased AP diameter – dx? Classic obstructive dz x-ray – prob getting air out, therefore the diaphragm is down and AP diameter is increased.
Example: 3 month old can have this same finding due to RSV
Example: Newborn with Chlamydia trachomatis pneumonia b/c he is trapping air.

B. There are 4 type of obstructive lung dz's: chronic bronchitis, bronchiectasis, emphysema, asthma. The ones associated with smoking are bronchitis and emphysema.

1. **Chronic Bronchitis**

Purely a clinical dx = Pt has productive cough for 3 months out of the year for 2 consecutive years. Where is the dz? Terminal bronchioles (you have main stem bronchus, segmental bronchi, terminal bronchioles, resp bronchioles, alveolar ducts, alveoli). As soon as you hit the terminal bronchioles, these are small airway; it is all turbulent air up to terminal bronchioles. After that, it is parallel branching of the airways. The turbulent air hits the terminal bronchioles and then hits a massive cross sectional airway where you can go diff path's b/c parallel branching of the small airways. So, the airflow changes from turbulent to laminar airflow. By the time you hit the resp unit, it is not moving the air. **Most small airway dz's are inflammation of the terminal bronchioles, leads to wheeze.** Terminal bronchioles are the site of chronic bronchitis. This is the same area as asthma and bronchiolitis. More prox to the terminal bronchioles, in bronchitis, you will get a mucus gland hyperplasia, and a lot of crap is coming up (that's the productive part). The actual area of obstruction is the terminal bronchiole. Have goblet cell metaplasia and mucous plugs. Think about having one terminal bronchiole and one mucous plug – this is affecting a major cross sectional area of lung b/c all the parallel branches that derive from here will not have CO2 in them, and they are trying to get air past the mucous plug, but cannot. So, **there is a HUGE vent-perfusion mismatch**. This is why they are **called blue boaters – they are cyanotic**. They have mucous plugs in the terminal bronchioles and cannot rid CO2.

2. **Emphysema**

Not in the terminal bronchioles. It is in the resp unit (**resp unit is where gas exchange occurs** – cannot exchange gas in the terminal bronchioles – aka nonresp bronchiole); it is the primary place for expiratory wheeze and small airway dz, however. **Gas exchange occurs in the resp bronchiole, resp alveolar duct and alveoli**. Only need to

know **2 emphysemas: centrolobular and panacinar**. Emphysema affects gas exchange and where it affects the airway is more distal, compared to chronic bronchitis (proximal). So, when you have emphysema with all the inflammation associated with it, not only destroy the resp unit, but also the vasculature associated with it. Therefore, **there is an even loss of ventilation and perfusion. So, will NOT have retention of CO2 in these pts.** When you have a problem with a mucous plug in the terminal bronchiole, which is way more prox and a great cross sectional area of the lung is affected, there is gonna be a problem there; however when you are out this far (in emphysema) and also destroying the vessels, you **will not have an increase in CO2**. This is why they are called **pink puffers**, and this is why many of them have resp alkalosis.

a) Centrolobular – most associated with smoking and involved with the upper lobes. So, it is an upper lobe emphysema, and the primary portion of the resp unit that is destroyed is the resp bronchiole (this is the very first thing that smoke hits). Neutrophils will damage it b/c all people that smoke have more neutrophils in their lungs, and smoke is chemotactic for neutrophils. ALL smokers have increased neutrophils in their lungs. What does alpha-1 antitrypsin do? It's an antielastase (its only purpose is to destroy elastases produced by neutrophils – that is its function. If you are a smoker, that is denatured. So, you also have an acquired alpha-1 antitrypsin def). Don't have adequate alpha-1 antitrypsin, and have too many neutrophils in the lungs. This is a terrible combo. This why neutrophils have no problem in destroying the elastic tissue support of the respiratory bronchioles. So, you breath air in, which is no problem; but you try to get it out, and there is no elastic tissue support and leads to lung expansion – this is why blebs are found – there are big cystic spaces in the lung – it has trapped air in there b/c there is no elastic tissue, so when it tries to get by, it just expands. This is **centrolobular emphysema of the UPPER lobes**.

b) Panacinar Emphysema (remember 'pan' means everything – ie in pancytopenia, ALL the cells decreased). So, panacinar means that the ENTIRE resp unit is decreased b/c it is associated with **NO alpha 1 antitrypsin**. This is a genetic dz – auto rec **– the LIVER does not make it**. So, at a young age, you develop destruction of entire resp unit of the LOWER lobes, **so this is a LOWER lobe emphysema**. So, you can see that the resp bronchioles are knocked out, the alveolar ducts are knocked out, alveoli knocked out. So, you breathe in, and this entire resp unit catches it – this is in the lower lobes.

Smokers, which have an acquired alpha-1 antitrypsin def, can get an element of panacinar emphysema in the lower lobes, too. So, smokers can get 2 emphysema's: centrolobular emphysema in the upper lobes (which knocks off the resp bronchiole) and in the lower lobes, get a panacinar type of pattern. Therefore, can get upper AND lower lobe emphysema, and 2 diff types of emphysema.

3. Bronchiectasis

Have bronchiectasis – see bronchi going out to the pleura (abnormal). When you see bronchi going out further than the hilum, this is bronchiectasis.

Mech: infection, destruction of the elastic tissue support, dilatation of the airways. Segmental bronchi; fill with pus. Example: pt has a productive cough of "cupfuls" (not just a tablespoon) of pus, b/c they are trapped.

a) Causes:

1) MCC bronchiectasis in USA = **cystic fibrosis.** If parent with child has cystic fibrosis, will see huge pus coming out of bronchi, a couple times per day.

2) MCC bronchiectasis in 3rd world countries = **TB**.

3) **Kartagener's syndrome** (aka immotile cilia syndrome). 9+2 configuration arrangement with cilia and microtubules. The problem with immotile cilia syndrome is an absent dynein arm. The 9 microtubules on the outside have arms that keep them together – these dynein arms are missing. So, when these arms are missing, the cilia cannot move. So, the places with cilia not moving are affected: these places are sinuses (why **sinusitis** is a problem), **bronchiectasis** (b/c there is cilia – psuedostratified columnar epithelium is affected), males and females are **infertile** (b/c the tail on the sperm cannot move – the tail is a modified cilia – they head is moving, but the tail is weak. Women are infertile; too, b/c the fallopian tube needs cilia to carry the egg down. **Organs are located on the opposite side (dextrocardia, withOUT transposition of great vessels).**

4. Asthma

Can be extrinsic (type 1 HPY) and intrinsic: Involves chemicals – people in the workplace can get triad asthma, which involves people taking NSAIDs Many people, ie athletes will get exertional asthma and wheeze – cromolyn Na is the DOC for these patients. Cold temps can cause asthma. Type I HPY has nothing to do with these causes of asthma. The wheezing is due to inflammation of the terminal bronchioles – it is not due to smoking, but b/c factors like LT C4, D4, E4, PG's causing inflammation and narrowing of the airways.

IX. Lung Cancer

A. Peripherally located vs. centrally located

1. Centrally located (mainstem bronchus):

Have the highest association with smoking. Include squamous cell carcinoma and small cell carcinoma. These are generally centrally located, hence mainstem bronchus types of locations. Squamous cell are more common than small cell carcinomas.

2. Peripherally located:

Adenocarcinomas (the more common primary lung cancer, more common than squamous) are more peripheral than central. Shifted to the periphery b/c of the filters of the cigarettes. The filters prevented the large carcinogens from

passing in, but the small carcinogens still passed through, and they are not trapped in the main stem, but trapped in the periphery.

There are at least 3 or 4 types of adenocarcinoma. One obviously does have a smoking relationship, while the others do not. The ones that do not have a smoking relationship include bronchiolar alveolar carcinoma, and large cell adenocarcinoma of the lung (scar cancers).

B. Cytology: know what squamous cancer looks like with a pap smear. A lot of people think that the Papanicolaou stain is only done for cervical carcinoma. This is not the case. **This is a famous stain** (pap smear) **used for all cytological specimens on for all organs. The stain stain's keratin bright red.** Slide: (pic) pt that is a smoker with a centrally located mass. Showing sputum sample with a Papanicolaou (pap smear) stain – has red keratin, which is squamous cell carcinoma. If this were a cervical pap smear from a woman that is 40 years of age, this is squamous cell carcinoma. The keratin is staining bright red! (bright red cytoplasm = keratin = squamous cell carcinoma). Papanicolaou stains keratin bright red.

Example: small cells that look like lymphocytes – this is **small cell carcinoma**. This is more difficult to dx, b/c sometimes diff to tell the difference from lymphocytes. Slide shows malignant cells. Small cell carcinoma is the most malignant cancer of the lung. Rx? Radiation and chemo (not surgery). **These are auput tumors with neurosecretory granules and S-100 Ag positive.** They can make ADH and ACTH.

A slightly less malignant tumor with auput origin is the **bronchiocarcinoid**. It is a low grade malignancy of the same types of cells that produce small cell carcinoma. So, they can invade, met, and produce carcinoid syndrome if they make increased amount of serotonin. They don't have to mets to produce carcinoid syndrome – it just goes straight into the bloodstream. It is very uncommon.

C. Cancer:

MC cancer of lung = mets – ie see many metastatic nodules all over lung; if you play odds, what is the primary cancer? breast (which the MC met to the lung, or in other words, it is the MC cancer of the lung).

Summary of lung cancer in the lung:
MC cancer = mets
MC primary cancer = primary adenocarcinoma of the lung, followed by squamous and small cell carcinoma.
Worst cancer (worst prognosis): small cell carcinoma.

Horner's syndrome – pancoast tumor/superior sulcus tumor – tumors that are in the upper lobe posteriorly (in post mediastinum); most of the time is caused by squamous carcinoma in that area. What's happening here? Tumor is locally invading into the local part of the lower trunk of the brachial plexus, so can get lower trunk brachial plexus like findings, and can also affect the superior cervical ganglion. This is in the posterior mediastinum, therefore will end up with Horner's syndrome; as a result, will end up **knocking OFF sympathetic activity** – **ptosis** (lid is lower), **anhydrous** (lack of sweating), **miosis** (in sympathetic, which is fight or flight, normally have mydriasis, which dilates the pupil – with fight or flight, want as much light as possible, therefore dilating pupil, but this is cut off, leading to miosis). Do not confuse with SVC syndrome; this is just blocking off SVC.

Myasthenia has to do with thymoma, which is located in the anterior mediastinum.

Exudate vs. transudate (< 3 grams, without many cells in it)
MCC pleural effusion due to transudate = HF

Exudate = protein > 3 grams, and has cells in it (ie pneumonia's, pulmonary infarction)

CHAPTER 9: GI

I. Diseases of the Mouth

A. Herpes simplex; Herpes labialis-(fever blisters and cold sores); primary herpes is a systemic infection. Have fever, viremia, generalized lymphadenopathy, and goes away; it stays in the sensory ganglia (dormant in the sensory ganglia) – every now and then it can come out with stress, menses, whatever, and will form vesicles. Recurrent herpes is no longer systemic – there is no more fever, and no more lymphadenopathy. Other virus that remain latent – herpes zoster – remains latent in the sensory ganglia; can involve the skin, lips, dermatomes. So, **primary herpes is systemic, recurrent herpes is not. (No fever = no lymphadenopathy**).If we enroot and stain, will see inclusion in herpes – it is a multinucleated cell with internuclear inclusions. Biopsy of a multinucleated cell from a pt with HIV, with multiple internuclear inclusions – herpes esophagitis.

B. Hairy Leukoplakia

This is not an AIDs defining lesion, but IS a preAIDs type of infection – as is thrush, shingles. Located on the lateral boarder of the tongue. Has nothing to do with dysplasia (leukoplakia). It is a result of an **infection from EBV**. So, do not get the idea that it is a preneoplastic lesion. Start seeing this before the helper T cell count get to 200. Rx - Acyclovir

C. Thrush (oral candidiasis)

In an adult, therefore can assume that it is in an immunocompromised patient, where there is a defect in cellular immunity. In kids (newborns), they can get it from the mom on the way out. However, it is not a sign of immunocompromise.
So, adult = IC'd

D. Exudative tonsillitis

30% chance that it is group A beta hemolytic strep. **70% chance that it is a virus; adenovirus, EBV.** So, when you see exudative tonsillitis, cannot assume it is bacteria and immediately give PCN. How do you prove it is group A strep? Latex agglutination test. So, most pus tonsils are not bacteria. Example: It is group A strep, and 3 weeks later, has bilateral rales, pansystolic murmur apex radiating into the axilla, polyarthritis – dx? Rheumatic fever. When you do a blood culture – what would you find? Nothing – it's not an infective endocarditis.

E. Leukoplakia

White lesion, plaque like, try to scrap off, but won't come off = clinical dx of leukoplakia – what is the first step in management? Bx

True in the vulva/penis area – white or reddish-white plaque like lesion that does not scrape off – first step in management? Bx. Why? Rule out dysplasia and/or invasive cancer.

F. Cancer of the mouth

MCC squamous dysplasia and cancer = smoking
2nd MCC = alcohol
If you do both, you increase the risk of both.
Invasive squamous cancer = color change

Lower lip cancer? Squamous cell carcinoma
Upper lip? Basal cell carcinoma

Veracious carcinoma – from chewing tobacco (squamous carcinoma); also has a HPV virus associated with it.

G. Hyperpigmentation – dx? **Addison's**

Addison's: diffuse pigmentation, low cortisol levels, increased ACTH (ACTH has melanocytes stimulating properties); very first place you see hyperpigmentation is in the Buccal mucosa.

H. Peutz-Jeghers

Blotchy (not diffuse) areas of hyperpigmentation. **Polyps in small intestine.** This is one of the exceptions to rule for polyps in the small intestine. Most polyps in the GI located in the sigmoid colon; however, polyps of Peutz Jeghers are located in the small intestine, and they are hamartomas, therefore they are not neoplastic, and their ability to change to cancer is ZERO.

II. Diseases of the Salivary Glands

Pleomorphic adenoma aka Mumps / mixed tumor (– NOT a teratoma, but a mixed tumor – it has two diff types of tissues, same cell layer). It is the MC salivary gland tumor overall, and is in the MC location – the parotid.
Mumps – paramxyovirus, increase in amylase; is the incidence of orchitis high? No; does it cause infertility? No, why? B/c its unilateral – if it were bilateral then it would a much greater chance. Usually in older teenage males or male adults is where orchitis will occur. Can also occur in females - oophoeritis – MC unilateral, therefore infertility is rare.

III. Diseases of the esophagus

A. Dysphagia and odynophgia = difficulty swallowing

Most of the time, there will be 5-6 clues per question. A pt has problem swallowing foods, is it solids or liquids?

If the pt can take down liquids and not solids (**difficulty in swallowing solids**), it is **due to obstruction** – can be due to esophageal web in Plummer Vinson syndrome, IDA with glossitis and cheilosis and an esophageal web, esophageal cancer

If pt **has problem swallowing solids AND liquids, it is a peristalsis problem,** which is very bad. If it's the upper 1/3 of the esophagus (which is all striated muscle), it is due to myasthenia gravis (b/c it affects striated muscle). If it's the middle 1/3 (combo of smooth and striated muscle). And if it's the lower 1/3 (smooth muscle) it's due to Scleroderma (aka progressive systemic sclerosis and CREST syndrome) and achalasia. So, they will tell you immediately if they can swallow liquids and/or solids, or neither (which is a peristalsis problem). How can you distinguish PSS/CREST from achalasia? In achalasia, they vomit up the food they ate when they go to bed at night; or they will tell you pt has Raynaud's, indicating that it is CREST.

Odynophgia = PAINFUL swallowing; always abnormal
In HIV pt = Candida esophagitis – is it AIDs defining? Yes.
MC fungal infection in HIV = Candida
When it gets into the esophagus, it is AIDs defining
When it is a thrush, it is PRE AIDS lesion (not aids defining)

Helpful hints with other diseases:
Palpable purpura = immune HPY type III = Henoch Schonlein (MC)
Epistaxis = platelet problem (don't think hemophilia)...they give clues!
Pansystolic murmur increases on inspiration = tricuspid regurg
Pansystolic murmur increases on expiration = mitral regurg

B. Tracheoesophageal fistula

Blindly ending esophagus (prox esophagus ends blindly) – distal esophagus arrives from the trachea. What does the mom have? Polyhydramnios – amniotic fluid is baby urine, so have to recycle it, or mom will have big belly. So, the baby swallows it and it is reabsorbed in the small intestine. So, if you have obstruction in the esophagus, or proximal portions of the duodenum, mom will have polyhydramnios. So, there are 2 answers: 1) Tracheoesophageal fistula 2) duodenal atresia in Down's syndrome – these 2 are associated with polyhydramnios. They block the ability to reabsorb amniotic fluid, leading to polyhydramnios. Also, when these kids eat, food gets caught and kids cough and sputter b/c the distal esophagus arises from the trachea and leads to distension of the stomach. This is very characteristic.

C. Zenker's diverticulum

Area of weakness – cricopharyngeous muscle. It has a lil slit in between the fibers of it. Not the whole area is cut (which would be a true diverticulum – this is a false diverticulum). It goes out and gets a pouch. The pouch collects food and leads to halitosis. They have a tendency of regurgitating undigested food out of the nose.

D. Achalasia

Peristalsis prob – prob with relaxation of the LES, therefore it is in spasm all the time. Why? If you bx that area, this means that the ganglion cells are missing. What dz does this remind you of? **Hirschsprung dz**. What is in those ganglion cells? Vasointestinal peptide (VIP). What is its function? To relax the LES. So, when you destroy those ganglionic cells, not only do you destroy the movement of the lower esophagus, but you also reduce VIP levels. So, you have constant constriction of the LES, leading to bird beak. Prox portion is dilated.

E. Parasites

Dz of South America where the leishmania forms invades the ganglion cells of the LES and the rectum –– produce acquired achalasia and Hirschsprung dz = **Chaga's dz**, vector = reduvid bug (aka kissing bug); swelling of the eye sign? Romana's. What does it do in the heart? Causes myocarditis and chronic heart failure – congestive cardiomyopathy. This is one of the more common causes of heart dz in South America.

F. Barrett esophagus

Ulcerated mucosa in the distal esophagus. Bx: see glandular metaplasia; therefore see goblet cells and mucous cell (which shouldn't be there). They are there b/c the esophagus cannot protect itself from esophageal injury. Therefore, run the risk of adenocarcinoma of the distal esophagus. Example: If the lesion in esophagus, dsyphagia of solids, but not liquids, lesion in noted in distal esophagus – do NOT pick squamous cell carcinoma – this is in the MID esophagus. If it is distal, it is adenocarcinoma, and the precursor lesion is Barrett's esophagus.

G. Esophageal varices

Dilated submucosal esophageal veins = therefore pt has cirrhosis, who was an alcoholic. Pt also has portal HTN – the left gastric vein is involved (one of the branches off the portal vein is left gastric vein). The left gastric vein drains the distal esophagus and proximal stomach. What drains into the left gastric vein? Azygous vein. Where does the left gastric vein drain into? Portal vein. However, b/c of cirrhosis, portal vein cannot empty blood sufficiently into it, the hydrostatic pressure increases; you reverse blood flow into the left gastric vein, splenic vein, and other veins, and end up producing varices that rupture.

Hematemisis = vomiting blood
Hemoptysis = coughing up blood
Hematochezia = blood pouring out of anus (actual dripping of blood – not coating of stool with blood, that is seen in anus). MCC = diverticulosis; not diverticlulitis b/c the vessel is next to the diverticular sac, so if it were '-titis', it would be scarred off. With -osis, it is intact, and just have to erode it, leading to 6 mL bleed.

H. Mallory Weiss Syndrome

Tear at esophago-gastric junction. Example: let's say its young woman (play odds) – what does she have? Bulimia. Classic Example: alcoholic with retching (trying to vomit, but nothing is coming out – causes tremendous pressures, leading to tear (hematemisis) or puncture (Borhave's - this is when the air gets into the pleural cavity, and leads to Haman's crunch of the anterior mediastinum).
So, seen with bulimia and leads to Borhave's (vs. an alcoholic).

I. Esophageal cancer

Squamous cancer (not distal, but mid); MCC's = smoking and alcohol (2nd MCC)
Dysphagia seen in this pt - initially, pt cannot swallow solids, but can take down liquids. Example: 50 y/o, male, alcoholic, wt loss, prob swallowing foods, not liquids – dx? Esophageal cancer – squamous cell carcinoma of the mid-esophagus (play odds). Example: pic of trachea and see cartilage rings, and elastic artery (esophageal in middle) this is esophageal cancer.

IV. Diseases of the Stomach

A. Congenital Pyloric Stenosis

Example: male, 3 weeks old and started **vomiting non bile stained fluid at 3 wks**; palpated the abdomen and felt a knot in RUQ and see hyperperistalsis. This is NON bile stain fluid at 3 weeks. Congenital Pyloric Stenosis

What if it is duodenal atresia in a down's kid? That would be **at birth vomiting** of bile stained fluid. And double bubble sign – atresia (lack of development of the lumen) is distal to where the bile duct comes in, so bile can still enter the proximal portion of the duodenum – this is why it is bile staining – b/c there is no movement, there will be air trapped in

there, and air is trapped in the stomach, therefore there is air in the stomach and prox duodenum – a double bubble sign. Also, mom will have polyhydramnios. So, do not confuse congenital pyloric stenosis (which has no relationship to down's) with duodenal atresia.

It does have multifactorial inheritance; therefore it can be increased in future children. Can see pyloric stenosis, as it has thickened. To Rx, split the muscle (called pyloroplasty).

B. NSAID ulcers

Non steroidal will block PGE2, which is responsible for the mucous barrier of the stomach, and vasodilatation of the vessels, mucous secretion, and secretion of bicarb into the mucous barrier. So, when you take NSAIDS for a period of time, the whole thing is destroyed. Leads to multiple ulcers and significant blood loss over time. They are punched out.

C. H. pylori

Silver stain (as is PCP, Legionella, bartenella hensilai). Comma shaped organisms (like campylobacter), but found out that they have different cell walls and etc. Nasty bug b/c it make lots of cytokines and urease which converts urea to ammonia, and is one of the reasons why they can burrow through the mucous layer – ammonia is very toxic – this is the test we use – when we take bx of gastric mucosa, we do a urease test on it and if its positive, know H pylori is in it. Can also use serological tests – Ab's against it. It's only good for the first time. Why? B/c the Ab's do not go away and, therefore cannot dx reactivation or recurrent. After that it is useless b/c won't tell anything b/c will always be positive b/c Ab's stick around.

Where does **pernicious anemia hit? Body and fundus**. That is where the parietal cells have autoAb's destroying them, and IF leading to atrophic gastritis.

This is NOT where H pylori exerts its affect. **H pylori affects the pylorus and antrum**. It destroys the mucosa, leading to atrophic gastritis of the pylorus and antrum. This is where cancers are. Most cancers are along the **lesser curvature of the pylorus and antrum** (exact same place where gastric ulcers are). The H pylori live in a mucous barrier and therefore is protected. **MCC stomach cancer = H pylori**. H pylori can also cause malignant lymphomas of the stomach (low grade).

Why don't we ever bx a duodenal ulcer? B/c they are never malignant. But gastric ulcers have a chance of becoming malignant therefore need to biopsy gastric and not duodenal ulcers. Only reason they bx a gastric ulcer is b/c they are trying to rule out whether it is cancer (malignant) or not – they know it's an ulcer and it has a 3% of benign malignant. Never have to bx a duodenal ulcer, so just leave alone. **H pylori is more commonly assoc with duodenal PUD than gastric**.

Why do you get melana with upper GI bleeds? Upper GI = anything that is a bleed from the ligamentum of trietz – where the duodenum hits the jejunum and up. Why is it black? Acid acts on Hb and converts it to hematin. Hematin is black pigment, leading to melana. This is imp to know, b/c if you have black tarry stools, and its 95% chance that is an upper GI bleed, and if you play odds, it is prob a duodena ulcer (vs. a gastric ulcer). So, Hb is converted by acid to hematin, which is a black pigment. Vomiting of coffee ground material = blood clots acted upon by acid and changes to hematin.

Example: Pt, an executive under great stress, and sudden onset of severe epigastric pain that radiates into the left shoulder. First step in work up? Flat plate of the abdomen; see air under diaphragm. Odds? Duodenal ulcer. Why did he have shoulder pain? Air got out, settled under the diaphragm, irritated nerve #4 (phrenic), and got referred pain to the dermatome (which is the same dermatomes)

D. Rhinitis Plastica: Adenocarcinoma of the stomach

With signet ring cells. Example: 52 y/o female with weight loss and epigastric distress. She had an upper gastrointestinal series, noted that stomach did not move (no peristalsis), and then she died. Dx? Rhinitis plastica – cells that are invading the wall of the entire stomach, called **signet ring cells** (which are stained with mucocarnine cells, are pink – signet cells are like a diamond ring, and the diamond has been pushed to the periphery). The mucous is inside, making the cell look empty, and pushing the nucleus to the side (just like fatty change of the liver). However, these are malignant neoplastic glandular cells, and are characteristic of rhinitis plastica type of gastric adenocarcinoma.

Misconception: **Krukenberg tumor** is not a tumor that is seeding out to the ovary. This tumor is due to hematogenous spread to the ovary. There is no such thing as a signet ring carcinoma of the ovary (there is no primary cancer of the ovary that looks like this). **The signet ring cells came from stomach cancer that has metastasize to ovaries = Krukenberg tumor**.

Most are ulcerative tumors in the lesser curvature of the pylorus and antrum. Leather bottle stomach – very hard due to all of the cancer cells and the fibrous response to it.

Gastric cancer is declining in US; other countries it is a primary cancer - Japan, b/c smoked products. Other ethnic cancers: nasopharyngeal carcinoma = china; stomach cancer and HTLV 1 = Japan; Burkitts lymphoma = Africa.

If there was a nontender mass in left supraclavicular area and pt with epigastric distress one week ago – dx? Metastatic gastric adenocarcinoma. Cervical cancer can also metastasize here. Left supraclavicular node drains abdominal organs; therefore pancreatic cancers but mostly the stomach cancers metastasize there. The right supraclavicular node mets are from lung cancer.

V. Malabsorption

Means bad absorption of everything: fats, carbs, and proteins. Diagnosis point of view we look for increased fat in the stool = steatorrhea = screening test for malabsorption.

A. Fat Digestion:

1) Need lipases to break down fat into 2 monoglycerides and FA's, so you need a functioning pancreas.

2) Need villi of the small intestine b/c if we didn't, the small intestine would have to be a mile long. Villi increase the overall absorptive surface without increasing the length. So, if you don't have them, you decrease the absorptive surface, and will lose the monoglycerides and FA's. Therefore, you need a functioning SI with villi.

3) Need bile salts to emulsify the fat and break it down to micelles (tiny particles that are 1 micron in diameter) and chymlomicrons. Emulsifying agents are many times in dishwashers b/c need to get fat off plates. Fat will come to the surface and break up into micelles, which are easier to absorb.

So, need functioning pancreas, bile salts, small intestine that has villi in order to reabsorb fat.

Bile salts are made in the liver from cholesterol. Cholesterol cannot be degraded; it either solubilized in bile (therefore run the risk of cholesterol stones) or is converted to bile acids. Cannot break down cholesterol. \

Bile salt deficiency is seen in: a) liver dz; b) anything that obstructs bile flow will produce bile salt def; c) bacterial overgrowth can eat and breakdown bile; d) terminal ileal dz, ex. Crohn's dz cannot recycle; and e) Cholestyramine: resins – used for treatment of hyperlipidemia, can produce bile salt def. This is the MOA of resins, by binding and then excreting them, b/c if you are not recycling them, you will make more. What's happening in the liver? Upregulation of LDL receptors synthesis, b/c need to make more bile salts, therefore need to suck more out of the blood and will make more LDL receptors. These drugs will eventually take more cholesterol out of the blood and lower it, so you can make more bile salts. It also takes drugs with it, so it's not good for people taking meds, b/c you will lose these meds in the stool, along with bile salts.

Dz's: screening test is looking for fat in stool (steatorrhea) – let's say it is positive. So, we have to figure which if the 3 areas is the cause of the malabsorption – pancreatic def, bile salt def, or something wrong with the small bowel (MC).

B. Celiac Dz (sprue)

Pic of small bowel lesion and a skin zit that has an association with it. This is celiac dz (autoimmune dz), and the skin zit is **dermatitis herpetiformis**. **Celiac dz is an autoimmune dz against gluten wheat, esp. gliadin**. It is very common and is the MCC of malabsorption in this country. So, when you eat wheat products, the gluten is reabsorbed into the villi and there are Ab's against gliadin, and leads to destruction of the villi (just like Ab's against parietal cells or intrinsic factors, which destroy everything around it). So, the Ab's attack gluten that has just been reabsorbed by the food, which will cause destruction of the villus. And there are no villi here – it is flat; blunting of villus – so you are not able to reabsorb fat, proteins, or carbs. There is no villus surface. The glands underneath are fine, however. The villi are absent. There is a **100% chance of dermatitis herpetiformis association with underlying celiac dz. Dermatitis herpetiformis is an autoimmune dz, and it is a vesicular lesion of the skin** –looks like herpes of the skin. They will show pic of a dermatitis herpetiformis, and will ask what the cause of diarrhea is? Ab's against gluten (gliadin).

C. Whipple's dz

An infection of the small infection due to an organism that you cannot gram stain. T. whippelii only seen with EM; cannot be cultured. See flat blunted villi and foamy macrophages (look like Niemann pic bubbly macrophages; can also be from an HIV "+" b/c it looks like Whipple's, but isn't). The macrophages have distinctive PAS-positive stains.

HIV positive pt and acid fast stain – pt with helper T cell count of 100. Have an acid fast stain with the foamy macrophages – **due to MAI** (this is more common that TB), and **can cause Whipple like dz with malabsorption**.

Whipple's, being an infection, has systemic signs and symptoms: fever, lymphadenopathy, polyarthritis, generalized pain. It's an infection therefore can be treated with antibiotics.

So, there are **2 dz's that cause malabsorption: celiac dz and Whipple's dz**. Other dz's are dz's of the pancreas – **chronic pancreatitis (MC in alcoholics** – 2 reasons for malabsorption in alcoholics – a lipase def related to chronic pancreatitis, or bile salt def due to cirrhosis, or both in an alcoholic).

D. Diarrhea

Best way to classify is to subdivide into 3 types:

1. Invasive: bacteria invades
2. Secretory: the bacteria produces toxins and that will stimulate cAMP (or other mechanisms) causing the small bowel to secrete small amounts of ISOTONIC fluid, which is NaCl.
3. Osmotic: lactase deficiency. Also produced by laxatives, and other inborn errors of metabolism.

Secretory and osmotic diarrheas are high volume diarrheas and you go frequently, whereas invasive diarrhea is a small volume diarrhea. Best/cheapest test to get in a pt with diarrhea = fecal smear for leukocytes. If there are NOT any neutrophil don't worry because not invasive. If there are inflammatory cells then you must do fecal smear test for campylobacter or shigella.

a) Osmotic diarrhea (fits in with osmotic water movement) is when there is some osmotically active substance in the bowel lumen that is sucking water out of the bowel, causing a high volume, hypotonic loss of fluid. Example: lactase def. = brush border or disaccharidase deficiency, a brush border enzyme. In a classic case but they will not tell you it's a lactase def, instead will tell you it's a disaccharidase def or even a brush border enzyme def. So if you're lactase def, it means that any dairy products which contains lactose (which breaks down into glucose and galactose) can't be indigested. So it will go to the colon, and act as desserts to the anaerobic bacteria which will eat the lactose and produces hydrogen gas, and other gases, and acids, and get acidic stools. The hydrogen gases causes the bloating, distention, and incredible explosive diarrhea.

b) Secretory diarrhea: two things to know, Vibrio cholerae and ETEC (traveler's diarrhea). These are not invasive diarrhea, therefore when you do a bowel biopsy there will not be one iota of inflammation, it's perfectly normal. It's purely a toxin that activates a pump either cAMP (Vibrio) or some other pump: guanylate cyclase (E. coli). Treatment: when you give fluid replacement to patients with v. cholerae, you need to give glucose along with the fluids. This is b/c you need glucose to co-transport Na that was in the fluids. Side note: Need to know the other E. coli related toxins: EHEC: O157:H7; EIEV; and EaggEC.

c) Invasive diarrhea: the MC in US is caused by campylobacter jejuni, and shigella is a close second. Classic case: a person with low vine(?) diarrhea, with some blood in it, and on gram stain there were comma shaped or S-shaped organisms that's campylobacter jejuni. Both of these organisms can produce pseudomembranes. Therefore all pseudomembranes does not necessarily mean you will see C. difficile.

d) Parasites that causes diarrhea:

Giardia: owl eyes that move. This is the MCC of diarrhea due to a parasite in the US. Treatment: metronidazole.

Cryptosporidium parvi: MCC of AIDS diarrhea is a partially acid-fast organism. It sticks to the wall of the colon. Classic case: there is a pt that has AIDS and has diarrhea, and when they stain it, there are oocysts that are partially acid-fast. It will kill if you are immunocompromised. The treatment is almost worthless. It comes at the end when the helper T-cells are near 50 or 75, and that's when all the organisms that will kill you: MAI, cryptosporidium, toxoplasmosis, and CMV all comes in at the end. P. carinii comes in around 200 helper T-cells.

Clostridium difficile: This is an autopsy pic of an older woman who was in the hospital with pneumonia, and she developed diarrhea. What was found on autopsy? Well, it is safe to say that if she had pneumonia, then she was taking antibiotics. So this is **pseudomembranous colitis, caused by clostridium difficile**. This occurs when taking antibiotics that wipe off the good organisms, leaving behind c. difficile. Everybody has c. difficile in their stools, but E. coli, enterobacter fragilis are keeping it in check. But when taking antibiotics such as ampicillin (MC), clindomycin (2nd MC) for a period of time, you knock off the good guys, giving c. difficile a chance to proliferate and make toxins that damage the superficial layers of the colon. The bacteria doesn't invade, it's the toxins that do. This is analogous to c. diphtheria, which also has a toxin that damages and produces pseudomembranes but the organism does not invade. The ribosylation thing, and the Elongation factor 2 (EF-2 allows for protein elongation) are messed up, therefore cannot elongate proteins. The first step in management is to do a toxin assay of stools, not gram stain b/c there are lots of gram stain organisms in the stools, not blood culture b/c it's not in the blood. **The screening test of choice is toxin assay of stool!** The treatment is to give metronidazole, used to give vancomycin b/c c. difficile became resistant to it. Metronidazole itself can produce pseudomembranous colitis but you take that chance.

VI. Diseases of the Small Intestine

A. Small bowel obstruction: See classic step ladder appearance of air-fluid levels: air, fluid, air, fluid (step ladder appearance). When you have a hollow viscous that peristalsis, you get a certain characteristically pain, called **COLIC pain**. It isn't like a crampy pain with no painfree intervals; colicky pain is when you have pain, a painfree interval, pain, and then a painfree interval. The intervals are not consistent, sometimes you have a 15 min painfree interval, and other times if may be longer or shorter. This is colicky pain; it means TOTAL small bowel obstruction. By the way, the bile duct does not have peristalsis, therefore you do not get colicky pain, and instead you get crampy pain. You have to have peristalsis to get colicky pain, it has to move. And what's it doing is trying to move against that obstruction and that's causing the pain. B/c you cannot perstalse you get stagnation of the food proximal to wherever the obstruction is, and get air-fluid levels. Distal to the area of obstruction there is no air. In obstruction, there are two things that can happen: **constipation or obstipation**. Constipation is where you have a problem with stooling, which does not necessarily mean obstruction. Obstipation means that not only do you have constipation you also have a problem passing gas, that means you have complete obstruction. So you have to ask the pt whether they have passed any stools or gas. **MCC of obstruction: adhesions from previous surgeries.** Slide: those are watermelon pits, with a narrow lumen. But if the case read that this pt did not have pervious surgeries and had colicky pain, this is due to the bowel being trapped in the **indirect inguinal hernia.** Example: there was a weight lifter who developed colicky pain in the RLQ area, had no previous surgery, the most likely cause is indirect inguinal hernia. Weight lifters often times create indirect inguinal hernias.

Side note: there was a pic of **Down's syndrome** kid. Trisomy 21 (abnormal number of chromosomes) is due to nondisjunction (unequal separation during the first stage of meiosis I) but not all down's have trisomy 21. But if the kid had normal 46 chromosomes, this is due to **Robertsonian translocation**. In this case, they would have 46 chromosomes but on one of those chromosomes 21, will be another chromosome attached to it. They will have three functional chromosome 21. The two GI diseases that are MC'ly seen in Down's are **duodenal atresia** (double bubble sign) and **Hirschsprung dz**.

B. Hirschsprung dz: the nerves are there but the ganglionic cells are missing. So, what happens if it's missing in the rectum, the stools cannot get by, even when there is an opening, b/c there is no peristalsis. So the stools just stay there. So, the dilation of the proximal colon has ganglionic cells, and there peristalsis occurring and you can't get the stools thru the rectal area. So this means that the rectal ampulla has no stools in it. Example: if you have a child that didn't pass the meconium in 24 hours and a rectal exam was performed. If there was **NO stools that came out on exam it means Hirschsprung dz.** If on exam, there was stools on the finger, it means tight sphincter. **This is a dz of the colon.**

C. Intussusception: most occur in children, and it's when the terminal ileum intussuscepts goes into the cecum. There will be colicky pain b/c you are obstructing, and not only that, you are compromising blood flow, so you get the bleeding. They will say: a 2 y/o kid, with colicky pain and bloody stools. They might way there is an oblong mass in the RUQ. In some kids, it spontaneously comes out, but if not, then the radiologists will do barium enema, and put a little pressure there, and he reverts it. So you get complete bowel obstruction and infarctions.

D. Volvulus: Twisting of the colon around the mesentery b/c there's too much of it causing complete obstruction and infractions due to compromising blood flow.

E. Gallstone ileus usually seen in older people, more women, and have signs of colicky pain, and obstruction. The gallbladder stone falls thru the fistula and settles into the ileocecal valve and causes obstruction. See a flat plane of the abdomen that produced air in the biliary tree. Boom, there's your Dx. There is a fistula that is communicating the gallbladder with the small bowel therefore air can get in the small bowel and the biliary tree. **Air in the biliary tree with colicky pain is gallstone ileus. Dz of gallbladder.**

F. Meconium Ileus = cystic fibrosis

VII: Diseases of the Colon

A. Vascular diseases of the colon:

1. Ischemic Bowel Dz:

The small bowel more commonly infracts than the large bowel, b/c it has only one blood supply. The entire small bowel, the ascending colon, and the transverse colon are all supplied by the SMA (superior mesenteric artery). So, what is the main diff in a small bowel infarct vs. an ischemic ulcer causing bloody diarrhea in the splenic flexure? The difference in Presentation. They both can have bloody diarrhea. However, the **small bowel infarction** will DIFFUSE abdominal pain (all over – not one specific area). In **ischemic colitis**, it will point to specific area on right side of abdomen. This differentiates btwn a small bowel infarct from a small infarct in the colon (can pinpoint area).

2. Angiodysplasia

2nd MCC **Hematochezia**, with diverticulosis being #1. It's in the cecum b/c law of Laplace (wall stress and radius). The diameter of the cecum is bigger than any other part of the colon. B/c the diameter is greater, the wall stress is greater. Therefore, putting stress on the vessels in the wall of the cecum, it actually pulls them apart and produces telangiectasias. As a result, it predisposes to angiodysplasia b/c increased wall stress. If one of them ruptures to the surface, you can end up with significant bleed. A very common cause of Hematochezia in older people. So, if diverticulosis is ruled out, angiodysplasia is probably it.

B. Meckel's Diverticulum/ Small Intestine Dz:

1. Rule of 2's: 2% of pop'n; 2 inches from terminal ileum; 2 ft from the iliocecal valve; 2 cm in length; 2 y/o or younger; and 2% of carcinoid tumors occur in M.D.

MC complication = bleeding. B/c it is a diverticulum, it can be inflamed, and leads to diverticulitis. Example: **hematemisis, pain in RLQ area, melana** –dx? Meckel's (involved melana AND hematemisis – definitely not UC or Crohn's).

Example: newborn with a sinus and umbilicus was draining poop –dx? Persistent vitelline duct (same as meckel's – sometimes it is open all the way through, therefore there is a communication between the small bowel and umbilicus, so feces coming out of umbilicus, which is persistence of the vitelline duct. If you have urine coming out of the vitelline duct, this is persistence of the uracus. So, **feces=vitelline duct, urine = uracus**.

C. Sigmoid Colon

MC location for cancer in the entire GI tract = sigmoid colon
MC location for polyps in the entire GI tract = sigmoid colon
MC location for diverticula in the entire GI tract = sigmoid colon

The area of weakness is where the blood vessels penetrate the valve. The mucosa and submucosa will herniate right next to the vessel. This is very bad 'next door neighbor". When feces are stuck (fecalith), can erode that vessel, and can see why **diverticulosis is the MCC of Hematochezia – massive lower GI bleed**. These extend outside of the lumen, which is diverticulosis. If you see polyps in the lumen, do not confuse with polyposis – **polyps go INTO the lumen**, not out.

D. Diverticulosis

MC complication = diverticulitis; has MANY complications.

Diverticulitis = Left side appendicitis (appendicitis dx: RLQ pain, McBurney's pt, rebound tenderness, fever, and neutrophilic leukocytosis) – this is the same presentation in diverticulitis), but diverticulitis occurs in the LLQ area, in an elderly person. **MCC fistulas communications in the GI = diverticulosis.** With a fistula, there is communication between 2 hollow organs. The **MC fistulas are colovesicle fistula's**, which is a fistula between the colon and the bladder, leading to **neumaturia – air in the urine**. **MCC of colovesicle fistula is diverticular dz**. They can rupture, and the rupture can cause peritonitis.

VIII. Inflammatory Bowel Dz: Crohn's and UC

Crohn's involved the terminal ileum 80% of the time. Sometimes it just involves the terminal ileum, sometimes it involves the terminal ileum AND the colon, and sometimes it just involves the colon. Crohn's likes the ANUS, UC likes the RECTUM (they have a preference for which part of the lower part they like). Crohn's likes to produce fistulas and fissures of the anus; UC likes the rectum, producing bloody diarrhea. Crohn's jumps around, transmural, noncaseating granulomas. UC doesn't jump; it stays in continuity, and involves the mucosa/submucosa. **Dx of Crohn's is simple – ie ileocecal valve, ascending colon, terminal ileum – there is a transmural inflammation with a very narrow lumen – therefore the presentation will be colicky, RLQ pain, with diarrhea in young person**. **Nothing except Crohn's produces colicky pain in the RLQ in a young person!** If is a 3rd world county, what is it? TB (m. bovis). In this country, if we get intestinal TB from swallowing it and it will be M .Tb. In third world countries, it produces presentation same as Crohn's; this occurs b/c they do not have pasteurization; M. bovis is the MCC; this is where payer's patches are. **String sign** – on barium study, looks like a string – see that it is transmural and that it is segmental. The proximal valve is dilated – have to push stool through that but you can't. See cobblestones and ulceration in Crohn's dz. Linear ulcers are apthus ulcers**. Non caseating granuloma is characteristic of UC**. **UC always begins in the rectum**, can stay there, or can move up in continuity and involved the whole colon, but it never involves the terminal ileum. It is involves the whole colon, it is called pancolitis, and this has the highest incidence of cancer. So, the more involvement and greater duration = greater chance of cancer related to UC. Pseudopolyps – see ulcerated mucosa and submucosa. Pseudopolyps are residual polyps that are inflamed, it is inflamed bloody mucosa. Everything is ulcerated off, and you see the submucosa of the colon. UC has the highest incidence with cancer, HLA B27 anklyosis spondylitis, and is the MCC of sclerosing pericholangitis (sclerosis/fibrosis around common bile duct, producing obstructive jaundice and high incidence of cholangiocarcinoma). Know the diff in UC vs. Crohn's.

IX. Tumors of the Colon Polyps

MC polyp in entire GI = hyperplastic polyp – it is a little nubbin – aka hemartomas (therefore not neoplastic), usually in sigmoid colon.

Tubular adenoma: looks like a strawberry on stick, therefore has a stalk with strawberry, which is the precursor lesion for colon cancer.

Juvenile Polyp: Slide: coming out of child's butt – kid with polyp in rectum; **all juvenile polyps located in the rectum and are hamartomas (no precancerous).**

Lets say it is an adult and the polyp is sticking out (a reddish mass) – dx? **Internal hemorrhoids**. **Rule: internal hemorrhoids bleed, external hemorrhoids thrombose**. Therefore, when you have blood coating the stool, it is internal hemorrhoid. Internal hemorrhoids are NOT painful, but they do prolapse.
Adult with something reddish sticking out of their butt = prolapsed internal hemorrhoid. **Internal hemorrhoids bleed and painless, while external thrombose and are painful.**

Sessile Polyp (villous adenoma) – looks like the villous surface of the small intestine (hence name villous adenoma); these are lil finger-like excrenses of the small intestine, hence the name villous adenoma. **These have the greatest malignant potential, and are usually in the rectal sigmoid.** B/c they are villous/finger like they have a lot of mucous coating the stool; mucous secreting villous. They have a 50% chance of becoming malignant. So, tubular adenomas are precursors for cancer (size determines malignant potential – if they are above 2 sonometers, they are very dangerous) and villous adenomas lead to cancer, too.

Familial polyposis – need to have over 100 polyps to have familial polyposis. This dz is autosomal dominant, uses APC suppressor gene, ras, and p53; APC is the major one. Will always get cancer in them, usually between 35-40. Therefore, will need to prophylactically remove the bowel. The autosomal dominant dz is famous for late manifestations, penetrance, and variable expressivity (as are all other AD dz's). This means that they will not be born with polyps at birth (they start developing btwn the ages of 10-20; in ADPKD, they do not have cysts are birth, they start developing btwn 10-20; in Huntington's chorea, do not have chorea at birth, but around 35-40 years, and they have late manifestations.

Affected colon has polyps and brain tumors = Turcot syndrome (like turban) – therefore, you have a polyposis syndrome with brain tumor; this dz is auto rec (not dominant).
Gardner's syndrome: Have multiple polyps in there, plus b9 salt tissue tumors: desmoids and osteomas in the jaw.

X. Carcinoid Tumors

Along with auput tumors. All carcinoid tumors are malignant, but have low grade potential. A lot of it depends on their size and if they are going to mets. Depends on their size in sonometers – if they are greater than 2 sonometers they have the ability to mets. **MC location for carcinoid tumor = tip of the appendix** – have a bright yellow color, but they **are NEVER the cause of carcinoid syndrome** – why? B/c the tip of the appendix will never be greater than 2 sonometers. So, where is the **MC location of carcinoid tumor that CAN be associated with carcinoid syndrome? Terminal Ileum – they are always greater than 2 sonometers**. What do all carcinoid tumors make? **Serotonin**. B/c the appendix and terminal ileum are drained by the portal vein, the serotonin made goes to the portal vein, goes to the hepatocyte, is metabolized into 5

hydroxyactoactitic (?) acid and is pee'd out; therefore it is not in the bloodstream. Therefore, there are no signs of flushing and diarrhea b/c there is no contact with the systemic circulations. However, if you mets to the liver, then those metastatic nodules that are making serotonin can dump some of it into the hepatic vein tributaries. This does have access to the systemic circulation b/c goes to IVC to Right side heart, and this is why you get right sided lesions – "**TIPS" = tricuspid insuff and pulmonic stenosis**. **Serotonin** is a vasodilator in some cases, but a vasoconstrictor in other cases. However, in terms of serotonin syndrome, it's a vasodilator **that causes flushing (which is the MC symptom of carcinoid), followed by diarrhea (2nd MC).** If it has access to systemic circulation, it has high levels of 5 hydroxyacetoacitic (?) acid, which is the screening test of choice b/c it is the metabolite of serotonin. So, **b/c making and LOSING a lot of serotonin, what aa can be deficient? Tryptophan is def, therefore the vitamin Niacin is def, therefore can have pellagra. You using up all the Tryptophan and making serotonin instead of niacin.**

XI. Colon cancer

Neurosecretory granules on EM – colon cancer; **left side obstructs, right side bleeds**.

This is easy to understand b/c the left colon has a smaller diameter than the right. So, when the cancer develops in **the left colon** and wants to form a polyp, it goes around – **annular (napkin ring)**, and produces constriction. Open bowel in left colon, see one edge of the cancer on each side of the bowel and bowel is constricted – have signs of obstruction (left side obstructs, right side bleeds).

In the **right colon**, b/c of there is a bigger diameter; it has a bigger chance of going out and forming a polyp. Therefore, it is sitting in the stool, leading to a bleed (therefore left side obstructs, right side bleeds).

So, which is side is more likely to have Fe def? Right sided lesion.
Which is more likely to have alteration in bowel habits (constipation/diarrhea)? Left sided.

Tumor marker for colon cancer = CEA (carcinoembryonic Ag). Not used to dx colon cancer, but used to follow it for REOCCURRENCE. MCC relates to diet (lack of fiber in stool – therefore, more fiber you have, the less chance of colon cancer b/c you are getting rid of lipocolic acid). Age is also a risk factor (pts over 50); smoking is a risk factor that is assoc with colon cancer. Polyposis coli syndromes also have an association (familial polyposis, Gardner's syndrome, turcot's syndrome)
NOT Peutz Jeghers, hyperplastic polyps, or juvenile polyps).

XII. Diseases of the Appendix: Appendicitis

Covered with pus; MCC appendicitis in adults = fecalith = impacted stool. So when you impact stool it presses on the sides of the appendix, and leads to ischemia, then get a breakdown of the mucosa, E. coli gets in there and acute appendicitis occurs. **This is the SAME mech for diverticulitis** (the diverticular sacs also get fecaliths in them and the same exact thing happens – the pathogenesis of acute diverticulitis and acute appendicitis is exactly the same). So, fecalith, ischemia along the wall, inflammation, E coli.

Another analogy: acute cholecystitis – except it is not a fecalith, but is a stone in the cystic duct pushes on the side, leads to ischemia, acute cholecystitis, E coli**.** So, there is a concept there – **we have acute cholecystitis, diverticulitis, and appendicitis all related to something obstructing the lumen, causing mucosal damage, and E coli inflammation**. In acute cholecystitis it's a stone, while acute appendicitis and diverticulitis is due to a fecalith.

What the **MCC of appendicitis in children? Measles and/or adenovirus infection**. Then, acute appendicitis occurs b/c there is lymphoid tissue in the appendix. With measles or adenovirus infection, get **hyperplasia of lymphoid tissue in the appendix, and can obstruct the lumen and set up inflammation for mucosal injury and leads to acute appendicitis**. So**, in children, it usually follows a viral infection**. As opposed to adults, where it is due to fecalith.

CHAPTER 10. LIVER

I. Bilirubin metabolism:

Most of the bilirubin in our blood is unconjugated and derived from the RBC's when they are old, phagocytosed and destroyed. Unconj bilirubin is the end product, goes to the bloodstream and binds with albumin, goes to the liver and is taken up. Majority of bilirubin is from breakdown of RBC's (99%), which is all unconj. None of this is in the urine b/c it is lipid soluble. So, it gets taken up by the liver and is conjugated. Any time the cytochrome p450 conjugates bilirubin, or metabolizes any drug, it renders it water soluble. So, we have a lipid soluble unconjugated bilirubin is converted to conjugated bilirubin (direct bilirubin), which is water soluble. One of the purposes of the liver is to render lipid soluble drugs water soluble, so you can pee them out. So, we conjugate it and have water soluble bilirubin. Once bilirubin is taken up by the liver, it is never close to a vessel. So, there is no way it can get into a vascular channel (once it is taken up by the liver). So, if direct conjugated bilirubin is in our urine, this is b/c something happened (either in the liver or bile duct) to have caused it to get there b/c it shouldn't have access to our blood stream. So, it is taken up in the liver, conjugated, and pumped into the bile ductules; which go into the triad, goes up the common bile duct, some is stored in the GB and goes into the small intestine through the common bile duct. Therefore, bile contains conjugated bilirubin. Its also contains bile salts, cholesterol and estrogen, but has conjugated bilirubin that we will get rid of. So, this conjugated bilirubin takes a long trip down to the colon and the bacterial have been waiting for the conjugated bilirubin and will break it down back into unconjugated bilirubin. Then, it continues to break it down. The bacteria breaks it down to stercobilinogen (what it used to be called). Stercobilinogen oxidizes to stercobilin produces the color of stool. This term is no longer used. Now, it is called urobilinogen (which makes the color of the pigment). It is easier to understand the concept. So, **the unconjugated bilinogen is broken down to urobilinogen**. All porphyrins are colorless when they are in an '-ogen' compound; however, when you oxidize them, they have color. So, **urobilinogen, when it becomes oxidized in the stool**

becomes urobilin, which is the color of stool. A small portion of urobilinogen is reabsorbed out of the colon. Most of it goes back to the liver. A little of it goes to the kidney and ends up in the urine, where it get oxidized into urobilin. This is the cause of the color of urine. So**, the same pigment that colors stool is responsible for coloring urine**. We were taught that stercobilinogen is in the stool and urobilinogen is in the urine; however, sterco = uro, so the same compound is responsible for color change in feces and urine. They are not diff pigments, they are the same. So, if you have obstructed bile flow (in the liver or CBD), what should the color of the stool be? Light colored – b/c the urobilinogen would not have access to the stool to color it. Also, would not have urobilinogen in the urine. This leads to jaundice.

II. Jaundice

To calculate jaundice, they take the total bilirubin and find out the percentage of bilirubin that is conjugated (direct bilirubin). Example: total is 10, conj = 5, therefore conj bilirubin = 50%. So, they subdivide jaundice into 3 types – conjugated bilirubin less than 20% (therefore most of it is unconjugated),
btwn 20-50% (therefore some is conj and unconj), and
greater than 50% (most of it is conjugated bilirubin). Its also means that you have obstruction.

If it is **under 20%**, this **primary unconjugated hyperbilirubinemia**. So what can increase unconj bilirubin? **Hemolytic anemias, spherocytosis, SCDz, ABO hemolytic dz of the newborn, Rh hemolytic dz of the newborn, physiologic jaundice of the newborn** (b/c they cannot conjugate it). So, there is increased unconjugated bilirubin b/c breaking down more RBC's, have problems with conjugating enzymes – either too immature or they are missing enzymes (**Craigler Najjar syndrome**). So, we are either making too much b/c we are breaking down too many RBC's or we have a problem with conjugating enzymes – which is little babies with physiologic jaundice dz of the newborn, or rare dz's where we are deficient in the enzyme (Craigler Najjar).

The dz's **btwn 20- 50%** are hepatitis. **Hepatitis** = inflammation of the liver (not just some of it, all of it). So, b/c it's a sick liver, it doesn't want to take up the unconjugated bilirubin. Unconj liver builds up behind the liver. Inflammation in the liver will maybe destroy the architecture in the liver and break open bile ducts that have conj bilirubin in them. Now, b/c you have disrupted the architecture, there is a possibility of water soluble bilirubin to get into the blood stream (b/c there is necrosis of liver cells and bile ducts – so you will get conjugated bilirubin in there, too) - leading to 20-50%. This **includes all the hepatitis (including alcoholic**).

If it is **greater than 50%**, this is a NO BRAINER – it is clearly an **obstruction of bile**. We have intrahepatic obstruction (**intrahepatic cholestasis**), meaning that you are blocking bile flow in the liver (triad is blocked). Also have **extrahepatic cholestasis** (outside of the liver). There is only one thing outside the liver that can lead to this – **CBD (common bile duct)**. Therefore, something is obstructing that – a stone in the common bile duct that came from the GB (play odds). Can also have carcinoma of the head of the pancreas – b/c ducts go through the head of the pancreas. As a result, you have complete bile duct obstruction. So, there is intrahepatic cholestasis and extrahepatic cholestasis. So, what will happen is like water behind a dam. If you block bile flow, it will back up – where does it back up? Backs up to where it was made (the liver cells – remember this is an excess of conjugated, direct bilirubin). In the liver cells, it bubbles outside, and has access to the sinusoids and now is in the blood stream. So, the predominant factor in the blood stream is **CONJUGATED bilirubin**, which is water soluble. So, will **have very dark yellow urine and the stool will be LIGHT colored.** This combo – **high conj bilirubin, bilirubin in the urine** (HAS to be conjugated b/c it's in the urine and therefore water soluble), **and light colored stools = OBSTRUCTION** (nothing else can do this, and it is either intrahepatic or extrahepatic).

A. Congenital Unconjugated hyperbilirubinemias

1. **Gilbert's syndrome**
   Seen if you fast for over 24 hrs and get jaundice, AD, b9 (therefore do not need a bx). **Mech: prob in taking up bilirubin and prob in conjugating bilirubin**, therefore it is **predominantly an unconjugated hyperbilirubinemia**. So, if you want to see if pt has it, do 24 hr fasting test. So, get baseline bilirubin when they are not jaundiced and don't eat for 24 hrs and come back. When they come back they are jaundiced. Let's say the baseline is 1, and you double the baseline after 24 hrs, pt has Gilbert's syndrome. Ex. pt comes back after fasting test and is 2.5.

   2nd MCC jaundice = Gilberts syndrome (MC = hep A). Ex. resident that gets jaundice, but didn't have needle stick = he has Gilbert's dz b/c was fasting (enzyme levels are normal, high unconj bilirubin levels). Rx? Nothing
2. **Craigler Najjar**

B. Congenital Conjugated hyperbilirubinemias

Dubin Johnson; Rotor syndromes: Genetic dz's involving prob getting rid of CONJ bilirubin in the bile ducts. So, this is **predominantly a conj hyperbilirubinemia**. In Dublin Johnson, have a black colored pigment that builds in the liver and get black liver.

III. Liver Function Test (LFTs)

What are **transaminases** used for? They are **indices of liver cell necrosis** (hepatitis). AST (SGOT) and ALT (SGPT); **ALT** is more specific b/c it is only found in the liver; **AST** is in muscle, RBC's and liver.

Therefore, if you have a **viral hepatitis**, with massive liver cell necrosis, which would be the predominant transaminases elevated? **ALT**. Ex: 2500 ALT and 2200 AST. So ALT will be the main liver cell enzyme **elevated in diffuse liver cell necrosis**.

In **alcoholic hepatitis**, this is not what happens. There is a reason: **AST** is present in the mito of hepatocytes. ALT is not – it's in the cytosol. Alcohol is a mito poison (remember that it uncouples). AST is predominantly in mito, and when pt has alcoholic hep, **AST is higher than ALT** (forget the 2:1 relationship). Therefore, if you see AST higher than ALT, this is due to alcoholic liver dz. Could be fatty change, alcoholic cirrhosis, and alcoholic hepatitis. If it's VIRAL hepatitis, ALT is bigger than AST.

So, what are the enzymes of OBSTRUCTION (**obstruction of bile ducts**)? **Alkaline phosphatase and Gamma glutamyl transferase**. Transaminases will also be up, but not to the same degree. Gamma glutamyl transferase is located in the SER. When the SER is rev'd up, it undergoes hyperplasia (ie due to drugs: alcohol, barbs, rifampin, and phenytoin); you not only increase the metabolism of the drug, but also increase the synthesis of gamma glutamyl transferase. So, what would the classic thing you would see in any **alcoholic liver dz? AST>ALT, along with INCREASED gamma glutamyl transferase**. There is a problem: alk phos is in other things other than the liver – in bone (osteoplastic activity), placenta. So, how will you know where the alk phos comes from (ie if it's from bile duct obstruction vs. other things)? Look at **gamma glutamyl transferase b/c its specific for the liver** (so, if alk phos up, look at gamma glutamyl transferase!). **If the gamma glutamyl transferase IS elevated along with alk phos, this is BILE DUCT OBSTRUCTION.**

Albumin protime = marker of severity of liver damage. It is made in the liver, therefore if you have severe liver dz (ie cirrhosis), it will be decreased. Even better than that is prothrombin time b/c coagulation factors are made there (most are made there – vWF is not, however). So, if you have liver damage, the production of coagulation factors will be decreased, and PT will be prolonged (increased). So, **albumin levels and PT are the 2 best tests for liver severity (PT is a little better than albumin**).

There is only one autoAb that is important: **anti –mito Abs in primary biliary cirrhosis.**

Tumor markers: alpha feto protein is a marker for hepatocellular carcinoma. Can also use **alpha-1 antitrypsin** b/c it is made in the liver (it is **increased** in hepatocellular carcinoma).

If you have fractionation of bilirubin (less than 20%, 20-50%, and 50+ %), can start d/d; then give transaminase levels – see how it correlates with liver dz: transaminases correlate with viral hep and conj bilirubin of 20-50, or obstructive liver dz (alk phos, gamma glut) and conj bilirubin over 50%.

IV. Viral Hepatitis

A. MC on hepatitis:

MC hep = A (followed by B, C, D, E – in that order)
A and E = fecal oral; all the others are transmitted parentally
Hep A = No chronic carrier state
Hep E = produces a chronic carrier state only if you are pregnant, leading to chronic liver dz
Hep D = Requires Hep B to infection
Hep A = Daycare centers (therefore should get vaccine to prevent; outbreaks can occur in daycare centers)
Hep A = Jail
Hep B = IVDA
Hep C = Post transfusion Hepatitis
Hep B = MC infection by accidental needle stick

B. Serology:

HAV: anti A IgM= have hep A; anti A IgG = had it and won't get it again
HCV: anti C IgG Ab's are NOT protective and mean that you have the dz; there are no known protective Ab's
HDV: (same as HCV) – anti D IgG = have the dz, and no known Ab's will help cure; if you are anti-D IgG positive it means you have the active dz now

So, only protective Ab's are HAV, HBV (surface Ab), and HEV.

Hep B (HBV)

First marker that comes up is surface Ag (HBsAg). It comes up about 1 month after you have the infection. You don't know you have it and are asymptomatic. The enzyme studies are normal. The next thing that comes up is the bad guys: **E Ag (HBeAg) and HBV DNA, b/c these are only ones that are infective**. Then the first Ab comes up a lil after the DNA and E Ag, which is **core Ab IgM (Anti-HBc)** (this is expected b/c the first Ab against acute inflammation is IgM). The majority of people with Hep B recover (about 90%); those with HIV+ never recover and will have chronic cases b/c they have no immune response to knock it off. If you do recover the **first things to go away are E Ag (HBeAg) and HBV DNA.** The **last of the Ag's that goes away is surface Ag (HBsAg)**. So, surface Ag is the first to come and the last to leave (like a "house within a house" – look at the chart and will see that S Ag is the big house and E Ag and HBV DNA are the lil houses under big house). In other words, it is IMPOSSIBLE to be E Ag positive and S Ag negative (**E Ag and DNA come up after S Ag and leave before**).

Surface Ab doesn't come up until about 1 month after **S Ag** is gone, so there is this gap, which is a '**window'** with nothing elevated (only has one Ab there; S Ag, E Ag, HBV DNA are all gone, and S Ab not there yet). So, how do you know the pt HAD Hep B? Core IgM doesn't leave – it stays there and becomes IgG over time. So, the marker for that **window period** when all the bad guys are gone and surface Ab hasn't arrived yet, is **core Ab IgM** (which tells you that you HAD Hep B and are in the process of recovery). There is no way you are infected during this period – why? B/c E Ag and HBV DNA are not there. Therefore, you are not infective – it just means that you HAD Hep B and are in the process of recovering. **YOU ARE NOT INFECTIVE** – this is between the 5th and 6th month.

So, if you had Hep B, there should be 2 Ab's that you have: **core Ab IgG and surface Ab IgG**.

If you have been **vaccinated**, cannot have anything b/c you had yeast make surface Ag, which is what the vaccine consists of. The only bad Ab you can get from injecting surface Ag is Ab's against it. So, only Ab you will have if you were vaccinated is **Surface Ab**. NOT core Ab IgG b/c were not injected with that. Core Ab is not a protective Ab.

C. Chronic hepatitis is a definition: "**How long have you had surface Ag?" If it's more than 6 months**, you have chronic Hep B. So, are you infective or not? – are you an infective carrier or healthy carrier? You automatically know if you are an **infective chronic carrier if you have HBV DNA**. This means that you are a patient with chronic Hep B that is infective. So, you're a walking hazard, and your intimate contacts need to be immunized b/c the dz can be transmitted sexually to those people, or by IV (IVDA's). **If you are negative for E Ag and HBV DNA but are surface Ag positive, then it makes you a "healthy" carrier** (this does not mean you are healthy – you are still a chronic carrier of Hep B). If you are a healthy carrier, however, the chances of recovery are excellent b/c in about one year, S Ag will disappear and S Ab will come up. Will also have core Ab IgG at this time – this means that you have a good chance of total recovery. Also have **a good chance of recovery with E Ag b/c pt is a candidate for Alpha IFN therapy (DOC). Never give corticosteroids to any chronic viral infections.**

D. Review:

What we expect in acute hepatitis B (what would the markers be)? S Ag, E Ag, HBV DNA, and core IgM
What if the pt is in the window period? Core IgM
What if had Hep B, but have recovered from it? Core Ab IgG and surface Ab IgG
What if pt was vaccinated (what is the ONLY thing you should have)? Surface Ab IgG
What if you have at the end of 6 months S Ag, core IgM, with everything else neg? Healthy carrier
What if you have after 6 months surface Ag, E Ag, HBV DNA and core Ab IgM? Infective carrier.

V. Inflammatory Liver Disorders

A. Amebiasis: Entamoeba histolytica –

Organism is resistant to acid – swallow it and will not die in presence of acid. It ex-cysts in the cecum, within an alkaline environment. Has a chemical that can drill a hole through the mucosa, leading to flask shaped ulcers, and leads to **bloody diarrhea**. Unfortunately, b/c the cecum is drained by the portal vein, and is forming an ulcer, there is a chance that it can drill and hole, get into the portal vein tributary and get to the right lobe of the liver, where it will produce an abscess. It will start dissolving the liver – hence term anchovy paste abscess b/c it looks like anchovy paste (a brownish liquid). If it wants to, it can drill a hole through the right diaphragm, go to the lungs, and produce an effusion, and go anywhere it wants in the systemic circulation – brain. Rx – metronidazole. **Trophozoites** (slide) with red particles in them, which are RBC's. The only protozoa that can phagocytose is **Entamoeba histolytica (no other amoeba can phagocytose RBC's**) – this is a very characteristic finding. Metronidazole is used in the treatment of giardiasis, Entamoeba histolytica, vaginosis, c diff, and trichinosis.

B. Hydatid dz

1. Definitive vs. intermediate host

Definitive host = sexually active worms that have the ability to mate and lay eggs.
Intermediate host = only have the larval form; do not have sexually active adults.
These are the stages: Adult, egg, larva. Adult lays eggs, and the eggs develop into larva. If you have the larva form in you, it will stay there b/c that it's the end stage form. If you have the egg form, it will develop into a larva, but the larva can't go anywhere else. If you have the adult form in you, it will give an egg, which changes to larva. Larva form cannot go anywhere – it is the end stage form.

Sheep herder's dz (gonococcus vermicularis or unilicularis (?))

The sheep dog eats some sheep meat (there are larval forms in the sheep; therefore, the sheep is the intermediate host). Dog eats sheep, and has larva in the dog. The larva form develops into an adult within the dog, and the dog becomes the definitive host. The dog has sexually active worms inside it and the worms lay eggs within the dog. Dog is petted, gets eggs on their hand and into pts food, which is eaten. So, now, the pt has the egg, which develops in the larva (cannot go any farther b/c larval form is end stage), and the pt (human) becomes the intermediate host. So, the sheep is an intermediate host, the dog is the definitive host and the sheep herder is an intermediate host. Do not want to rupture these cysts, b/c if the fluid gets into the abdominal cavity, leads to anaphylactic shock.

C. T. solium (pig tapeworm)

You go to a barbecue and eat undercooked pork (larva in the pig meat, which is eaten). The larva develop into the adult form within the pt (so, there is a sexually active worm inside). So, pt becomes definitive host, while the pig was the intermediate host. Now you have a family member that is a definitive host (has sexually active worms inside them) – lets say this family member is making salad that night, and didn't wash their hands, so some of the eggs got into the salad. The pt eats the salad with the eggs in it. What is the egg going to form inside me? Larva. What is this called cystocerci. Do they form adults? No, stops there. Therefore, pt has cystocercosis. What are the **larvae going to do? They like the eye and the brain (where they form a cyst in the brain, calcify and lead to seizure activity for the rest of the pt's life)**. So, in this dz, the pt can have two forms of it. If pt ate the infected pig, they can be the definitive host. If you get the egg in your mouth, you become an intermediate host, and the egg can become larva, which will go on to cystocercosis. So the larvae form is the dangerous form in T. solium.

(MC S/E of cataracts = glucocorticoids)

VI. Nutmeg Liver

MCC = RHF

Thrombus in portal vein will NOT lead to nutmeg liver because portal vein is before emptying into the liver. Would you have ascites? Yes. Portal HTN? Yes. Varices? Yes. But is liver big and congested? No.

Thrombus in hepatic vein: is called Budd Chiari syndrome (MCC polycythemia Rubivera, 2nd MCC = birth control pills). Would you have a nutmeg liver? Yes – hepatic vein empties the liver. You get a huge liver, and is a surgical emergency and die 100% of the time if you don't have surgery.

So, these are pre/post hepatic thromboses **(Prehepatic = portal vein, posthepatic = hepatic vein).**

VII. Alcoholic liver dz

MC manifestation is fatty change (steatosis). B/c alcohol metabolism, have NADH's, acetate, and acetyl CoA. NADH's mess with pyruvate and convert it into lactate leading to fasting hypoglycemia, and metabolic acidosis. Acetyl CoA can make FA's and glycerol 3 phosphate and TG and fatty change, or can be converted into ketone bodies, which causes an increased anion gap: metabolic acidosis. Fatty change is reversible if the alcoholic stops drinking.

Alcoholic hepatitis is very bad; can have hepatic encephalopathy, ascites, etc. Alcoholic hep is diff from fatty change b/c there is fever, neutrophilic leukocytosis, very high AST>ALT, and gamma glutamyl transferase is up. You're big time sick and if you do not stop drinking you will die. It is very serious systemic dz. If pt hospitalized for alcoholic hep, is released and takes alcohol, they will die. See **Mallory bodies** (ubiquinated keratin microfilaments). Toxic compound that causes cirrhosis is acetaldehyde bound to a protein, not acetaldehyde by itself. Ito cell normally is the cell that stores Vit A. In an alcoholic the acetaldehyde protein complex stimulates the Ito cell to make fibrous tissue and collagen. The Ito cell, which is responsible for storing vit A, is now putting down collagen tissue and is responsible for causing fibrosis. Fibrous tissue is a big part of alcoholic tissue dz.

VIII. Cholestasis

Cholestasis = obstruction to bile flow, due to a stone in the CBD. Ex: have a cholesterol stone with a deep green colored liver. Bile is blocked, which has conj bilirubin in it and is backed up into the liver. The conj bilirubin will eventually reflux into the sinusoids, and leads to bilirubin in the urine and light color stools, with NO urobilinogen in the urine. The yellow urine is due to water soluble conj bilirubin in the urine. What enzymes are elevated? Alk phos and gamma glutamyl transferase. What is the mech for getting rid of cholesterol? Bile. So, you reflux cholesterol, bilirubin and bile salts (they are all recycled). Would it surprise you that they have hypercholesterolemia, too? No b/c it is recycled. The bile salts deposit in the skin, leading to itching.

2 other causes of cholestasis:

Bile duct radical, surrounded by fibrous tissue, bloody diarrhea with LLQ crampy pain, jaundice – what is the IBDz? **UC**

Common bile duct surrounded by fibrous tissue – dx? **Primary sclerosing cholangitis**. MCC primary sclerosing cholangitis = **UC**

What cancer can develop b/c it involves the bile duct? **Cholangiocarcinoma** (MCC in this country, in 3rd world countries, it is due to Clonorchis sinensis – Chinese liver fluke).

IX. Primary Biliary cirrhosis

50 y/o woman with generalized itching, find enlarged liver on PE, normal bilirubin (no jaundice), alk phos and gamma glutamyl transferase are huge (obstructive type of enzymes), transaminases are elevated – dx? Primary biliary cirrhosis, which is **an autoimmune dz that leads to granulomatous destruction of the bile ducts in the portal triad** – why doesn't she have jaundice? Let's say you have 1 million triads, have the dz and knock off 250,000 of them. Still have 75% that can handle the bilirubin load. 3 years later, only have 50% (500,000 destroyed). Still no jaundice, eventually, more knocked off and get jaundice way down the line. So, the reason why pt won't get jaundice is b/c pt has a reserve that can handle the bilirubin. Therefore, there is no reason to have jaundice early and it comes late. What is the Ab to order in this pt? **Anti-mitochondrial antibodies** (antimicrosomal = hashimoto's).

X. Drug effects

Birth control (OCP) and anabolic steroid have the same effect on the liver. **The OCP and anabolic steroids both produce intrahepatic cholestasis**. Ex. wt lifter (assume he'on steroids) develops jaundice, and viral serology is negative, high alk phos and gamma glutamyl = due to steroids (not hepatitis). One of the MCC's jaundice in pregnancy is b9 intrahepatic cholestasis. This is b/c of the estrogen during pregnancy, which produces intrahepatic cholestasis. Rx? Deliver baby (goes away after delivering baby). Lets say woman takes OCP and gets jaundice; when she become pregnant, she will develop jaundice, too b/c of the estrogen effect. So, intrahepatic cholestasis is a normal complication of OCP's and anabolic steroids. **Both of these drugs also predispose to a b9 liver tumor, called liver cell adenoma aka hepatic adenoma**. It has a nasty habit – **it likes to rupture, leading to intraperitoneal hemorrhage (which can kill you).** Example: wt lifter (assume he's on anabolic steroids) who is lifting and suddenly becomes hypotensive and collapses. Find abnormal liver/cavity – what is most likely cause? Ruptured liver cell adenoma b/c pt is on anabolic steroids. **So, OCP's and anabolic steroids have 2 similar effects: both can produce b9 intrahepatic cholestasis (which goes away if you stop the drug) and liver cell adenoma which is susceptible to rupture.** For women, if they are on birth control, then get off it to get pregnant – let's say they have a liver cell adenoma they did not know about (that developed with OCP use), then get pregnant, then get an intraperitoneal hemorrhage, and then what is d/d? Ruptured ectopic pregnancy or rupture intraperitoneal hemorrhage. Step 2: pregnant women have the tendency to have splenic artery aneurysm = rupture.

XI. Hemochromatosis

Example: **hyperpigmented pt – adult that is diffusely hyperpigmented and has diabetes (type I diabetic) = bronze diabetes = hemochromatosis = Fe overload, auto rec, reabsorb too much Fe.** Hemosiderosis is acquired iron overload by being an alcoholic. Iron supplements are contraindicated in the elderly b/c it will create hemosiderosis and have iron overload. Back to hemochromatosis: it's an autosomal recessive dz and what happens is that instead of reabsorbing 10-15% of iron from foods, you are absorbing 100% of iron. Target organ is the liver. Whenever Fe is absorbed into cells, it produces hydroxyl free radicals. So, the Fe doesn't damage anything, it's the free radicals (the hydroxyl free radicals –Fenton rxn). If you are damaging liver cells, will lead to fibrosis and cirrhosis. **They ALL have cirrhosis in Fe overload**, **either by hemosiderosis or hemochromatosis.** In cirrhosis, you see liver with brownish pigment, Prussian blue stain (to see Fe), and a VERY HIGH incidence of hepatocellular carcinoma. Can also go elsewhere–pancreas–therefore can have EXOcrine and ENDOcrine dysfunction, leading to malabsorption. Destruction of islet cells leads to very brittle type I diabetes. Also deposits in skin and lead to hyperpigmentation (bronze look). This is a combo of Fe depositing there and by stimulating melanocytes, therefore there is Fe pigmentation and melanin. Can go into joints and lead to polyarthritis, can go to pituitary, leading to hypopituitarism, can go to heart and produce restrictive cardiomyopathy. How you do **screen for iron overload? Serum ferritin. Serum Fe = high. Excess Fe stores, therefore decreased syn of transferrin. The TIBC is decreased. % sat is increased, serum ferritin is increased. Rx? Phlebotomy**. Do not use chelation therapy. They purposely make you Fe def. This dz is the next to the most common autosomal rec dz. **Hemosiderosis = ACQUIRED Fe overload – from alcohol.**

XII. Wilson's dz

Kayser Fleischer ring – brown ring around cornea. What is degeneration called? **Hepatolenticular degeneration**. **Pt with abnormal movement (chorea) disorder, dementia, and cirrhosis. Auto recessive. Defect in ridding Cu in bile; so, the Cu builds up and accumulates in the liver.** Very toxic. So, over a period of months to years, you go from chronic active hepatitis to cirrhosis. When you get a total Cu level, what does it include? Free Cu and binding protein for Cu. **The binding protein is called ceruloplasmin.** So, some Cu is attached to ceruloplasmin. So, the total Cu measured includes bound and free. 95% of a normal total Cu level is related to Cu attached to ceruloplasmin. So, most of the total Cu level is bound to ceruloplasmin, not the Cu that is free. **So, 95% in a normal person the total copper is Cu that is bound and inactive to ceruloplasmin.** So, is ceruloplasmin a protein? Yes. So, with cirrhosis, are you synthesizing ceruloplasmin? No. Therefore, there is a decrease of binding protein for Cu. So, **free cu increased. So, the total Cu level is decreased (b/c less ceruloplasmin), but the free Cu is increased (more unbound).** Rx? PCNamine (Cu binder). Lenticular nucleus messed up (caudate nucleus in HD)

XIII. Cirrhosis

Never focal, always diffuse. The bumps all over it are called regenerative nodules. Know that liver tissue is stable, therefore it's usually in the Go phase, and something has to stimulate it to go into the cell cycle to divide. The liver has an amazing regenerative capacity. Regeneration of liver cells are hepatocytes with no triad, no central vein, and no sinusoids. **Just wall to wall hepatocytes which are worthless**. Bumps are regenerative nodules, no triad; there are just wall to wall hepatocytes surrounded by fibrous tissue. Starts off as micronodular (less then 3 mm) and ends up macronodular (over 3 mm). So, have liver, but cells not working. How is a portal vein gonna be able to empty into the liver when there are no sinusoid/triads? It's a problem – portal HTN.

Complications: Pitting edema, ascites, esophageal varices, and metabolic probs (**cannot metabolize estrogen**, leads to gynecomastia). Cannot look at gynecomastia, have to feel it.

Side effects of problems of estrogen metabolism: Side note: There are 3 times in a lifetime where males can develop gynecomastia. 1. Newborns males have boobs b/c estrogen from mom; newborn girls with periods b/c estrogen from, then drop off, leads to bleeding. 2. Males also get boobs in teens (puberty). 3. Males also get boobs when they turn old b/c testosterone goes down and estrogen goes down, leading to gynecomastia – so, get boobs (gynecomastia) three times throughout life, and this is normal. Example: 13 y/o unilateral subalveolar mass, what is management? Leave it alone. Gynecomastia is not always bilateral, it is usually unilateral. Women have diff size breasts b/c each breast has different susceptibility to estrogen, progesterone, and prolactin. Men do not have breast tissue, therefore more likely that one will enlarge, the other will not. Palmer erythema (related to estrogen), spider angioma, vit def's, dupatron's contracture in palm (fibromatosis – increased fibrous tissue around the tendon sheaths, causing fingers to coil in, commonly assoc with alcoholics) – these are all estrogen abnormalities.

Complication of Ascites – adult with ascites – spontaneous peritonitis due to E coli. Child with nephrotic syndrome and get ascites and spontaneous peritonitis, what is the organism? Strep pneumoniae. So, adults with ascites and spontaneous peritonitis = E coli, while kid with ascites and spontaneous peritonitis = Strep pneumoniae.

XIV. Hepatocellular carcinoma

Nodularity; Cancer in hep vein tributary (ie). This cancer almost always develops in the background of cirrhosis. It is very rare for hepatocellular carcinoma to develop without cirrhosis present. Since alcohol is the MCC's cirrhosis, is it also the MCC of cancer? NO. **MCC's hepatocellular carcinoma = pigment cirrhosis: hemochromatosis; hepatitis B and C.** This cancer can produce ectopic hormones – EPO (leads to 2ndary polycythemia), insulin like GF (leads to hypoglycemia). Tumor marker: alpha feto protein. Example: pt with underlying cirrhosis, and is stable. But suddenly the pt begins to lose wt and ascites is getting worse. Do a peritoneal tap and it is hemorrhagic (do not assume it is traumatic from the needle, unless they say it). If there is blood in the acidic fluid it is pathologic bleeding. So, **this hx (wt loss, beginning to deteriorate suddenly, blood in acidic fluid). Know it is hepatocellular carcinoma, but will ask – what test do you do? Alpha feto protein.** Many tumors in liver = mets, prob from lung; lets say it's a nonsmoker, what is the primary cancer? Colon cancer, b/c he is a nonsmoker, therefore it won't be from a primary lung cancer, so the 2nd MCC is colon cancer and it doesn't have a high association with smoking.

Remember the 2nd most common cause: example of a small bowel obstruction, the MCC is adhesion from previous surgery, but if the pt did not have any surgeries then it's due to indirect inguinal hernia.

GALLBLADDER DZ

I. Ask about pathogenesis of stone – too much cholesterol in bile or too little bile salts. You will have a supersaturated stone with cholesterol – will get **cholesterol stone (MC stone).** Or, too little bile salts, both lead to stones. Anything that causes bile salt def (cirrhosis, obstruction, Cholestyramine, Crohn's dz) can lead to gallstones b/c too lil bile salts.

II. Pigment stones

Yellow stones (know they are not cholesterol stones) – 25 y/o female, RUQ crampy pain, fever, point tenderness, neutrophilic leukocytosis, stones revealed on ultrasound. CBC showed a mild normocytic anemia and a corrected reticulocyte ct of 8%. Splenomegaly on PE and family hx of splenectomy. **Dx? Congenital spherocytosis**; b/c she has been hemolyzing RBC's all her life, she puts a lot of bilirubin into conj bilirubin and therefore has supersaturated bile with bilirubin, and forms **Ca bilirubinate stones that are jet black**. Seen with ultrasound.

What is the **screening test of choice** for stones? Ultrasound. Screening test of choice for anything in the pancreas = CT – reason why is b/c bowel overlies pancreas and messes up ultrasound, therefore not as sensitive. Always put CT for pancreas; GB = ultrasound (can tell diameter of CBD to tell if there is a stone in it).

PANCREAS

I. Cystic Fibrosis

Cystic fibrosis – growth alteration b/c mucous in ducts of the pancreas. See **atrophy** b/c block lumen of exocrine ducts, and pressure goes back to the glands and that pressure atrophies the glands, **leading to malabsorption**. Can cystic fibrosis also lead to diabetes? Yes – b/c eventually fibrose off the islet cells, leading to **type I diabetes**, too.

Molecular bio: c'some 7 with 3 nucleotide deletion, and those 3 nucleotides codes for phenylalanine. So, you are **def of phenylalanine in the cystic fibrosis transmembrane regulator protein (CFTR).** So, all its missing is phenylalanine. Most things, after they are made in the ribosome in the RER, have posttranslational modifications in the Golgi apparatus, which is where the real defect is. **The real problem is when it gets to the Golgi apparatus – it's supposed to be modified and secreted to the cell surface. It ends up being degraded in the cell, and you end up having the CFTR.** So, the prob is in the Golgi apparatus – it screws it up, and never makes it to the surface, therefore has no function.

So, what does it do? **In the sweat glands, normally, it would reabsorb Na and Cl out of the sweat gland. B/c they are def in this, they are losing salt, which is the basis of the sweat test.** 3 y/o kid, failure to thrive, chronic diarrhea, resp infection, mom states that the baby taste's salty when she kisses the baby. This is the give away for CF, b/c they lose considerable salt and become salt depleted when they are overheated. Why are all the secretions so thick in the lungs, pancreas, and bile ducts? CFTR regulator – what does it do? – In **lungs**, need to have salt and secretions in the lumens of the resp tract to keep it viscous (to keep it nice and loose); if you are missing CFTR, Na is reabsorbed OUT of the secretions in the airway (therefore a lil dehydrated). And, chloride cannot be pumped into the lumen of the airway – so you are taking away the 2 imp ingredients with this pump: taking Na out and not putting Cl in. Therefore these secretions are thick like concrete. The same is true for secretions in the pancreas (Na pumped out and Cl not put in). **MCC death = pseudomonas aeruginosa. Fertility**: what is chance of male with cystic fibrosis having children? 0-5% (most are infertile); for females, they can get pregnant, but only have 30% chance of getting pregnant. The problem is that the cervical mucous is as thick as concrete and therefore the sperm cannot penetrate, and that is one of the reasons why they are infertile

II. Acute pancreatitis

MC due to alcohol; 2nd MCC = stone caught in accessory ducts of the pancreas. Amylase is elevated. Characteristic pain: **Epigastric pain with radiation into the back** (b/c it's a retroperitoneal organ).

Have an hx of acute pancreatitis; after 10 days, have a mass in the abdomen and they ask what do you do? CT – what is it? **Pancreatic pseudocyst** - a lot of fluid accumulates around an inflamed pancreas and forms a false capsule and has a potential to rupture (not good to have amylase in peritoneal cavity).

RUQ with dystrophic calcification (dots on x-ray); what do you think it is? **Pancreatitis.** Is it acute or chronic? **Chronic** b/c there are so many. Is this pt likely to be an alcoholic? Yes. What else would you expect – ie which of the following you expect? – Steatorrhea (one of the causes of malabsorption – need enzymes), or may say you have bile salt def (no, b/c pancreas has nothing to do with bile salts), hemorrhagic diathesis (yes, Vit K def related to malabsorption), etc…

Carcinoma of the head of the pancreas – MCC = smoker, 2nd MCC = chronic pancreatitis, painless jaundice (mainly conjugated bilirubin), light colored stools, palpable GB (Courvoisier's sign). C sign – permanently indenting the duodenum, do barium study, also a sign of pancreatic cancer.

Acute pancreatitis with inflammation. What will that do to peristalsis of that duodenum next to it? How does the bowel react to the presence of inflammation next to it? **It stops peristalsing** (not through the entire bowel, just there). If this is true, there would just be air in the area it doesn't peristalses – what is this called? **Sentinel sign** (sentinel is someone that is supposed to keep watch) – keep watch of what? Inflammation (so, **the sentinel sign keeps watch of inflammation**); the

classic area is the pancreas. This **is called localized ileus (ileus, by definition is lack of peristalsis). Whenever the bowel lacks peristalsis, will see air accumulate and will get distension.** What if you have a segment of bowel that is distended in the RLQ? Has to be inflammation, the cecum is in the RLQ and appendix could be the reason. So, appendicitis producing sentinel's sign.

CHAPTER 11: KIDNEY

I. Cast –
mold of whatever is going on in the nephron/tubule. It is a protein that is congealing around whatever is present in the tubule at that time; there is a mold made, and is passed into the urine and we can see it under the microscope. **This is imp b/c now we do not have to do a renal bx of the renal tubules b/c the cast will tell you what is going on**. Example: if you have glomerulonephritis (inflammation of the glomerulus), you have damaged the capillaries and get hematuria, so the RBC's are in the nephron and trapped in the cast, and will have an RBC cast that tells you there is a glomerulonephritis occurring. Example: With renal tubule necrosis, the tubules are sloughing off with coagulation necrosis. This will form a cast and is called renal tubular cast, and will tell you there is renal tubular necrosis. Example: man/woman with acute pyelonephritis with neutrophils invading the interstitium and the tubules, there are cast of neutrophils (WBC casts), telling me there is infection of the kidney. Example: spilling lipid in urine in nephrotic syndrome and form cast of fat and a fatty cast that you can see and polarize in the urine.

II. Urinalysis

The first thing that disappears in renal failure is the ability of the kidney to concentrate urine. This occurs before Cr/BUN think about increasing, or even having renal tubular casts. Example: taking urine in the morning and doing the specific gravity of the urine and seeing what it is. B/c, **specific gravity can tell you if it is concentrated or dilute urine.** If the specific gravity is greater than 1.023, this means that the pt is concentrating urine and that the kidneys are ABSOLUTELY NORMAL (this is a CHEAP test). Example: let's say I did a specific gravity of urine overnight and it is 1.010 – this is very hypotonic urine, and it means that the pt could not concentrate, and that the pt is in renal failure. (BUN/Cr will not help determine this). The urine that should be concentrated is from a pt that is sleeping overnight.

Hyaline cast – cast of a protein; mostly b9/harmless (all other casts have pathological significance).

III. Crystals:
Uric acid crystal – looks like a star; pH of the urine has to be acidic to form a uric acid crystal. Pt with gout – want to stop crystals from forming, and you know they form in low pH, what do you want to do with the urine? Alkalinize it. How can you do that? Carbonic Anhidrase inhibitor (acetazolamide). By blocking bicarbonate reclamation will alkalinize the urine, and prevent stones from forming. So, simple manipulation of the pH can prevent urate nephropathy.
Calcium Oxalate crystal – look like the back of an envelope; why is this imp to know? Example: street person comes in, stupurous, has increased anion gap metabolic acidosis. Do a urinalysis, and see bunch of calcium oxalate stones – what did he drink? Ethylene glycol. What is the **MC stone we pass? Ca oxalate**. So if you have a Ca Oxalate stone, you will have crystals associated with it.
Horse kidney –joined at their lower poles. Will ask what is restricting the movement of the kidney? IMA – it traps the kidney.

IV. Cystic dz of the kidney –

A. Infantile polycystic kidney dz,
which is auto recessive; therefore it is present at birth. Do you think this baby is urinating? No, therefore has oligohydramnios (decreased amniotic fluid). So, baby is in an amniotic sac, with hardly any amniotic fluid around it, and therefore have malformation due to pressure. Look at the nose and ears; this is **called Potters face, which is a sign of oligohydramnios in polycystic kidney dz: flattened nose, low-set ears, and recessed chin)**. This child wasn't able to breath, and when it tried to breath, it couldn't; the lungs are hypoplastic – they never fully developed b/c the kid couldn't fill them up. These cysts are also seen in the pancreas, the liver and just incompatible with life.

B. Adult polycystic kidney disease: APKDz

Some autosomal dominant dz show Penetrance – have the abnormality when they look for it on the gene, but do not express it. (so you have the genetic abnormality, but have never expressed it in your life). That's the good news – the bad news is that you can transmit it to your child, therefore it is difficult to recognize on the pedigree. Example of penetrance: familial polyposis = 100% penetrance – if you have the gene, you have the dz. Example of incomplete penetrance: marfan – abnormality on c'some 15, normal parents, they do not express the gene, but passed on to child (this is incomplete penetrance). APKDz is another example of incomplete penetrance.

So, APKDz is an autosomal dominant dz that is not present at birth b/c AD dz have **delayed manifestations**. See cysts by 10-12 years of age, always get **HTN which will then predisposes 2 types of bleeds**: (1) **Charcot-Bouchard aneurysms** (a blood clot) and (2) see blood all over the brain, due to subarachnoid hemorrhage, therefore the blood is due to **rupture berry aneurysm**. **Subarachnoid hemorrhage** = "worst headache of my life", blood in subarachnoid space.

MVP (mitral valve prolapse): Example: hx of HTN, abnormality of ultrasound in the renal pelvis, and had click murmur (therefore MVP) – dx? APKDz. There is a high assoc of MVP with this.

Diverticulosis also has a high incidence. Example: pt with HTN, abnormality on ultrasound in renal area, lost 600 mls of blood all of a sudden, leading to hematochezia (MCC hematochezia = diverticulosis).

V. Glomerular stuff

A. Nomenclature of the Kidney dz:

"-itis" = type III HPY – therefore it's an immunologic dz (glomerulonephritis)

Example: Lipoid nephrosis – does that have type III? No
Example: Focal segmental glomerular sclerosis? No
Example: Diabetic glomerulosclerosis? No.
Example: IgA glomerulonephritis, diffuse membranous glomerulonephritis? Yes

When we say 'diffuse', this means that EVERY glomerulus has something wrong with it on renal bx. What is 'focal'? not all glomeruli involved.
What if dz is focal and dz in the glomerulus is focal? Have a problem – this is called Focal Segmental Glomerulus
What does proliferative mean? Have lots of them. So, you have many nuclei. If all the glomeruli have a lot of nuclei, this is diffuse proliferative glomerulonephritis
If you just see thick membranes, its membranous glomerulonephritis
If you see both increased cell and thickened membrane? Membranoproliferative glomerulonephritis

B. Anatomy/schematic

The order is: blood, endothelial cells of the capillaries, underneath there is a BM, and then the visceral epithelial cells (looks like feet = podocytes; which have spaces in between them called slit pores) that line the bowman's capsule. Who **makes/synthesizes the GBM? Visceral epithelial cells (podocytes)**. What keeps Albumin out of the urine normally? Strong negative charge of the BM. Who is responsible for strong "-"of the BM? A **GAG called heparan sulfate, which has a strong neg charge.** If we immunologically damage the visceral epithelial cell, what do we automatically also damage? The BM, which means you're gonna spill a lot of protein in the urine, which means you potentially can have nephrotic syndrome if you spill >3.5 grams in 24 hrs).

C. Test on Renal Bx

Stains – routine H & E hemotoxylin stains, silver stains. **Immunofluorescent** stain – pattern can be linear or granular (aka lumpy bumpy), which are the only 2 patterns. These patterns are immune complexes or patterns/Ab's that they are detecting. Take bx, and have Ab's with a fluorescent tag on them. Ie want to see IgA in the glomerulus and have anti IgA Ab's with a fluorescent tag – if there are any, it will attach to it and make a fluorescent tag. There are also tags for IgG, C3, fibrinogen – so can get an idea of what's in the glomerulus and an idea of what pattern it is in (ie linear vs. lumpy bumpy granular pattern). It doesn't tell us where these things are, it just tells us that they are there. What tells us where immune deposits and immune complexes are located are **EM**. So, we do stains, fluorescence, and EM. How can we tell that the podocytes are fused? Can only tell by EM b/c its so small.

VI. Difference between Ab recognition vs. immune complexes

Detect with Ab which have 2 Ag recognition sites on the Ab. **Goodpasture syndrome is an IgG anti BM Ab's.** So, they get in the blood they get into the glomerular capillary and are directed against the BM. Wherever there was a spot on the BM you will see an IgG Ab. There wouldn't be one spot on the BM without IgG. So, what if we do a fluorescent tag for IgG overlying the glomerulus – what would you see? Would see outlines of all the BM's of the entire glomerulus. It is linear.
MCC linear pattern on immunufluorescence = Goodpastures.

Immune complexes – Ag with Ab attached and is circulating in the bloodstream, hence **Ag-Ab complex** – ie **lupus = immune complex dz: Ag = DNA, Ab = anti-DNA** – they attach to e/o and float around and deposit in certain places; in this case it will deposit in the glomerular capillary; **type III HPY (b/c immune complex).** B/c they are immune complexes, they are larger than individual Ab's b/c they are Ag and Ab attached together – therefore they are bigger, have diff solubilities, have diff charges – they won't fit nice and neat in the glomerulus. So, depending on the size and charge will depend on where they locate themselves. Ie if too big, will locate under the endothelial nucleus. So, this would be called a subendothelial membrane – they are so big that they fit under a podocyte (they cannot get through the BM). Lupus is like this, too – they cannot get passed the BM and hangout under the endothelial cells. **Post strep GM – bacterial Ag with Ab against (immune complex), which is very small, and very soluble. They can go all the way past the BM and deposit under the epithelial side – this is a subepithelial deposit**. So, how do you find out where the deposits are? Cannot see with immunufluorescence, but will be able to see with EM b/c they are electron dense (meaning that they increase the density wherever they are). So, immune complexes have diff solubilities, diff charges, and randomly go underneath the endothelium, under the subepithelial surface; they will not have a nice smooth linear pattern like anti basement membrane Ab's. Example: **dz that isn't linear (so its not Goodpastures) – it could be any immune complex dz – lupus, post strep, IgA glomerulonephritis.** Can get a hint of what the dz is, depending on what is in there – ie what is the **only glomerular nephritis that you can only dx with immunufluorescence? IgA glomerulonephritis**. B/c if you are gonna call it glomerular nephritis, this means that there is no IgG in there, but IgA. So, the only way to accurately dx IgA glomerulonephritis is to prove that it is IgA and nothing else. **Granular/lumpy bumpy pattern – when you see this, what does it mean? Immunocomplex type III dz; remember anti BM's and anti BM Ab's against the BM is not a type III, but a type II. Whereas, immune complexes are type III.**

VII. Nephritic vs. Nephrotic Glomerulonephritis

There are 2 types of glomerulonephritis: nephritic or nephrotic (cannot be both at same time; however, it can start out nephritic and become nephrotic)

A. Nephritic Syndrome:

Has unique cast that is red, and looks like biconcave disk – **RBC casts** (unique to nephritic dz's); b/c you have inflammation you will spill protein, but not greater than 3.5 grams in a 24 hr period (b/c if it did, it would be nephrotic) – so it is mild to moderate proteinuria. You are spilling protein, but not to the same level as nephrotic, therefore **will not** have pitting edema, ascites, etc… If are inflaming the glomerulus, will you have oliguria? Yes – all the glomerular capillaries have swollen up, GFR would decrease, and this would lead to oliguria. Are you decreasing the absorption or not filtering Na? yes. So does the Na build up? Yes – therefore run the risk of HTN. **So, classically what you see in nephritic dz's is hematuria, RBC's casts, oliguria, HTN, and mild/moderate proteinuria (this is the definition)**

B. Nephrotic Syndrome:

Has a different cast (**fatty cast**), **have greater than 3.5 grams of protein in a 24 hr urine sample. Will also have pitting edema.**

So, if you started out nephritic (RBC casts, mild/moderate proteinuria) and all of a sudden you start seeing pitting edema, start seeing over 3.5 grams of protein in the urine over 24 hrs, and fatty casts – then nephritic has become nephrotic.

VIII. Nephritic Syndromes

A. Proliferative Glomerulonephritis
All the glomeruli are diffuse, too many nuclei

B. Post strep GN

Example: scarlet fever 2 weeks ago, presents with hematuria, RBC casts, mild to moderate proteinuria, HP, periorbital puffiness. EM: lumen of capillary, bump on lumen is endothelial cell, underneath is BM (grayish), and epithelial cells under. Has boulders that are denser than the normal glomerular BM – these are immune complexes. In this case, it the bacteria is the Ag-Ab immune complexes. Which side are they closer to? Closer to epithelial side, therefore they are subepithelial deposits – hence post strep GMN.

C. Lupus GN

Example: 35 y/o female with "+" serum ANA with a rim pattern (meaning you have anti DNA Ab's present). **Lupus almost always involves the kidney.** There are 6 types, and the **important one to know is type IV**, which is a **diffuse proliferative glomerulonephritis,** which is the MC overall one seen in Lupus. Has many nuclei, therefore proliferative; has wire loops. (orient to EM) deposits in BM are anti DNA deposits. Would you agree that they are in the endothelial cell? Yes. So what is this location? Subendothelial deposits. Podocytes with slit pores in btwn are not fused b/c if they were, it would be nephrotic syndrome. Also see lumen, endothelial cells and deposits. Immune complexes are so big they can't get through the BM.

D. Crescentic GN

Glomerulus surrounded by proliferating cells that are parietal cells b/c not in the glomerulus, and has crescent shape, hence the name crescentic glomerular nephritis. This is the **WORST glomerular nephritis to have b/c in 3 months; pts will go into acute renal failure and die unless pt is on dialysis**. Many dz's have a crescentic glomerulonephritis, but the only one I need to know is **Goodpastures; this is a NEPHRITIC dz; this dz has crescentic glomerulonephritis on bx (therefore a BAD dx).**

IX. Nephrotic Syndromes:

Pt with casts (fatty casts), polarized specimen with maltese cross – this is cholesterol in the urine. When cholesterol is polarized, it looks like a maltese cross. **These fatty casts are pathonognomic for nephrotic syndrome.** Greater than 3. 5 grams protein for 24 hrs, fatty casts in the urine, ascites, pitting edema, risk of spontaneous peritonitis if you are a child. Organism? Strep pneumonia in kids, E coli in adults.

A. Lipoid nephrosis aka Minimal Change Dz:
Example: EM of 8 y/o boy that had an URI one week ago, and now is all swollen, has pitting edema throughout body (anasarca) and ascites, normo-tensive, no HTN; saw nothing on renal bx; but then did a EM – see RBC in glomerular capillary lumen. So, see endothelial cells, see BM (without electron dense deposits), podocytes (fused) – **fusion of podocytes is ALWAYS seen in any cause of nephrotic syndrome.** Maltese crosses in urine. Dx? **Lipoid nephrosis.** All pt with nephrotic syndrome have hypercholesteremia. Since they have glomerular dz and some of the cholesterol can get into the urine, some can form casts in the urine. Aka minimal change dz. Why is this happening? Has lost neg charge in GBM, therefore albumin can get through. These pts have a select proteinuria – the only protein in these pt's urine is albumin, and it is greater than 3.5 grams per 24 hrs. Rx – corticosteroids (usually goes away in 1 year never to come back again). The **MCC nephrotic syndrome in kids.**

B. Focal Segmental Glomerulosclerosis

Example: **pt that is HIV "+",** pitting edema – therefore look at urine and note that is greater than 3.5 grams over 24 hrs. Has fatty casts in urine and has HTN. Do bx, and already know what you are gonna see b/c it the **MCC nephrotic syndrome in AIDs pt**. On bx, some of the glomeruli are abnormal and others are normal, but only a part of the glomerulus is messed up. Therefore, it is focal segmental. B/c the renal bx with EM and immunofluorence did NOT show deposits, therefore it's glomerulosclerosis. So, this is called focal segmental glomerulosclerosis. This is **the MC lesion in AIDs pts and IVDA's**. Next to rapidly progressive crecentric glomerulonephritis, this is the next worse glomerular dz.

C. Diffuse membranous glomerulonephritis

Example: adult with pitting edema, over 3.5 gram per 24 yrs, fatty casts. Do a bx and see not many 'dots' therefore not a proliferative dz. However the BM is thicker. Dx? **Diffuse membranous glomerulonephritis = MCC nephrotic syndrome in adults**. This is subepithelial deposit. **Epimembranous spikes – spike like lesion on the outside of GBM seen with silver stain** = diffuse membranous glomerulonephritis (only one that looks like that).

Many things can cause this (drugs, cancer, nothing, infections); some the drugs include NSAIDs, Hep B, captopril (king of treatment of diabetic nephropathy and heart failure), malaria, syphilis, colon cancer (immune complex is anti-CEA Ab's). Eventually leads to renal failure and can die unless you get a renal transplant

D. Type I and II Membranoproliferative Glomerulonephritis
(ends in "-itis" therefore it is type III HPY – immune complex!)

1. Type I has a relationship with Hep C – how do you remember? Membranous = Hep B (also remember the vasculitis – Polyarteritis Nodosa), Membranoproliferative = Hep C (also remember cryoglobinemia).
   So, **type I is a subendothelial deposit that produces nephrotic syndrome**.

2. Type II is less common, and has an Auto Ab against C3, called C3 nephritic factor. It causes C3 convertase to become overactive and is constantly breaking complement down. So, the lowest complement levels you will see is in type II glomerular nephritis – this is called dense deposit dz b/c the entire BM an immune complex.

tram tracks – mesangial cell (structural component of the glomerular capillary) – the mesangial cell is extending itself between the BM and the endothelial cell, making it look like a tram track; so, it's a mesangial process btwn the BM and endothelial cell – tram track Membranoproliferative dz

E. Diabetic Glomerulosclerosis

Classic sign: big round balls on H and E stain. When there is excess red in the cell, think **hyaline arteriolosclerosis**; this is a small vessel dz of diabetes and HTN. The very first vessel that is hyalinized is the efferent arteriole. Let's say it is hyalinized. So, b/c the lumen is narrow in the efferent arteriole, the GFR will increase. So, what is the Cr clearance? Increased. So, in early diabetic nephropathy, there is an **increased GFR and Cr clearance**. Why? B/c the efferent arteriole is hyalinized and obstructed. Is this bad? Yes – as a result the glomerulus will take a pounding for the next ten years – leading injury called hyperfiltration damage. What is the process where glucose attaches to an aa in a protein)? Nonenzymatic glycosylation. Lets say this is also going on b/c the pt is not watching himself too well, therefore **we are nonenzymatically glycosylating the GBM**. What would happen when you glycosylate a BM – what is it permeable to? Protein. So, have all this pressure on the glomerular capillary b/c the efferent arteriole and also nonenzymatically glycosylating the GBM, so its permeable to protein. So, tons of protein going into the urine. When you initially start seeing it, is called **microalbuminuria.** Will the standard dipstick for protein detect that? No. There are special dipsticks that are available to detect this – called microalbuminuria dipsticks. So, what does it mean when your diabetic pt has a "+" dipstick for microalbuminuria? **Have to give pt ACE inhibitor** b/c you want to stop progression of this. How will it work? Afferent arteriole is controlled by PGE2; the efferent arteriole is controlled by AT II (which constricts it). So, when you give an ACE inhibitor, what happens to AT II level? It decreases. So, b/c AT II decreased, you take off the vasoconstrictive element it has on it. Even though it was hyalinized, it will open then lumen, taking pressure off the glomerulus, and decrease the filtration rate. So, the constant pounding on the glomerulus is taken away. Need to get glycosylated Hb (HbA1c) under 6%, but the ACE inhibitor cant do it all, so must have perfect glycemic control, otherwise will go into chronic renal dz. If they can do this, the ACE **inhibitor will prevent the dz. The ACE inhibitor also helps HTN**. Pink stuff is type IV collagen in the mesangium. It builds up, ez to see big circle (big balls/golf balls/Christmas balls) aka Kimmelstiel-Wilson nodules – this is nodular glomerular sclerosis.

F. Amyloid

Like to deposit in the kidneys. Its a special protein. **Stain with Congo red, and after you polarize it, it has a (granny smith) apple green birefringence**. Light green is what the amyloid is supposed to look like when you polarize it with a Congo Red stain. Amyloid and diabetic glomerular sclerosis are nephrotic syndromes.

G. Summary nephrotic:

Lipoid sclerosis = MCC nephrotic in kids
Focal segmental glomerulosclerosis = IVDA's, AIDs
Diffuse Membranous glomerulonephritis = MC in adults
Type I and II Membranoproliferative glomerulonephritis = type I with hep C relationship, type II with autoAb against C3 (lowest complement levels seen)
Diabetic nephropathy
Amyloid

X. Combo of Nephritic and Nephrotic Syndrome

A. IgA Glomerulonephritis (burger's dz)

IgA glomerulonephritis is a VARIANT of Henoch Schonlein purpura b/c it is an immune complex dz, anti IgA Abs (so is Henoch Schonlein – palpable purpura in buttocks of legs, polyarthritis, GI bleed, hematuria (RBC casts))

On immunofluorence, everything shows up in the mesangium. Example: in **kids**, presents with episodes of gross hematuria, goes away, comes back a few years later; in **adults**, presents with episodic bout of microscopic hematuria. So, have a lil hematuria, goes away, and comes again. Lil proteinuria, no HTN. When it starts getting worse (10 years later), that's when it will be bad (so its not b9). **It is the MC of all glomerulonephritis and is type III HPY.**

XI. BUN/Cr – Prerenal Azotemia

Can separate prerenal azotemia vs. renal failure
BUN = blood urea nitrogen and **Cr** = end product of creatine metabolism. Urea can be filtered and reabsorbed in the prox tubule (so its not a perfect clearance substance); Cr is only filtered in the kidney and is reabsorbed or secreted. (Inulin clearance is better). **If you take the normal BUN level (10), and normal Cr level (1mg/dL), will have the normal ratio of 10:1.**

When you have **prerenal azotemia**, there is an increase in BUN (this is what azotemia means). Pre = before, therefore there is something wrong 'before' the kidney – in other words, there is nothing wrong with the kidney, but the CO is decreased (from any cause - ie CHF, MI, hypovolemia, cardiomyopathy, etc). **Anything that decreases CO will lead to prerenal azotemia b/c the GFR will decrease.** If you have less renal blood flow, you will filter less and the GFR will decrease. So, when it decreases, it gives the prox tubule more time to reabsorb little bit more urea than normal. So, there is increase prox tubule reabsorption of urea. What about Cr? We know that it is not reabsorbed, but you do have to get rid of it through the kidneys. So, even though it is not reabsorbed, the GFR is decreased, there is a back up of Cr and will not be able to clear it as fast. Therefore, there will be an increase in serum Cr. There is little more of an increase is urea b/c it is being reabsorbed than with Cr. So, there is a disproportionate increase of BUN/Cr. All you have to remember is 15:1. So, **greater than a 15:1 BUN/Cr = prerenal azotemia.**

Example: the pt has CHF, BUN is 80 and Cr is 2. So, both are elevated, but the BUN/Cr ratio is 40:1, indicating that it is prerenal azotemia, and the pt does NOT have ATN.

Lets say pt truly has **renal failure** – **oliguria, renal tubular casts, acute renal failure**. This **will affect the BUN/Cr EQUALLY** b/c something is wrong with the kidney, therefore the same effect on the BUN is the same on Cr. For both, urea has to be filtered out of the kidney and it has failed – both increased proportionate to each other b/c both have the same problem and kidney is screwed up; cannot get rid of urea, can't get rid of creatinine, so they increase in proportion to each other b/c the urea is not being reabsorbed anymore b/c the kidney is in shock. Example: BUN = 80, Cr = 8, therefore the BUN/Cr ratio is 10:1, and pt is in renal failure. So, even though the 10:1 is maintained, still have renal failure b/c it has increased so much. **If the ratio is 15:1, it is prerenal azotemia; if it is increased and still 10:1, its renal failure.**

XII. Acute Renal Failure

A. Acute Tubular Necrosis:

MCC = Ischemic Acute Tubular Necrosis – this is what you worry about the most when the **CO decreases, pt develops oliguria**. When a pt's CO decreases, and have prerenal azotemia, you have a decrease in GFR, which is another cause of the oliguria. So, decrease in CO and oliguria is VERY BAD, and start to see BUN/Cr go up – need to know if its prerenal azotemia, or renal azotemia – to distinguish, get a BUN/Cr. It its 15:1, its still prerenal. But it can progress to renal failure – ischemic acute tubular necrosis. **MCC ischemic acute tubular necrosis = not treating prerenal azotemia. So, ischemic ATN is the worst the get and the BUN/Cr ratio will be normal, but increased in values (ie 80/8)**

Coagulation necrosis: Sloughs off, blocks lumen and contributes to oliguria, and see casts in the urine. The casts are renal tubule casts. So, **combo of renal tubular casts, oliguria, BUN/Cr of 10:1 = ATN**.

Why does this have such a bad prognosis? When pt has ischemic necrosis, not only are you killing the tubular cells, but the BM also gets damaged, so the structural integrity of the tubule is being taken away, which is not good. When you have liver damage, and damage liver cells, and the cells regenerate, the cells are not regenerating sinusoids and triads, but only themselves. If the BM isn't there, and the patient has recovered from ATN or is in the process of doing that, can you regenerate a tubular cell without a BM? No. So, the more necrosis, the more BM are destroyed, the worse the prognosis b/c cannot regenerate and cannot get back normal function. This is why it is such a bad dz. **There are 2 parts of the nephron that are most susceptible to ischemia – what are they? Straight portion of the prox tubule and thick ascending limb of the medullary segment (where the Na/K/2 Cl co-transport pump is).** These two parts undergo coagulation necrosis and sloughing off. So, will see these fall off in the proximal tubule and also in the thick ascending limb of the medullary segment.

B. Nephrotoxic ATN:

Gentamycin, AG's. If they are nephrotoxic, what is the first thing they will filtered from the glomerulus? Proximal tubule. So, **nephrotoxic tubular necrosis related to drugs involves the proximal tubule**. And, the BM remains intact;

therefore the prognosis of nephrotoxicity is way better for 2 reasons: only affecting the proximal tubules and not affecting the BM. The **MCC nephrotoxicity = AG's (2nd MCC = intravenous pyelograms)**. What is GFR in 80 y/o? It is decreased – the Cr is 4 mls/min; which is normal in older people. Cr clearance decreases along with GFR as they get older; so, if you are giving a drug without nephrotoxicity the same dose as a young person, you will be killing the older person. This is obviously occurring b/c AG's are the MCC ATN and doctors are not decreasing the dose of the drug to decrease nephrotoxicity.

XIV. Tubular and Interstitial Disorders of the Kidney

A. Acute Pyelonephritis:

How do you separate it from a lower UTI? Very easily. Pyelonephritis is seen more in women b/c of their short urethra. **Acute pyelonephritis is a systemic infection and is an infection of the kidney proper.** How does it get into the kidney? At the uretovesicular junc, the muscle squeezes so there is no reflux of urine from the bladder into the ureter. This is true in normal people. However, not all people have a normal vesicoureteral junction. So, what happens in a pt with a bladder infection and the junction is incompetent, it leads to **vesicouretal reflux**, and the infected urine refluxes up into ureters, and leads to ascending infection that goes all the way up to the kidneys. So, they will ask you, **"what is the mech of ALL UTI's?" (urethritis, cystitis, pelvitis, or pyelonephritis) – due to ascending infection from the beginning of the urethra.** Every woman (has nothing to do with cleanliness) has the same E coli serotype in her stool at the introutus of the urethra and her vagina. So, with trauma or certain serotypes of E coli, it can ascend up the urethra into the bladder. If the pt has an incompetent uretovesicular junc, up the ureters into the kidneys. So, all UTI's are ascending from the beginning of the urethra on up.

With **acute cholecystitis, have painful urination (dysuria), increased frequency, suprapubic pain, NO fever, no flank pain, NO WBC casts (with neutrophils in them) – why? B/c the WBC casts develop in the renal tubules; they do not develop in the ureter or the bladder; they develop in the kidney in the tubule.**
So, fever, flank pain, and WBC casts = ACUTE PYELONEPHRITIS. So, its an **ascending infection due to incompetent vesicouretal junc**. This usually shows up in newborn girls (and will be a prob for rest of lives).

Example: kidney with white spots = abscesses seen in pyelonephritis. If you have constant acute attacks of pyelonephritis, can become chronic. Therefore have increased risk of HTN and renal failure.

B. Chronic Pyelonephritis

Example: scarred kidney (on cortex), blunting of the calyces (occurs under the scar), seen on intravenous pyelograms – dx? CHRONIC pyelonephritis. So, **blunting of the calyces = CHRONIC pyelonephritis.**

C. Acute Drug-induced interstitial nephritis

Can **drugs** produce a nephritis involving the interstitium and tubules? Yes – can be acute and chronic and ez to diagnose. Why? B/c will have fever, and develop a rash. **Fever + Rash** (obviously due to drug, b/c started after taking the drug), **oliguria**, **eosinophiliuria** (**eosinophils in the urine – pathognomonic**). This is called **acute drug induced interstitial nephritis**. This is more and more common, and is a very common cause of chronic renal failure. So, put pt on drug, get fever, rash, oliguria = discard/stop drug (never give again) – this is a combo of type I and IV HPY.

Analgesic nephropathy
Example: discoloration in renal medulla, pale infarct, renal papilla sloughed off – ringed signed; and on pyelograms there will be nothing there just an empty space. Dx? **Analgesic nephropathy**. This **from combo of acetaminophen and aspirin over a long period of time. Acetaminophen** is producing free radicals. B/c of the poor circulation in the medulla, there is free radical damage on the tubular cells of the medulla. **Aspirin** will block PGE2 (a vasodilator), therefore angiotensin II (a vasoconstrictor) is in charge of the renal blood flow. Vasoconstrictor of the efferent arteriole. The peritubular capillaries arise from the efferent arteriole. So, with vasoconstriction of the efferent arteriole, pt is affecting peritubular capillaries going around collecting tubules and renal medulla. So, is that producing ischemia? Yes. So, pt **has free radical damage and ischemia leading to analgesic nephropathy**. This is why the renal papilla necroses, sloughs off, and leads to **renal papillary necrosis**. So, **aspirin and acetaminophen toxicity. Diabetic nephropathy (b/c causes ischemia), acute pyelonephritis (b/c abscess formation), SCDz and trait, can all lead to analgesic nephropathy.**

XV. Chronic renal Failure

Definition: Pt has BUN/Cr ratio 10:1 for more than 3 months. If both kidneys failed: will not be able to excrete the things we normally get rid of (so those **things will build up** – ie salt); EPO production will decrease, leading to **normocytic anemia with a corrected reticulocyte ct of less than 2%**. Will not be able to get rid of organic acids, leading to **metabolic acidosis**, increased anion gap. With metabolic acidosis, bones try to buffer all the acid. B/c the bones are buffering the extra H ion, bone dz can develop, leading to **osteoporosis**. The prox tubules are messed up in the renal tubules, and 1-alpha hydroxylase will decrease (this responsible is hydroxylating Vit D); so, with renal failure will also have **hypovitaminosis D** (vit D def). This means that there will be **hypocalcemia** and **hypophosphatemia**, leading to **osteomalacia**. So, there are two bone dz's – osteoporosis (b/c buffering and wearing away bone matrix) and osteomalacia; also, PTH is reacting to chronic hypocalcemia and leads to **secondary hyperparathyroidism** (also affects the bone). The bun/Cr ratio is 80/8. So, if you know normal renal func you know what happens.

XVI. Other Problems related to kidneys:

Example: pt has essential HTN over 10 yrs, and pt is not compliant with medication – kidney with cobblestone appearance = **nephrosclerosis**. Underlying dz causing it: hyaline arteriolosclerosis b/c there is decreased blood flow, tubular atrophy, glomeruli are fibrosing off, renal function is going down, and leads to renal failure.

Example: lets say the pt wakes up with a big headache and blurry vision. Pt is getting dizzy, goes to dr, and pressure is 240/140, in the retina, dude has papilloedema with flame hemorrhages and hard and soft exudates, grade 4 hypertensive retinopathy, BUN/Cr are 80/8 – **dx? Malignant HTN** (aka flea bitten kidney – petechia visible on surface of kidney – see vessel changes ie hyperplastic arteriolosclerosis, and the BV's are rupturing, leading to petechial lesions on the cortex – called flea bitten kidney). This is all you have to know. They can also ask **Rx: IV nitroprusside to get the BP down**. So, they have CNS edema with papilloedema, and if the BP isn't lowered, they are gonna die.

Example: kidney with abnormal areas that are pale and depressed – so, if you take a section through one of these, and you see an irregular irregular pulse, will see pale infarction with coagulation necrosis b/c what you are looking at are **infarcts**. Irregular irregular pulse is from atrial fib, and atrial fib is most dangerous for **embolization**. So, these infarcts are from **multiple emboli**, leading to multiple pale infarcts of the kidney. This is NOT pyelonephritis b/c has microabcesses

Example: atrophy due to dilatation of the renal pelvis, leading to **hydronephrosis**.
So, if you have hydronephrosis and increased pressure pressing on the cortex and medulla, what happens to that? **Get ischemia and atrophy – which is called compression atrophy.** This is very similar to cystic fibrosis ducts filled with mucous – the pressure is impacted back to the glands, and they undergo compression atrophy. Cortex and medulla are very thin, along with very dilated renal pelvices. **MCC = stone**

Example: **staghorn calculus – urine pH is alkaline and smells like ammonia; therefore, there must be a urease producer, and this is Proteus. B/c it is a urease producer,** they break urea down to ammonia, and get an alkaline pH. This is why a **staghorn calculus is Mg ammonium phosphate**, and only develops in infections in pts that have urease producers. E coli are not urease producer and proteus species are and they predispose to these stones. Do not pass these stones (too big), therefore need to extract these (surgery). So, **urease producer, alkaline pH, ammonia smell to the urine.**

XVII. Tumors of the kidney

If you see a mass in a kidney, and its an adult, it is a **renal adenocarcinoma**. If it's a kid, it's a Wilm's tumor. So, if you see a mass in the kidney, its prob not mets (b/c not many things go there), its not b9, pick cancer.

So, adult = renal adenocarcinoma, kid = Wilms tumor; they derived from the proximal tubule and the MCC = smoking; they make lot of ectopic hormones: EPO, parathyroid hormone (leads to hypercalcemia), invade the renal vein.
Cells are clear, full of glycogen.

Example: flank mass in child, HTN = Wilms tumor; HTN occurs b/c it's making renin; usually unilateral. Histology: cancer where pt is duplicating embryogenesis of a kidney – everything is primitive. Can see rhabdomyblasts; likes to mets to lung
If **AD, from c'some 11, and have 2 classic findings: aniridia (absent iris), and hemihypertrophy of an extremity (one extremity is bigger than another) – this is a sign that the wilms tumor has a genetic basis.**

Papillary lesion in the bladder = transitional cell carcinoma (TCC)
What is the MCC transitional cell carcinoma of the bladder? Smoking
Dye use to look? Aniline dye; what is chemotherapy agent used to Rx Wegener's? Cyclophosphamide. What are the complications of Cyclophosphamide? Hemorrhagic cystitis and transitional cell carcinoma.
How do you prevent this? Mesna.

XVIII. Urinary Tract Infection

MC urine abnormality seen in the lab

Example: arrow pointing to neutrophils in urine; RBC's in it, too, bacteria – E coli (play odds). So, **see neutrophils, RBC's and bacteria. The dipstick will pick up all three of these things.**

"+" dipstick for blood due to RBCs. Hematuria is very frequent and sometimes a lot of blood comes out (**hemorrhagic cystitis**) and most of the time its **E coli**, but sometimes it can be from adenovirus.

Also, the **dipstick has leukocyte esterase** and it's measuring the enzyme in the leukocyte.

Most urinary pathogens are nitrate reducers, meaning that they convert nitrate to nitrite. On a **dipstick, they have a section for nitrites**. B/c E coli is a nitrate reducer, there should be nitrites in the urine, which are dipstick "+" for that.

So, you have a pt, woman or man, who has dysuria, increased frequency, suprapubic pain and have a urine sediment of neutrophils, RBC's, bacteria or dipstick findings of hematuria, leukocyte esterase pos, nitrate "+" **= UTI**

Is it lower or upper? If the pt has fever, flank pain, WBC casts its upper, if none of these things are present, its lower.

Example**:** pt with dysuria, increased frequency, neutrophils in the urine, few RBC's, no bacteria, "+" leukocyte esterase, urine culture is neg, and sexually active person, dx? **Chlamydia – normal urine cultures do not pick up Chlamydia trachomatis. It is the MC STD.** In men, called nonspecific urethritis, in woman its called acute urethral syndrome. We also use the term called sterile pyuria. We don't have bacteria present, but do have neutrophil present. On routine stool culture, its neg. So, **one cause of sterile pyuria is Chlamydia infection and the other one is TB.**

MC organ that military TB goes to = kidney, therefore will have TB in the urine, and it will be sterile b/c urine cultures do not pick up. So, remember Chlamydia and TB as causes of sterile pyuria.

Day 4 Last part

Audio file #8 Renal 2

Penis

Embryo: what is the embryology of **hypospadias**? Opening on the undersurface (you pee and it goes on your shoes) – failure of closure of urethral fold
Epispadias? Opening on upper surface (pee and goes in face); defect in genital tubercle

Peyronie's dz: like Dupuytren's contracture
Priapism – permanent erection, seen commonly in SCDz bc of the RBC's and sickle cells trapped in the vascular channels.

MC cancer of the penis = **squamous** bc lack of circumcision. It is more commonly seen in an uncircumscribed pt – they usually do not clean (poor hygiene) predisposes – the **smegma is carcinogenic.**

Testicle

Cryptorchid testis – testicle doesn't want to come down. There are two phases in the decent of a testicle: transabdominal migration down to inguinal canal. MIF is responsible for this. The second part of the trip is androgen dependent. This includes testosterone and dihydrotestosterone. So, the first phase is from MIF and the second phase is androgen dependent. Need testicle down by two years of age bc if not, has a risk of seminomas. Still at risk if you get it down. Lets say you went in, and it look atrophic and other testicle looks normal, have to take normal one out, too bc it is also at risk. So, must have testes examines to make sure you don't have a seminoma.

Analogy: in turners, they are infertile and have menopause before menarche, bc by two years of ages, they have no follicles in their ovaries, and this is called a streak gonad. This is an ovary without any follicles. This is analagous to cryptorchid testes: just like the cryptorchid testes predisposes to seminomas (which is a germ cell tumor), so does the streak gonad predispose to a germ cell tumor – however, do not call them seminomas in women, but **dysgerminomas**. So, in pts dx'd with Turner's syndrome, they surgically remove both ovaries bc of the great risk. They don't keep them in there bc lead to cancer.

Orchitis – mumps

Epididymitis – less than 35 = N gonorrhea/chlamydia, greater than 35 = pseudomonas

Varicocele – on left side bc spermatic vein connected to left renal vein, wheras the spermatic vein on the right is connected to the IVC; bc of this, the pressures increase, and a varicocele on the left, leads to increased heat and is one of the most common causes of infertility – ie what would happen if you blocked the left renal vein? Would develop a varicocele. So, if you block the left renal vein, you will increase the pressure in the spermatic vein and will lead to a varicocele.

Torsion – spermatic cord twisting; when there is a torsion of the spermatic cord, it shortens it. This means that the testicle will go up into the inguinal canal. This is painful. You will lose your cremasteric reflex (in normal male, if you scatch the scrotum, it will contract, which is lost in torsion of the testicle).

Hydrocele – persistence of tunica vaginalis; when you have big scrotum, you don't know whether its big bc there is fluid in it, or its big bc there is a testicle in it. So, what do you do? Transilluminate. If it transilluminates, it is hydrocele. If it doesn't its cancer. d/d for painless enlargement of testicle : cancer, cancer, cancer!! (why they don't even do bx, just remove)

Seminoma – MC (best prognosis); huge cells with lymphocyctic infiltrate. They are the counterpart of a woman's dysgerminoma. These will melt with radiation, **have little beta hcG**; met to paraortic lymph nodes – why? Bc they came from the abdomen, and that's where they will go.

MC testicular tumor in child? Yolk sac tumor; tumor marker? Alpha feto protein

What is worst testicular cancer? choriocarcinoma – not the same prognosis of a gestationally derived choriocarcinma in a woman – you're dead
Example:: 25 yo male with unilateral gynecomastia and dyspnea. Chest xray reveals multiple nodular masses in the lung. So, gynecomastia and mets dz, - what is the primary cancer? testicle – choriocarcinoma. Source of gynecomastia: **BHCG is like LH, and therefore it stimulates progesterone in the male, which increases duct growth and breast tissue and leads to gynecomastia**

Example:: same scenario, but older man – will lead to malignant lymphoma
So, older pts get malignant lymphoma (not as primary dz, but from mets); the testes mets a lot , esp in leukemia and lymphomas

Summary:
Worst = choriocacinoma
MC = Seminoma
MC in kids = yolk sac tumor
MC in old = mets malignant lymphoma

Prostate

Hyperplasia occurs in the periurethral portion of the prostate gland. This is why you get dribbling and urinary retention as the most common symptom. Prostate cancer is in the periphery of the prostate gland within the periphery of your finger. So, when you press on it, you feel hardness.
Example 75 yo man with urinary retention and bladder is up the umbilicus and has dribbling – what is the most likely cause? NOT prostate cancer – why? Bc for prostate cancer to do that, it has to invade all the way through the prostate gland to the urethra/bladder neck. This is prostate HYPERPLASIA bc it is already around the urethra, and this is the MCC, not cancer. What male hormone is totally responsible for prostate? Dihydrotestosterone – in embryogenesis, this hormone fuses the labia to form a scotrum, extends the clitoris to form a penis and makes a prostate gland. So, prostate HPY and cancer are NOT testosterone dep cancers, but dihydrotesterone dep cancers. If you use a 5 alpha reductase inhibitor, that will increase testosterone. This drug will decrease DIHYDROTESTOSTERONE
MC cancer in men = prostate cancer
Produces osteoblastic mets.

Day 5

Audio file #1 Gyn1

Hirsutism and Virilization

Hirsutism = increased hair in normal hair bearing areas
Virilization = hirstuism, plus male secondary sexual characteristics (zits, acne, deeper voice), clitoromegaly (pathognomonic)

Testosterone is predominantly synthesized in the ovary. Most testosterone in a woman is from the ovary.

DHEA sulfate is 95% from adrenals, and is an androgen. Therefore, if a pt has hirstuism, have to get two tests – get a testosterone level – have to fractionate it bc sometimes the total can be normal, but the free test can be increased, and you get a DHEA sulfate test. So, if testeterone is predominantly elevated, it is coming from the ovary and if DHEA is elevated, it is coming from the adrenals.

If it is adrenal orgin, it consists of hydroxylase def (adrogenital syndrome), Cushings, etc..
Hirstuism from the ovaries is a common phenomenon.
So, when you are evaluating hirsutism, look at DHEA levels (adrenal origin) and testosterone levels(ovarian origin).
One of the common causes of ovarian origin are polycystic ovarian syndrome.

Polycystic ovarian syndrome

MCC hirstuism = polycystic ovarian syndrome (or idiopathic)

(Also due to stromal hyperplasia – stroma of the ovary can make testosterone, or tumors others ovary)

This dz is a hypothalamic-pit abnormality where FSH is suppressed and LH is increased. If you know what LH does, it makes the pathophys easy. In a woman, LH is responsible for synthesis of theca interna (which is around the developing follicle). During the proliferative phase of the cycle, what is predominantly being synthesized is the 17 keto steroids DHEA and androstenedione. The androstenedione is converted by oxydoreductase into testosterone. Then, the test goes across the membrane of the developing follicle into the granulosa cells, where there is aromatase. FSH is put in there. Then, the aromatase in the granulosa cell converts test into estrodiol and this is where the woman gets her estradiol (from the aromatization process). LH is responsible for synthesis of 17 keto steroids and testosterone in the ovaries. This is why we will see hirstuism in a woman with polycystic ovarian syndrome (bc increase of 17 ketosteroids, DHEA, androstendione, and testosterone). Obesity is a common correlation with this dz. This makes sense bc excess adipose = more aromatase, so the sex hormones test and androstenedione can be converted to estrogens in these pts. Androstenedione is aromatized into estrone (a weak estrogen). Testosterone is aromatized into estradiol, which is a strong estrogen. So, we have a paradox – have a woman with signs of excess androgens (hirsutism, acne – not signs of virulization). At the same time, these are being converted to estrogens so will have endometrial hyperplasia and therefore have a risk of endometrial caricinoma. So, there is a combo of increased androgens and increased estrogens. It is the increased estrogens that causes suppression of FSH via negative feedback, while there is a POSITIVE feedback on LH. So, bc increased estrogens, pt is constantly suppressing FSH and constantly increasing LH, so the cycle repeats itself. So, you can break the cycle with an OCP bc the progestin in it will block LH. So, why do they have cysts? Functions of FSH is to prepare the follicle. Also, they increase the aromatase activity. If the FSH is constantly suppressed, the follicle degenerates and leaves behind a cystic spaces where the follicle used to be. So, pt has POLYcytic ovarian syndrome related to chronic FSH suppression. Can feel these by pelvic exam and seen with ultrasound.

Menstrual dysfunction

Dysmenorrhea = painful menses (primary and secondary – MCC primary is too much PGF – a PG that increases contraction of the uterine musculature. The MC secondary cause is endometriosis).
There are also problems with dysfunctional uterine bleeding – this is NOT a bleeding abnormality related to a bleeding/organic cause. So, in other words, it is not bleeding from an endometrial polyp, its not bleeding from a cancer; this type of bleeding is a hormone imbalance that causes abnormality in bleeding.
MCC abnormal bleeding in young lady from menarche to 20 yrs of age = anovulatory bleeding. So, if a young lady is bleeding, that is the usual cause.
What is occurring? There is a persistent estrogen stimulation that is occurring on the mucosa, and not enough progesterone stimulation. So, they develop a lil hyperplasia, there is a build up of mucosa as the month progresses, and then eventually the stroma sloughs off and leads to significant bleeding. So, its mainly an estrogen primed uterus, without the effect of progesterone and they do not ovulate related to this. This is the MCC.

Amenorrhoea

Primary amenorrhea and secondary amenorrhea
When you think amenorrhea, it can be a prob with the hypothalamus/pituitary. In other words, is the hypothalamus putting out GnRH or not? Is the pit putting out FSH/LH or not? So, is it a hypothalamic-pit abnormality? Is it an ovarian prob? Maybe the ovary is not making enough estrogen. Is its an end organ prob?
This is anatomically related – maybe she doesn't have a vagina - **Rokitansky-Kuster-Hauser syndrome**, or maybe she has an imperforate hymen – she's been having periods all along, and has blood built up behind it, or cervical stenosis (DES exposure) – these are all anatomical reasons for the amenorrhea.

Asherman's syndrome – secondary amenorrhea, woman has repeated dilatation and curotoshes(?), where the stratum basalis is scraped away; have to leave something behind from which you can proliferate endometrial mucosa – if you scrape all the way down the the muscle, will not be able to menstruate again, and will scar everything off, leading to an infertile woman.
So, amenorrhea is primary or secondary : hypothalamic-pit problem, ovarian prob, or end organ prob. FSH and LH levels help in distinguishing those 3.
If pt has hypothalamic-pit prob, what would FSH and LH be? Low.
If had a primary ovarian problem, what would they be? High.
If you have an end organ defect, what would FSH and LH levels be? Normal.
What is the first step in the workup of any case of amenorrhea? Pregnancy test.

Turner's syndrome:
Primary cause of amenorrhea, webbed neck, females
Majority are XO, therefore do not have a barr body. Defects in lymphatics. Can make dx at birth via PE – see swelling of hand and feet (lymphedema) = turners
Webbed neck is due to lymphatic abnormalities – get cystic hygromas, which are dilated lymphatics in the neck area and fill with lymphatic fluid and stretch the skin – bc they stretch the skin, looks like webbing. Have preductal coarctations. Do not have MR. some cases are mosaics – XOXX and there is a remote possibility that they may be fertile. There are also XOXY's that are mosaic's. have menopause b4 menarche. All of there follicles are gone by the age of 2, and this is the streak ovaries (gonad). Therefore, they are susceptible to dysgerminomas (seminomas are in males are analogous).

Uterine Disorders

Adenomyosis – glands and stroma within the myometrium –very common cause of dysmenorrheal, dyspyrunia, menorragiah, hysterectomy; does NOT predispose to cancer.

Endometriosis – functioning glands and stroma outside the uterus (myometrium is INSIDE); MC location = ovary, causes bleeding in the ovary – see chocolate cyst (endometroma's - not cancer, just endometriosis of the ovary), tube, in pouch of Douglas

Example: good question to ask if pt has endometriosis: "Does it hurt when you defecate ? Yes. How about when your period goes away?" No, it goes away – this is endometriosis bc there is bleeding in the rectal pouch of the pouch of Douglas (there is endometreosis there). The rectum is filled with stools, and streches the pouch of Douglas, leading to pain. So, pain on defecation during the period leads to endometriosis.

Endometrial Hyperplasia
From unopposed estrogen. Always dangerous to have unopposed estrogen, meaning no progesterone effect, bc then pt runs risk for endometrial cancer.
MCC endometrial cancer = endometrial HPY due to unopposed estrogen

Pouch of Douglas can collect seeding from ovarian cancer, pus from PID, unclotted blood from ruptured ectopic pregnancy
(low part of a woman's pelvis includes: vagina, cervical os, uterus, bladder)

Endometrial cancer:
Early vs late menarche – early is worse bc longer time for estrogen to circulate
Early vs Late menopause – late is worse bc more estrogen exposure
Obese vs not obese – obese bc the estrogen factor in adipose (more aromatase), therefore, obese woman are more susceptible to cancers related to estrogen - breast cancer, endometrial cancer, ovarian cancer

Type II diabetics are at increased risk bc 80% of type II pts are obese (so, the obesity is the cause of increased risk of endometrial cancer).

Cancer and age brackets
45 = cervical
55 = endometrial
65 = ovarian
55 yo, postmenopausal is when you usually see endometrial carcinoma. Any woman that has been in menopause for over 1 yr, and then has rebleeding has endometrial cancer until proven otherwise.
1st step in management? Endometrial Bx

Leiomyoma – MC b9 tumor in a woman
Leiomyosarcoma – mitosis prob; MC sarcoma of the uterus; big bulky tumors (as are all sarcomas); leiomyoma is NOT a precursor for leiomyosarcoma.

Example: young woman sudden onset of severe lower abdominal pain – **must do a pregnancy (look at beta –HCG level) test to rule out ectopic pregnancy.**

Ovarian masses

Surface derived – derived from the surface of the ovary
Germ cell types - dysgerminomas (men have these, too)
Sex chord stromal tumors – make estrogens (ie granulosa cell tumors - therefore can have hyperestrinism which leads to bleeding and endo carcinomas), some make androgens (sertoli leydig cell tumors of the ovary – assoc with virulization and hirstuism).
(males just have germ cell tumors)

Follicular cyst

MCC of ovarian mass in a young woman = follicular cyst
Follicle that ruptured, not neoplastic, accumulates fluid and leads to peritonitis. It is bad if its on the right side bc it can be either ruptured follicular cyst, appedicitus, ectopic pregnancy (ruptured), PID; look at with ultrasound

Under 35 yo, most ovarian masses are b9
Over 35 yo, most ovarian masses have a greater potential of being malignant.

Surfaced derived (overall MC)
MC surfaced derived = serous cystadenoma (B9); serous cystadenocarcinoma (malignant)
(these are the MC overall b9 and malignant ovarian tumors)
These are also the MC that are bilateral, and the cystadenocarcinoma has psommoma bodies (bluish colored – due to apoptosis, destruction of the tumor cell and replacement with dystrophic calcification). Also seen in papillary carcinoma of the thyroid and in meningioma's
Example:: 65 yo, bilateral ovarian enlargement (remem they tend to arise at this age)
Any woman that is over 55 and has palpable ovaries is cancer until proven otherwise bc a postmenopausal woman should be have ovaries that are atrophying.
Example:: 62 yo woman with ovarian mass on the right – already know its bad bc shouldn't have a palpable ovary.

Cystic teratoma
Tooth, sebaceous glands, cartilage, skin, thyroid,,
MC overall germ cell tumor, usually B9
If it is making thyroid, it is called struma ovary

Sex chord stromal tumors
MC = fibromas (B9)
Meigs syndrome: ovarian fibroma, ascites, and right side pleural effusion – goes away when you take the ovary out.
Granulosa cell tumor of ovary: low grade malignant tumor; what does the granulosa cell normally do? It aromatizes androgens and estrogens, so a granulosa cell tumor is more than likely an estrogen producing tumor.
Signet ring cells – is this a primary cancer, or mets from another site? Site is from stomach – called a krukenburg tumor; **there is NO primary ovarian cancer that has signet ring cells.**

Gestational Disorders

Placenta
Chorionic villus – outside layer = syncytiotrophoblast, clear cells under the outside layer = cytotrophoblast; which is making hormones? Syncytiotrophoblast.

What hormones is it making? B-hcG and Human Placental Lactogen (HPL) – growth hormone of pregnancy. Has myxomatous stroma. Vessels coalesce into umbilical vein, which has the highest o2 content.

Neoplasms of chorionic villus:

Hydatidiform mole – can be complete (46, XX, both X c'somes come from father – called androgenesis) or partial (triploid, 69 c'somes, can have a fetus present)
The complete moles have a greater propensity to moving on to choriocarcinoma.

Causes of choriocarcinoma:
15% of choriocaricnomas are from preexisting hyadiform mole
25% from spontaneous abortion
25% from normal pregnancy
Hyatidiform moles are b9 tumors of the chorionic villus; choriocarcinomas are a malignancy of the trophoblastic tissue (do not see chorionic villi). Loves to go to the lungs and responds well to chemotherapy (can even go away in the presence of mets)

Breast

Picture a schematic with nipple, lactiferous duct, major ducts, terminal lobules (where milk is made), and the stroma
Nipple = Pagets dz of the breast
Lactiferous duct = Intraductal papilloma (MCC of bloody nipple discharge of woman under 50) – b9 papillary tumor, if you press on it, blood will come out of the areola
Major ducts = where most of the cancers arise from – invasive ductal cancers, medullary carcinomas, mucinous carcinomas
Terminal lobules (where milk is made) – MC tumor = lobular carnicoma, is famous be BILATERAL (so, lobular tumors are to the breast as serous tumors are to the ovary in terms of their bilatterallity); **mammography doesn't pic up lobular cancers.**

MCC of mass in breast of woman under 50 = fibrocystic change

MCC of mass in breast of woman over 50 = cancer: infiltrating ductal carcinoma (not intraductal – this means that we are not picking up the cancer early enough by mammography and picking up in the intraductal phase, and our techniques are insensitive – so we are missing the ductal stage and we are picking up the cancer when it has invaded – to pick up early, need to get at 5mm or less).
So, if they are intraductal, has a good prognosis

Example: 35 yo woman with movable mass in breast that gets bigger as the cycle progresses = fibroadenoma
These are the most commons in terms of age and location

Slide: **fibrocystic change** – cysts, lumpy bumpy in breast, more painful as the cycle progresses bc they are hormone sensitive
Example:: ductal hyperplasia – cannot see; precursor lesion for cancer that are estrogen sensitive epithelial cells in the ducts (just like the endometrial glands are estrogen sensitive, the glands lining the ducts are estrogen sensitive).

Sclerosing adenosis – in terminal lobules, b9 part of fibrocystic change (see cysts)

Fibroadenoma

MC tumor that moves around in the breast in a woman under 35 = fibroadenoma – is the neoplastic components the glands or the stroma? It's the stroma – as it grows, it compresses the ductstems, so they have slit like spaces; very common. Even if you know it's a fibroadenoma, still get a bx

Breast Cancer

Slide: How do you know its breast cancer? nipple is hard as a rock – when breast cancers invade the stroma, they elicit a fibroblastic and elastics tissue response, making it hard – this is good bc it makes it palpable. **This is why a woman over 50, that has a painless palpable mass, its cancer.**

If its painful and under 50, its rarely cancer (fat necrosis, fibrocystic change). So, the magic word is painless.

Outer quadrants of the breast are the MC sites bc this is where most of the breast tissue is. Therefore, this would be the MC site for breast cancer. The 2nd MC site is around the areola.

Slide: nipple being sucked in, whitish mass, stellate (classic for invasive cancer); on mammography, see density with spicules coming out and has calcified. This is highly predictive for cancer. What is the first step in management of a palpable mass? FNA – bc can make a dx and tell if its solid or cystic (this is also the first step in management of cold nodule in thyroid, not ultrasound).

Slide: intraductal cancer – netlike arrangement, called comedocarcinoma, junk that comes out (like caseous necrosis); has erb-2 oncogene (aggressive cancers).

Slide: invasive cancer, see tumor cells invading stroma; see Indian filing – sign of invasive lobular cancer; seen more often in infiltrating ductal carcinoma

Slide: eczematous dz around the nipple = pagets dz of the breast – rash around nipple – cancer of the duct that has spread to the skin

Slide: inflammatory carcinoma – worst, red, dimpled skin bc the lymphatics are plugged with cancer underneath and the lymphatic fluid leaked out, but the ligaments are still attached, but increasing the fluid in the interstium, and as it expands out, it dimples – p'doeu orange – so, inflammatory carcinoma looks like that bc its lymphatic filled with tumor, and is the worst of the worst.

Slide: lobular carcinoma – MC cancer of the terminal cancer (at the end of the ducts); it is famous for bilaterality

Slide: lymphedema is a woman that is postradical masectectomy; when you are doing a modified radical mastectomy, what are you removing? The entire breast including a nipple, leaving behind pec major, axillary resection, and taking pec minor. MC complication = winged scapula (bc cut the long thoracic nerve)

The lumpectomy removes the underlying tumor with a good border of normal tissue around it, take a few nodes from the axilla (bc have to use for staging bc they go to lower axillary first), and then you do radiation of the breast (good for breast conservation – same prognosis as mastectomy)
Example:: ERA-PRA = estrogen receptor/progesterone receptor assay – what does it mean? Relationship betwn estrogen and its receptor synthesis. So, if you are in a reproductive period of your life when estrogen is abundant, the receptors will be downregulated. This is why in women that are young, in the reproductive period of their life, have breast cancer and are ERPRA negative bc this is what we would expect bc estrogen would down regulate receptor synthesis. Whereas, if you are postmenopausal, it leads to up regulation of the receptors and those women are ERPRA positive. But what does this mean? It means that the tumor is responding to estrogen and need to take away that estrogen affect bc it is feeding the tumor. How can you take it away? Tamoxifen – this is weak estrogen, so it hooks into the receptor of breast tumors, so if there is any left behind, normal estrogen in a woman can't get into it and won't be able to feed the tumor. So, it's a blocker of the receptor.

Complications? Menopausal type symptoms; also, it is an estrogen so you have the risk of endometrial cancer. A benefit in the postmenopausal state with an ERA PRA pos woman is that it does prevent osteoporosis. So, cannot give estrogen to a woman that is ERA PRA pos, but is a candidate for tamox and will prolong recurrence.

Audio file Day5 #2 Gyn2 (But it is Endocrine)

Ch 22: Endocrine Disorders

Primary vs Secondary vs Tertiary

Hashimotos = destruction of the thyroid gland = PRIMARY hypothyroidism (the gland screws up the hormone)
Hypopituitarism and hypothyroidism = SECONDARY hypothyroidism (no TSH to stimulate)
Hypothalamic Dz = Sarcoidosis destroying TRH: TERTIARY (no TRH)

Example: adenoma on parathyroid producing PTH leading to hypercalcemia = primary hyperparathyroidism

Example: have hypocalcemia/vit D def, and asked the parathyroid to undergo hyperplasia, that is called SECONDARY hyperparathyroidism

Example: what if after a long time PTH keeps being made = tertiary hyperparathryroidism (rare)

Overactivity vs underactivity of glands

Stimulation test: if pt has underactive gland, would use stimulation test to see if the gland is working.

Supression test: if pt has overactive gland, would use suppression test to see if gland will stop working.

Most of the time, things that cause overactivity, we CANNOT suppress them.

There are 2 exceptions where we suppress them, and they deal with overactivity in the pituitary gland

– 1)**prolactinoma** can be suppressed bc it can prevent the tumor from making prolactin; bromocriptine suppresses it (dopamine analog – normally, women do not have galactorrhea bc they are releasing dopamine, which is inhibiting prolactin (therefore dopamine is an inhibitory substance – bromocriptine is also used for treating parkinson's bc bromocriptine is a dopamine analog (which is what is missing in parkinsons dz)

2) **Pituitary Cushings**: b9 tumor in the pitiuitary that is making ACTH – you CAN suppress it with a high dose of dexamethasone. These are the only two exceptions for a tumor making too much stuff.
(There is no way to suppress a parathyroid adenoma making PTH, or an adrenal ademona making cortisol, or a an adrenal tumor from synthesizing aldosterone – these are AUTONOMOUS)

Example: pt with hypocortisolism – lets do an ACTH stimulation test – will hang up an IV drip and put in some ACTH; collecting urine for 17 hydroxycorticoids (metabolic end product of cortisol) and nothing happens – so what is the hypocortisol due to? Addison dz – gland was destroyed – therefore, even if you keep stimulating it, you will not be making cortisol.

Example: Let's say after a few days you see in an increase in 17 hydroxycorticoids, then what is the cause of hypocortisolism? Hypopituitarism – in other words, it's atrophic bc its not being stimulated by ACTH, but when you gave it ACTH over a period of time, it was able to regain its function. So, with that single test, you are able to find cause of hypocortisalism.

Can also look at hormonal levels – ie Addison's causing hypocortisalism, what would ACTH be? High; if you have hypopituitarism causing hypocortisalism, what would ACTH be? Low

Hypopituitarism

MCC in adults = nonfunctioning pituitary adenoma (within sella turcica – in the sphenoid bone, hence surgery is transphenoidal surgery, where the expanded sella turcica is).
Pit Adenoma – usually nonfunctioning and destroys the normal pituitary over time as it grows, leading to hypopituitarism.

Sheehans (postpartum necrosis)
Example:: have a pregnant woman, has abruptio placenta and goes in to hypovolemic shock, but get out; doing fine and breast feading baby at home, but suddently stops breast milk production – dx? Postpartum necrosis – therefore she has infarcted her pituitary (coagulation necrosis), and this is residual pitiuatary
(This is not liquefactive necrosis bc the pituitary is not part of the brain).
Mech is ischemia and coagulation necrosis. Pregnant woman have a pituitary gland two times the normal size. Prolactin is being synthesized – but a pregnant woman does not have galatorrhea bc the estrogen and progesterone inhibit release. So, the moment you give birth, the inhibitory effect is released and start having galactorrhea. This is the 2nd MCC hypopit in adult.

MC in kids = craniopharnygioma
Rathke's pouch origin – this is part of the embryological development of the pituitary gland – pieces of it remain and can become neoplastically transformed into a craniopharygioma. Its not a malignant tumor, but a b9 tumor in a bad place. It is MC supra-sellar – (above the sella) – and it goes down and destroys the pituitary, but likes to go forward and bumps into optic chiasm, leading to **bitemporal hemianopsia**, leading to visual field defect.
Example:: child with headaches and visual field defect – do a schematic of it and will ask what the cause is – craniopharyngioma – tumor of rathke's pouch origin.

Growth Hormone

When you have a tumor that is expanding in the sella turcica, different releasing factors (hormones) decrease in a certain succession. The first thing that is destroyed is gonadotropin. So, in a woman, what would happen? She would have amenorrhea (secondary amenorrhea). What if I were a man (what is the analogous condition)? Impotence; impotence is to a male as amenorrhea is to a female. Impotence = failure to sustain an erection during attempted intercourse. The next thing that goes is growth hormone (which has 2 functions: 1) **increases aa uptake** and 2) **involved in gluconeogenesis** (hormone that produces bone and tissue growth is insulin like growth factor-1, which is present in the liver – aka somatomedins; so, GH release will stimulate the liver to release IGF-1 to cause growth of bones linearly and soft tissue); an adult with the loss of growth hormone will not get smaller, but will have the effects of lack of growth hormone: will start to lose muscle mass and will have fasting hypoglycemia bc GH is normally gluconeogenic. So, its not there and not contributing is func to glucogngeogenesis, leading to hypoglycemia. What would you see in a child? Pituitary Dwarfism. Would see **hypoplasia** (incomplete development of something). So, pit dwarfisim is an incompletely developed child, but everything looks normal. What is the best stimulation test to see if you are GH or IGF-1 defecient? Sleep. You grow when you sleep – exactly at 5 am (that's when GH comes out). So, the best test is sleeping, then checking blood at 5 am (if it isn't your def).Why is histidine and arginine deficient? They are essential to normal growth of a child bc they stimulate growth hormone. These are basic aa's. This is why wt lifters buy arg/his supplements. So, best test is sleep, followed by measuring arg and his levels. The third hormone to go is TSH, which leads to hypothyroidism (therefore low TSH and low T4 – cold intolerance, brittle hair, fatigue, delayed reflexes). The next thing that goes is ACTH , leading to hypocortisalism. Will be fatigue will a low cortisol level. Will also lead to hypoglycemia bc cortisol is gluconeogenic. That last thing to lose is prolactin.

Diabetes Insipidus

Central (lacking ADH) vs Nephrogenic (kidney doesn't respond to ADH)

Central: one of the common causes is car accident, leading to head trauma. The head is shifted and stalk is severed. One of the first things that goes is ADH bc it is made in the supraopitic paraventricular nucleus of the hypothalamus. In the same nerve it is made in, it goes down the stalk and is stored in the POSTERIOR pituitary. So, if you sever that stalk, you sever the connection and leads to ADH def. Also def in all the releasing factors that are made in the hypothalamus that stimulate the pituitary, leading to hypopituitarism (eventually – but initially will have s/s of DI = polyurea and thrist).

Nephrogenic: have ADH, but doesn't work on the collecting tubule to make it permeable to free water. Other polyurea's (DM – mech = osmotic diuresis, polydipisia – mech = drink too much water (psychological problem), hypercalcemia leads to polyurea).
Constantly diluting, but will never be able to concentrate urine; SIADH is the exact opposite, where ADH is always there, and will constantly concentrating, and will not be able to dilute. In DI, constantly diluting urine, losing free water, and will never be able to concentrate the urine. So, you are losing all the water, and serum Na will go up, correlating with an increased plasma osmolality (bc most of plasma osmolality is Na).

To test: restrict water – in a normal person, if you restrict water, the plasma osmolality will go up to 292 (the upper limit of normal for the osmolality), 750 urine osmolality - what does that mean? Pt is concentrating the urine. So, if you are depriving a normal pt of water, it should concentrate the urine; water is being retained get into the ECF to get the serum Na into normal range.

Example: pt restricted water and have a 319 and 312 plasma osmolality (which is elevated). So, they have hypernatremia. If you look at urine osmolality, it is 110 and 98. So you know that have DI. So, how do you distinguish central from nephrogenic? Give them ADH (aka vasopressin). So, you give it to them and see what happens to urine osmolality.
If it increases greater that 50% from the baseline: then it's central.
It its less than 50% it's nephrogenic. So, gave ADH to first guy and it urine osmolality change to 550, indicating that he has central DI. For the second pt, ADH was given, but only a lil increase in urine osmalality, indicated nephrogenic DI.

Acromegaly

What is cheapest way for screening for acromegaly? Ask for an old pic of the pt 10 years ago. Gigantism in kid bc epiphyses haven't fused, therefore an excess in GH and IGF-1 lead to an increase in linear growth. Bad dz bc can die from cardiomyopathy. So, they have excess GH and excess IGF-1. So, what if you're an adult with acromegaly? Will not get taller bc the epiphyses have fused, but bones will grow wider. One of the bones in the head that does that is the frontal bones, so they stick out. So, get a gorilla like increase in the frontal lobe (bc it increases size of the sinuses), so the hat size will increase. Your hands get bigger, feet get bigger, and every organ in the body gets bigger. Also, you produce a cardiomyopathy, which leads to death.

Galactorrhea/Prolactinoma

Men do not get galactorrhea bc we don't have enough terminal lobules to make the milk. So, if a male has a prolactinoma, do not expect him to have galactorrhea. This has many causes. When woman comes in with it, make sure you ask what drug they are on - bc there are many drugs that can stimulate prolactin synthesis.

Example:: OCP's, hydralazine, Ca channel blockers, psychotropic drugs. Primary hypothyroidism can also be a cause, therefore get a TSH level. Why? Bc if you have hashimoto's, not only is TSH increased, but you also have increased TRH. TRH is used as a stimulation test for prolactin. So, you must rule out hypothyroidism in a woman with galactorrhea (so in this case, there is nothing wrong with the pituitary, but the thyroid, leading to galactorrhea). **So, must r/o hypothyroidism**.

If all this is ruled out and pt has high prolactin level, dx is prolactinoma (any time there is a prolactin level over 200 it is always a prolactinoma). When pts have prolactinoma, why do they develop amenorrhea? Bc prolactin has a negative feedback on GnRH. So, this is a cheap birth control pill for the first three months after pregnancy bc mom is breast feeding, and the high prolactin levels are feeding back on the pituitary on GnRH.

Thyroid

Thyroid studies – do NOT have to know resin T3 uptake and T4 indexes; 3 things need to know: T4, TSH, I 131 uptake
If TSH is normal, the thyroid is normal. If TSH is decreased, pt has hyperthyroidism or hypopituitarism. If TSH is increased, have high primary hypothyroidism.

Thyroid binding globulin is the binding protein for thyroid hormone

What is the binding protein for—
cortisol? Transcortin;
calcium? Albumin;
Fe? Transferrin;
Cu? Ceruloplasmin; what % of binding sites occupied? 30%).

3 of 9 binding sites on TBG are occupied by thyroid hormone.

Free T4 level. When we measure total T4 level, there is free T4 and bound T4. The free T4 is the part that is metabolically active and is converted to T3. This part is doing all the work (that part that is bound is not).

What happens if you are on an OCP with an increase of estrogen? TBG and transcortin increase. So, increased syn TBG, and is immediately 1/3 occupied (9 sites on TBG, and 1/3 occupied by T4, so that is 3 T4's). Bc everything is in equilibrium, the thyroid senses that it lost 3 T4's and replaces them immediatetly. So, has the FREE T4 altered? No. So what is the TSH? Normal. What is the T4? Increased (but the free hormone level and TSH not altered). So, an increase T4 with a normal TSH means the pt is on estrogens. This is true for any woman on estrogen or any pregnant women. So, the total T4 is elevated bc increased TBG (not be increased free hormone level) and it automatically has 3 sites occupied by T4). Same is true for cortisol – if pt is pregnant or on OCP, cortisol is elevated but do not have signs of cushings. Why? Bc transcortin is increased bc estrogen increasing the synthesis of it, so there is more cortisol bound to it, but the free cortisol levels are still normal.

Example:: if football player/wt lifter, assume pt is on anabolics. They work the opposite. Anabolics break down proteins that you normally would use for other things to build up and put them into muscle. The proteins it likes to go after is binding proteins. So, when they are on anabolics, thyroid binding globulin is decreased bc the aa's that you would have used to make the binding protein are instead utilized to make muscles stronger. So, they won't work if you are not working aa supplements.

Example: pt on anabolics, so less TBG being synthesize bc proteins being used elsewhere (muscles). The same number of site are occupied, but missing TBG. So, free T4 is the same, but missing TBG. So, if a person has a low T4 with a TSH, they are on anabolic steroids. If a woman has a high T4 and a normal TSH, what is she on? Estrogen. If a person has high T4 and low TSH, what do they have? Hyperthyroidism. If pt has low T4 and increased TSH, what do they have? **Primary hypothyroidism**. Do not need resin T3 uptake to make these dx's.

I 131 uptake is a radioactive test (remember that thyroid hormone is tyrosine with iodine on it). (What are other things involved with tyrosine? Melanin, tyrosine tyrosinase, dopamine – goes into the golgi apparatus and becomes melanin, phenylalanine, dopamine, dopa, NE, epi (catecholamines), if you put iodides on tyrosine you have thyroid hormone). So, with hyperthyroidism (ie graves), thyroid gland will be making more thyroid hormone. Would we need more iodide to do this? Yes. So, if you gave a pt radioactive iodide, will there be increased uptake of radioactive iodide in that overactive gland? Yes. So, will have increased I131 uptake. What if I were taking excess thyroid hormone to lose weight – what would that do to my TSH level? Suppress it. So, when that pt is taking too much hormone, the gland has atrophied. So, if you have a radioactive I 131, would there be an increased

uptake? No bc is has atrophied. So, radioactive I 131 is the main way to distinguish whether a person has true evidence of hyperthyroidism (GLAND is making too much thyroid hormone) vs someone that is surreptitiously/purposely/unknowingly taking too much thyroid hormone and producing hyperthyroidism. I 131 is the best test to distinguish these two types of hyperthyroidism. So, if its increased, pt has graves (gland is using it); if its decreased, pt is taking thyroid hormone.
Example:: pt from wt loss clinic – they are taking thyroid hormone, so they will lose wt at the expense of hyperthyroidism

Slide: midline cyst – dx? **Thyroglossal cyst.** Remember that the thyroid gland was originally at the base of the tongue and migrates down the midline to the current location.

Slide: cyst in anolateral portion of neck – dx? Branchiocleft cyst
(know all branchiocleft derivatives – esp the one in the head area).

Thyroiditis (inflammation of the thyroid)
The only imp one is hashimoto's

Grave's Dz – exophalmos **Unique to Grave's Dz** – excess GAG's deposited in orbital fat, and pushing the eye out (pathonomognic for graves); apathetic graves
OLD people with graves dz have heart prob with atrial fib. They get heart manifestations. So, any pt with atrial fib, must get a TSH level to rule out graves.

s/s hyperthyroidism:

heat intoleranc, sinus tachy, atrial fib, brisk reflexes, diarrhea, systolic HTN, hypercalcemia, increased bone turnover (all symptoms are adrenergic – they are all catecholamine things – why? T4 increases the synthesis of beta receptors (catecholamines are cousins of Thyroid hormone and they work together. All the symptoms are adrenergic. What is the INITIAL Rx of graves? Beta blockers (blocking adrenergic response, then give PTU to stop the gland from making it – can stop all the symptoms with beta blocker except one – sweating)
so, thyroid studies on graves pt: T4 is high, TSH is low, I 131 is HIGH

Audio File Day5 #3 Endoc

In hyperthyroidism, want to always look at the face and will see periorbital puffiness, which is seen a lot bc of GAG's (also in vocal cords, leading to hoarseness, tibial area leading to nonpitting edema)

Mitral Valve Prolapse also has an increase in GAGs bc dermatan sulfate is responsible for causing excess and redudency of the valve). Also seen in Hashimotos. Graves is due to IgG Ab against TSH receptor, causing it to synthesize too much. What type of HPY rxn is this? Type II (Ab against the receptor); MG is also type II HPY (have Ab against receptor which is destroying the receptor). In hashimoto's thyroiditis, they also have an IgG against the receptor, except instead of activating the gland, it inhibits it. So, in Hashimoto's and Graves, these are both autoimmune dz's but at opposite ends of the spectrum. One as stimulatory IgG while the other has an inhibibitory one. So, an overlying symptom that they both have is pretibial myxedema and GAG deposition. Where do you see a decrease in GAG's (ie metabolism of GAG's)? Lysosomal storage dzs – Hurlers, Hunters – need lysosomal enzymes for breaking down dermatan sulfate, etc…

s/s hypothyroidism –

weakness (MC) bc all pts with hypothyroidism have proximal muscle myopathy, so they cannot get up out of chairs , serum CK's are elevated. Also have brittle hair, course skin, slow mentation, periorbital puffiness, delayed reflex, diastolic HTN

Slide: bx of thyroid gland in Hashimotos's – no follicle, but do see germinal follicle bc there is autoimmune destruction of the gland. There are cytotoxic T cells that destroying it, and are synthesizing Ab's (IgG Abs, hence you see the germinal follicles), and therefore looks like a lymph node). Will see a low T4, high TSH, low I 131 (not necessary to do this test).

Example: pt on estrogen – what will happen to T4? Increase TSH? Normal (no need for I 131 – this is bad bc babies thyroid would take it up and its thyroid would take it up and leads to cretinism)
thyroid hormone is responsible for brain growth in the first year, so it imp to do thyroid hormone screens to avoid cretinism (will be severly MR bc brain depends on thyroid hormone for development).

Example: Grave's dz – T4 high, TSH, low, I 131 high

Example: pt on anabolic steroids – T4 low, TSH normal

Example: Hashimotos – T4 low, TSH high, I 131 low

Example: factitious (taking too much thyroid hormone and have hyperthyroidism) – T4 high, TSH low, I 131 low (main factor that distinguishes from graves)

Goiter
Anytime thyroid is big. Lots cysts.
MCC goiter = Iodine def
Most often due to low iodide levels, so they have hypothyroidism or borderline hypothyroidism, so the glands are getting rev'd up, T4 goes up and TSH goes down (so TSH will be stimulating it, then not, then it is, etc..).

Rx of choice – thyroxine
Sometimes have a nodule – nodules that develop in the thyroid gland get hemorrhaged. There is sudden increase in hemorrhage due to cyst. Dx with FNA. Then, give thyroid hormone and many times these things will get smaller.
In this country, we iodinize salt, so don't see much. However, some places people have iodine poor diets – ie Great Lakes in Chicago area, Britain; when they get graves dz, due to increase in T3 bc they are iodide def and do not have enough iodine.

Cold nodule vs Hot Nodule

Means if nodule is taking up I 131 or not. If it does not, there is an area of lucency, and therefore cold. If it is hot, there will be a black dot. Why? Bc if the nodule is autonomously making thyroid hormone, what is the TSH? Decreased. If the TSH is decreased, would that suppress the normal portion of the thyroid? Yes, so it undergo atrophy and not take it up, leading to black dot (wouldn't see anything else). What is chance that a cold nodule is malignant in a woman? 15-20%. Most cold nodules in an older woman are benign. Most are cysts. A small % is follicular adenoma. Any cold nodule in a MAN is cancer until proven otherwise. Any cold nodule in a child is cancer until proven otherwise. Any PERSON that has been exposed to radiation and has a cold nodule has CANCER (papillary carcinoma of the thyroid – radiation exposure in head/neck area).

Cancers of the thyroid
Need to bx (cannot tell if malignant just by looking at it) – this is true for follicular adenoma, something b9, multinodular goiter. Done with FNA.

1. **Papillary cancer** would show up with a cold nodule, and has **Psammoma bodies.** Papillary carcinomas mets to cervical lymph nodes next to them. They commonly do this, and have a good prognosis. This is the only assoc with radiation. Annie orphan nuclei.
2. **Follicular cancer** – 2nd MC type, invades vessels. Do not go to lymph nodes. Spread hematogenously, therefore often go to lungs and bone.
3. **Medullary carcinoma** – some cases are sporadic and other cases have AD relationship; assoc with MEN syndromes (multiple endocrine neoplasia I, IIa, IIb) Pink stain – stain with congo red and see polarized apple green birefringence = amyloid A (which came from calcitonin); what is the tumor marker? Calcitonin (which is the screening test of choice)

Example: where would the cancer be located in the body where the tumor marker is converted into amyloid? **Medullary carcinoma of the thyroid**

MEN I – pit tumor, parathyroid adenoma, pancreatic tumor (usually Zolinger Ellison, leading to peptic ulcer).
MEN IIa – medullary carcinoma, pituitary , pheochromocytoma
MEN IIb – medullary carcinoma, pheochromocytoma, mucosal neuroma
How do you screen? Ret protooncogene (unique to coding for receptors in this syndrome).

Prognosis (best to worst): Papillary>Follicular>Medullary

PARATHYROID GLAND

Pt can have tetany with a normal total Ca. Ca is bound and free – it's the free Ca that is metabolically active (which is true for ANY hormone – the part that is bound is totally metabolically inactive). So, who does Ca interact with? PTH

So, if Ca is low, the PTH is high, and if Ca is high, PTH is low. Roughly 1/3 of the binding sites in albumin are occupied by Ca. So, in other words, roughly 40% of the total Ca is bound to albumin. 47% is ionized Ca floating around and the rest is phosphate and sulfates. The ionized Ca is the metabollicaly active form. MCC overall of hypocalcemia = hypoalbuminemia. Have low albumin level, therefore decreased level, and less of albumin binds Ca. So, before you look at PTH levels, look at albumin levels – if that is low, this is the cause of hypocalcemia. This is not affecting the free hormone level, just that albumin is decreased. This the same as TBG being decreased, leading to decreased T4.

Alkalosis (resp or metabolic): have decreased H ions, and pH is increased. What are the acidic aa's? Glutamate, Aspartate. Why are they acidic? Have COOH groups (as opposed to basic aa's , which have more basic NH groups).
The reason why albumin is such a great binder of Ca is bc it has the most negative charges in the body, bc it has the most acidic aa's in it. So, if you have an alkalotic state the COOH groups become COO "-" groups. Bc if you have less H ions, its COO"-". So, albumin has MORE of a negative charge in an alkalotic state, which means it can bind more Ca. So, where does it get it from? Ionized free Ca (so a bunch of ionized free Ca binds to the the albumin). However, we have NOT altered the total, just took it. It doesn't affect the total, but it DOES decrease the ionized Ca level, leading to TETANY. So, total is the same, but the ionized level has decreased. What is the mech of tetany? Have threshold for the AP before the nerve is stimulated. Then you have a resting membrane potential. So, a decreased ionized Ca level will lower the threshold for activating the nerve and muscle. If its -60 for normal threshold. Pt is partially depolarized, therefore doesn't take a lot to activate the muscle or the nerve (which is the mech of tetany) – so you are lowering the threshold. In hypercalcemia, the opposite occurs and you are increasing the threshold, so it takes more ionized Ca to activate the nerve.

PTH on y axis and Ca in x axis – ht of square = PTH and width = Ca

Low serum Ca, low PTH = primary hypoparathyroidism
MCC = previous thyroid surgery

Example: pt goes in to remove thyroid cancer (these days they autotranplant it to the arm)

Example: newborn with cyanosis, irritable and xray of chest shows not anteriormediastinum shadow – dx? DiGeorge – hypoparathyroidism and no thymus

Example: **low Ca, high PTH = secondary hypoparathyrodism** – so whatever is causing the hypocalcemia is causing a compensatory increase in PTH (called secondary hypoparathyrodism – the MCC of this is renal failure bc these pts have hypovitaminosis D, which decreases Ca and increases PTH). So, any decrease in Ca with cause a compensatory increase in PTH.

Example: **high Ca, high PTH = primary hyperparathyroidism** = gland is not obeying negative feedback. This is MCC hypercalcemia is a community;
If pt is in a hospital, MCC hypercalcemia = mets to bone (malignancy induced). Most hypercalcemia pts are asmptomatic; if they ARE symptomatic, they have stones (Ca stones, which is the MC symptomatic presentation for hypercalcemia).
Labs: increased Ca, increased PTH, low phosphate (normally PTH increases Ca reabsorption and decreased phophorus reabsorption).
Almost always over 50 yo

Example: **high Ca, low PTH = all other causes except primary hyperparathyroidism.** MC due to malignancy. Can PTH like peptide cause hyperCa? Yes (so if you measure PTH it will be normal). Squamous cell of the lung, renal adenocacinoma, or mets to bone (breaking bone down), sarcoidsis (leading to hypercalcemia), multiple myeloma (leading to hypercalcemia) all will have LOW PTH. So, what is the ez'est way to determine hyperCa in a pt? PTH level
(if its high, its primary hyperparathyroidism; if its low, its all the causes – ie malignancy).

ADRENAL GLAND

Cushing Syndrome
PURPLE striae, obesity, thin extremities
MCC = pt on long term steroid therapy (ie pts with renal transplants, pt on immunosuppressant, Lupus)

If this is excluded, need to think of 3 sources: pituitary Cushings, adrenal Cushings, ectopic Cushings. Which of the three will have the highest ACTH levels? Ectopic (small cell carcinoma). Which would have the lowest ACTH levels? Adrenal. Why? Bc its making cortisol, which would suppress the ACTH. Pit Cushings is usually a b9 tumor making ACTH.

There are 2 good screening tests for Cushings (when you have excluded the fact that they are not on steroids). The screening tests are: 24 hr urine test for free cortisol. This is looking for cortisol in the urine, not attached to any protein (so it's free). It must mean that you have a lot of excess of it to have that much of it in your urine. This is the BEST screening test for Cushings. This test distinguishes Cushing's syndrome from Cushingoid obesity.

Example: see obese pt with Cushing's symptoms and you think they have Cushings; however, get a 24 hr urine cortisol test and it's normal. If it's increased, they truly have Cushings – in other words, they have 99% sens and specificity.

They will ask about **dexmeth suppression test** (low vs high dose). What is dexamethasone? It's a cortisol analog. If you give dexamethasone to a normal person, it will suppress ACTH. If you suppress ACTH, the cortisol levels with be low, indicating the cortisol levels are suppressible. So, what happens when you give a LOW dose of dexamethasone in a pt with Cushings – will you suppress their cortisol? No. So, you see a lack of suppression. Therefore pt has cushing's. However the LOW dose just tells you pt has Cushings, not what kind they have, so it just a screening test (if you did a 24 hr cortisol urine level, it would be positive). Remember that there are two endocrine dz's that you CAN suppress – PITUITARY Cushings and prolactinoma. So, if you give high dose of dexamethasone, you are able to suppress the ACTH release by the pituitary and cortisol goes down. It will not be suppressed in adrenal and ectopic Cushings (small cell).
[Read last sentence if you get a long question]

Example: for one of these, they will describe Cushings, and ask about dexmeth suppression – first thing to do is look at high dose suppression – if its suppressed, its automatically pituitary cushings (not a hard question!)

So, why do the pts look like this? Pt has hypercortisolism, which is gluconeogenic. So, need substrates for gluconeogenesis – main substrate is aa from muscles. Where are the muscles located? Arms and legs – so pt will get a break down of muscle in the extremities, which is why they have thin arms and thin legs. Then will get alanine transaminated and get pyruvate. So, will always have thin arms and extremities. Bc it is gluconeogenic, what will the glucose be? High. What does that do to insulin release? Increases it. What does insulin do to fat? Increases fat storage. What part of the body have the most adipose? Face and trunk. So, you are getting an increase in deposition of TG in the face and trunk and back. So, the thin extremities is due to breaking down muscle for aa's in gluconeogenesis. The moon facies, buffalo hump and truncal obesity is due to increase in insulin and fat deposition. The stretch marks are due to obesity, and they are purple bc cortisol decreases collagen synthesis. Will get structurally weaker collagen. Its like purpura within the stretch mark (like senile purpura). Break down the vessels bc increase in cortisol.

Example: **Trousseau's sign** – sign of tetany; this pt has HTN, hypernatremia, hypokalemia, and metabolic alkalosis – dx? Primary aldosteronism. (have tetany bc alkalosis – neg charges on albumin are increased, and ioninzed Ca level decreases). Aka Conn's syndrome

Adrenal Medulla tumors
MC in adults = pheochromocytoma (b9, HTN) (so, adult, HTN, tumor in adrenal medulla = pheo); have unstable HTN – anxiety, sweat a lot; get a 24 hr urine test for VMA and metenephrine (these are metabolic endproducts of NE an Epi (so, anxious, sweating, HTN). Are there assoc with pheochromocytoma? Yes – MEN IIa and MEN IIb, neurofibromatosis (ie pt with neurofibromatosis with HTN – what test you get? VMA and metanephrine 24 hr urine, bc high assoc with pheo).
MC in kids = neuroblastoma (MALIGNANT)

Both of these are from renal medulla, both are neural crest origin, both produce HTN. Pheo = adults ; neuro - kids

Waterhouse Friderichsen Syndrome
N. menigitidis
Example:: 12 yo, gram "-" diploccocus, high fever, nuchal rigidity, spinal tap found neutrophils and gram "-", kid then 'crashed' – started to get petechial lesions all over the body, hypovolemic shock, died, on autopsy both adrenal glands are hemorrhaged – Dx? Waterhouse Freidrickson
MCC meningitis from 1 month to 18 yrs of age = N meningitidis. It is the ONLY meningitis with petechial lesions (and they always mention this).

So, if they give meningitis and petechia, know is N meningitis. If they are hypovolemic, they hemorrhaged their adrenals and went into hypvolemic shock, also, they have no cortisol or mineralocorticoids.

Cause of hypocortisolism that is chronic = Addison's dz
MCC Addisons = autoimmune destruction of the gland (used to be TB due to autoimmune destruction). The entire adrenal cortex is destroyed, therefore the mineralocorticoids and glucocorticoids are low. So, there is low cortisol with HIGH ACTH. What does that do to melanocytes? Increases them, leading to hypigmentation in the mouth and elsewhere. There is NO aldosterone. There are 2 pumps (Na/K pump and proton/K pump). Are you gonna lose Na? Yes – which will lead to hyponatremia and HYPERkalemia (peaked T waves). Will you be able to get rid of the protons in the urine? No – therefore will have metabolic acidosis. So, you have hyponatremia, hyperkalemia, metabolic acidosis, hyperpigmentation.

Example: ambiguous genetalia – what is first step in management? C'some analysis – have to find out what the genetic sex is. It's XX. So, pt has ambiguous genetalia, female, phenotypically cannot tell, **so it's female pseudohermaphrotide –** (play odds) – adrenogenital syndrome due to **21 hydroxylase def.**

17 hydroxylase is responsible for 17 ketosteriods (include DHEA, androstenedione, and are weak androgens). Androstenedione can be converted into testosterone and testosterone into dihydrotestosterone.

17 hydroxycorticoids are 11 deoxycortisol and cortisol
So, if you have an increase in 17 hydroxycorticoids, this is an increase in 11 deoxycortisol and cortisol
If you have an increase in 17 ketosteroids, (17, KS) it's an increase in DHEA and androstenedione.

When you have an enzyme def, things prox to the block increase and things distal to the block decrease

With 21 hydroxylase def, decrease mineralcorticoids and glucocortiocoids and increase androgens, lead to ambiguous genetalia (excess androgens), lose salt, high ACTH, therefore hyperpigmented
With 11 hydroxylase def – decreased cortisol, decreased aldost, but increased 11 deoxycorticosterone (weak mineralcoricoid), increased 17 hydroxy's and 17 ketos – lil girl will have ambiguous genitalia, lil boy will have precocious puberty (excess androgens), HTN
17 hydroxylase def – no androgens, increased in mineralocorticoids (HTN), so if it's a lil boy he won't have test and will look like a female bc no development (no external genitalia bc no 17 keto's, test, or dihydrotest). In a lil girl – she will be underdevoped.

Islet cell tumors
Only 2 to know: Insulinomas and ZE syndrome
ZE: making too much gastrin, leads to peptic ulcers
Insulinoma: is pt injecting or do they really have insulinoma?
When you break proinsulin down into insulin, you release C peptide, so for every insulin molecule that is released, there is C peptide that is released with it. So, if you inject human insulin into yourself, and produce a low glucose level and C peptide will be SUPPRESSED.
If you have a islet cell tumor, glucose will be low, insulin will be high and C peptide will be INCREASED.
Example: pts that have access to insulin get this (Drs, nurses, pharmacists)

Audio file Day5 #4 Musculoskeletal

Diabetes Mellitus

Type 1
Absolute insulin deficiency
Antibodies against islet cells
DKA
HLA relationship
Insulin used (always)

Type 2
Family history of diabetes
Obesity
Amyloid in islet cells
Hyperosmolar non-ketotic coma
Insulin used when eventually pt get resistant to SFU

PATHOGENESIS: 2 mechanisms:

1) **Osmotic Damage**

Tissue has to have aldose reductase: only 2 have them:
i) Lens, glucose→ sorbitol, osmotic reactive, absorbs water into the lens

Retinal vessels in lens get weak, then destroyed due to microabsesses and can rupture and lead to blindness.

ii) Scwann Cells: MCC cause of peripheral neuropathy is Diabetes: MECH: osmotic damage

2) **Non-enzymatic Glycosylation**

Renders the BM permeable to proteins: Hyaline arteriolosclorosis, diabetic nephrophathy

HbA1c: long term control of DM.

Slide: Retina in a diabetic-microaneurysms (red dots)

Slide: Retina in a diabetic-neovascularization

Example: 50 yr old, blurry vision; gets a prescription from a optometrist, new glasses, one month later, blurry vision again. Gets new prescr, one mth later, blurry vision again. Dx: Diabetes.
Glucose is being converted to sorbitol-water is going in and changing the refractive index. Classic question. HAVE to get a FASTING BLOOD GLUCOSE.

Lab: Fasting glucose >126 mg/dl on two separate occasions.

Example: Beh Sc link: The FBS level has been decreased from 140 mg/dl to 126 mg/dl. Is this increasing the specificity or the sensitivity of the test?
A: HIGH Sensitivity. By bringing it lower ie closer to the normal range, you are going to be able to pick up more people with diabetes. When it was 140, it was high sp: to eliminate false positives. So it was unequivocally a diabetic if it was > 140.

Glucose tolerance test, don't worry about it.

Gestational Diabetes
Def: Woman who did not have diabetes, but after becoming pregnant develops diabetes.

Risk factors for baby:
RDS, premature delivery

Women with GD, are at a higher risk for developing diabetes later on.

Amyloid in Beta islets: Type 2

Antibodies against islets; inflammation: Type1
(Coxackie virus implicated)

HLA correlation: **HLA DR3 and DR4=Type 1;** propensity for developing Type 1, if certain environmental factor comes in such as infection: Coxsackie, mumps, EBV

HLAB27: Ankylosing Spondylitis
Env factors:
Chlamydeal Infection
Ulcerative Colitis,
Shigellosis
Psoriasis

Musculoskeletal System

Need to identify crystals in synovial fluid

Gout

Pseudogout
Rhomboid crystals in synovial fluid==pseudogout

But Pseudogout could also have needle-shaped crystals (like those of mono-sodium urate in Gout) which makes DD difficult. So you use a special filter to make the whole slide red and then the crystals are made to look yellow or blue.

When the color of the crystals is yellow when the plane of filter is parallel to the analyzer= **Negatively birefringent =GOUT**

East west direction: color is blue and parallel to analyzer=**Positively birefringent = PSEUDOGOUT** (calcium pyrophosphate)

Arthritis

Osteoarthritis

Progressive wearing down of articular cartilage

Sometimes leads to reaction to injury: SPUR formation—at the margin of the joint= Heberden's node: osteophyte in the joint

Note the enlargement of the DIP (Heberden's nodes) and PIP joints (Bouchard's nodes), enlargements represent osteophytes.

Rheumatoid Arthritis

Inflammatory joint dz; enlarged MCP joints
Rh factor sets up the inflammation: IgM Ab against IgG. IgG is in synovial fluid. IgM-IgG form complexes, activate the complement system, damage the joint, synovial fluid gets inflamed, starts growing and growing, starts growing over the articular cartilage= PANNUS; hyperplastic synovial fluid. (different from Tophus)

Joints can get fixed, and ankylosed and cannot move.
Don't get fixing of the joint in OA.
If rheumatoids don't keep moving their joints, and if it is not controlled using anti-inflammatory drugs then eventually they cannot move it at all.

Slide: Rheumatoid nodules. Can be seen in Rheumatic fever as well.

Example: older pt having trouble eating and swallowing crackers, feels like there is sand in my eye all the time. On examination: eyes and mouth are dry. Dx? **Sjogran's Syndrome.** Pt with RA and auto-immune destruction of lacrimal glands, salivary glands. Keratoconjunctivitis sicca

Rheumatoid nodules in lung + pneumoconiosis==Caplan Syndrome

Treatment of RA= Methotrexate

Example: Pt with RA, develops a macrocytic anemia with hypersegmented neutrophils, neuro exam is normal, interstitial fibrosis in lung. What is the drug? Methotrexate

Gout = podagra

Big toe, usually first one to be involved; usually at night.
Monosodium urate crystals are precipitated and taken up by the neutrophils that phagocytose it and release chemicals—inflammatory reaction.

Don't define Gout based on Uric acid level. Elevated uric acid does not necessarily lead to gout. About 25% of people might have elevated uric acid.

Dx: HAS to be by presence of uric acid crystals in the joint.

Treatment: Indomethacin to control inflammation.

Cause: over production (Rx=allopurinol: blocks Xanthine oxidase) or under excretion of uric acid (>90% of cases) Rx=uricosuric drugs like probenecid and Sulfinpyrazone

Chronic Gout = tophus: deposition of monosodium urate in soft tissue—malleolus
Very disabling as it erodes the joint.
Rx= allopurinol

Slide: Tophus that was polarized showing MSU crystals

Slide: X-ray of digit showing erosion by tophus

Genetics of Gout:

Multifactorial inheritance

AVOID red meats (full of purines)
AVOID Alcohol. Mechanism:

Metabolic acidosis: uric acid has to compete with other acids for excretion in proximal tubule. Alcohol increases all the lactic acid, and beta hydroxyl butyric acids. So all these acids compete and win against uric acid, and get excreted. Uric acid keeps waiting and waiting; and builds up and causes gout.

Ankylosing spondylitis (AS)

HLAB27 association

Slide: Note anterior flexion which often results in restrictive lung disease. Hunched over, restricts movement of chest cavity, blood gas abnormalities,

20 yr old, morning when he woke up, sudden pain in sacro-lumbar region. Inflammatory reaction seen on X-ray, as the day progresses pain decreases. Eventually, the inflammation spreads to the vertebral column, and it fuses==”Bamboo spine”

Also develop: Uveitis, Aortitis, iridocyclitis, blurry vision, eventually go blind.

Example: Genetic dz where degenerative arthritis in vert col, on autopsy, black cartilage; urine on exposure to air turns black.

Alkoptonuria

Aut rec, homogentisic acid oxidase enzyme def

Slide: 20 yr old, dysuria, increased freq, urinalysis= leucocyte esterase positive, sterile pyuria--sexually active, had non-specific urethritis, conjunctivitis, was treated. It was Chlamydia trachomatis conjunctivitis, but one week later, got sterile conjunctivitis and tendonitis in Achilles tendon.

So patient with non-infectious conjunctivitis, previously had Chlamydia trachomatis infection and then developed conjunctivitis and arthritis (HLA B27 positive): **Reiter's syndrome**

Another Env trigger in HLAB27 positive pt: Ulcerative Colitis

Septic arthritis due to disseminated gonococcemia

Note the hot knee and the pustule on the wrist, on aspirating: gram negative diplococcic

STD= Sexually Transmitted Disease

S=Synovitis=joints
T= Tenosynovitis= joints in hands and feet
D= Dermatitis=pustules
MCC of septic arthritis in US= Gonorrhoea
For it to become disseminated, need to be deficient in the final pathway of Complement system: **C5-C9** (some say C6-C9)

Slide: Note the Ixodes tick (vector of Borrelia burgdorferi and Babesia microti), note the erythematous rash in the bottom screen - the tick bite is in the center of the rash and the rash extends out in concentric circles from that point, the rash is called **erythema chronicum migrans** (pebble thrown in water) Pathognomonic of **Lyme's disease**

Early form Rx: tetracycline

Chronic Lyme’s Disease: Apart from disabling joint disease: myocarditis plus bilateral Bell’s palsy: CN VII involved + pt will have Babesiosis

Idiopathic: is usually Unilateral Bell’s Palsy= Herpes Simplex

Above Pt develops Hemolytic anemia, what did he see in his peripheral blood smear? Babesia microti (ring form similar to Plasmodium falciparum)

Remember: the Ixodes tick has the reservoir for Borrelia burgdorferi (white tailed deer that has Babesia microti) AND Babesia microti intra-erythrocytic parasite

Rx: Ceftriaxone

Bone Disorders

Osteogenesis imperfecta
Slide: Kid with an eyeball, blue sclera: AD disorder with defect in synthesis of type I collagen, note the blue sclera- loss of collagen in sclera allows bluish color of choroidal vessels to shine through: **Osteogenesis imperfecta** (NOT foreign body!) “brittle bone disease” cant break bone down

Question: what’s the defect? Defective synthesis of type 1 collagen

Question: what’s the mechanism of development of blue sclera?
Collagen in sclera, type 1 is defective, so it is so thin, so you can see the underlying choroidal veins that gives the blue color.

Osteopetrosis = “marble bone disease”

Defect in too much bone: defect in osteoclasts

Osteoporosis
Slide: Decreased width of inter vertebral cartilage. Note the collapse of the vertebra due to loss of bone mass: patients lose more bone than is replaced

Slide: Dowager's Hump
Mech: Postmenopausal osteoporosis is due to the loss of the inhibitory effect of estrogen on the release of interleukin 1 from osteoblasts; not enough estrogen to stop the activity of Interleukin-1 (osteoclast activating factor) from breaking your bone down.

Osteoporosis: Overall reduction in bone mass. Both mineral AND organic component. WHOLE mass of bone is reduced.

Osteomalacia: Decreased mineralization of bone: organic part of bone is normal. Cartilage is ok, osteoid is ok; its not getting mineralized

Dx of osteoporosis: Dual beam Absorptiometry: density of the bone in whole body is measured. Non invasive, very easy.

MC fracture: compression fracture: lose stature,
2nd MC fracture: Colle's fracture of distal radius.

Question: Is swimming a good exercise for preventing osteoporosis: NO. Because no stress on bones. It is great exercise for aerobics. But it does not prevent osteoporosis. Walking is good. Weight bearing is even better than walking! Walk with Dumbells! Get aerobics and inc in bone mass!
HAVE to stress bone to build it up.

Example: In space, lack of gravity and astronauts are given bisphosphonates, Vit D and calcium to get bone density back: because serious prob of osteoporosis in space.

Tip: reproductive women need to:
1) Exercise
2) 1500 mg of Ca everyday
3) 400-800 units of Vit D
4) Vit pill that contains Iron

Bone Tumors

Exostosis (osteochondroma)
Note the cartilaginous cap on the surface of the bone. This causes a protuberance of the bone. This is the most common benign bone tumor.

Chondrosarcoma of the hip
MC malignant one

Osteogenic sarcoma
Slide: Note metaphyseal origin of the cancer and extension into the muscle, note the splinter of periosteum that is elevated which would correspond to Codman's triangle

Slide: X-ray of proximal humerus showing the "sunburst" appearance of osteogenic sarcoma that is extending into the muscle, osteogenic implies that the cancer is making bone

Adolescent, sun burst app, codmans triangle, knee area==Osteogenic Sarcome

Suppressor Gene relationship: Rb suppressor Chromosome 13

Muscular Disorders

Duchenne's Muscular Dystrophy

Gower's maneuver
Elevated Serum CK, Absence of dystrophin protein

Sex linked recessive, missing Dystrophin gene

Variant: Becker's dystrophy: make dystrophin but it is defective

Analogy: alfa 1 antitrypsin def: MCC of HCC in children
Adults get panacinar emphysema: many diff sub types of alfa 1 anti-trypsin:

1) Absent alfa 1 anti-trypsin: get pan acinar emphysema.

2) Alfa 1 anti-trypsin is present but it cannot get OUT of the hepatocytes: so get HCC

Audio file Day 5 #5 Skin

Myotonic dystrophy - MC adult dystrophy, AD
Triplet repeat dz – repetition of tri-nt's (there are 4 dz's with this abnormality – HD, Fragile X – have macrorchidism (big testes in adolescents), Friedrich's ataxia, Myotonic dystrophy).

In future generations, dz gets worse – anticipation. Therefore, can anticipate that in future dz's it will get worse. For each generation, there are more triplet repeats added on, leading to a more defective protein and the dz gets worse and worse.

Example: genetic counselor telling couple that they have a dz, where if are to have children, the dz will be fatal in their children. The couple didn't listen to their counseler, had a child and the child died only after 1 month. What was it and what is this: an ie triplet repeat disorder (anticipation) Muscle weakness in face (so mouth is drooped open).

Example: pt with failure to release grip on golf stick (or when shaking hand) – they cannot relax their muscle grip, diabetes, cardiac abnormality

Myasthenia Gravis
AutoAb against Ach receptor – it's an IgG Ab, therefore is an Example: of type II HPY, like Grave's, which is an IgG Ab against the receptor (by definition, this makes it type II). Whether you destroy the receptor or just block it is irrelevant. Ach cannot hook into it and therefore there is muscle weekness. The first muscles are the lids, which leads to lid lag. They also get double vision bc muscles of the eye are messed up, leading to diplopia. Eventually, they get dysphagia for solids and liquids (gets stuck in upper esophagus, bc this is where there is STRIATED muscle). Eventually muscle dz prevails throughout.
Feel energized in the morning and feel tired at night. Tensilon test positive. Can die.

Rx is acetylcholinestrase inhibitors. By giving an inhibitor, block the breakdown of Ach and build up Ach. With few receptors you have in there, there is a larger chance of hooking up to the receptors and pt does well. However, eventually, no receptors there and it doesn't matter how much Ach is there, so pt is screwed. Then, her only option is a thymectomy.

The thymus is in the anterior mediastimun. Trick question: they can ask, what is the pathology? They can describe MG and ask, what do you expect to see in the mediastinum? Do NOT put thymoma. This is a malignancy of the thymus and does occur in 15-20% of cases, but isn't the MC pathology seen in the thymus in a pt with MG. See germinal follicles in the thymus (remember, this T cell country, not B cell country, so its abnormal to have germinal follicles here) – they are the ones making the Ab causing the MG. So, by doing a thymectomy for Rx, you are removing the Ab producing tissue. 1/3 pts get a complete cure. 1/3 get a partial cure, and 1/3 die bc they waited too long for thymectomy and Rx and didn't have receptors, anyway. So, B cell hyperplasia is the MC thing you see, not thymoma. This where the Ab is being made.

Lupus
Butterfly distribution on the face (malar rash)
Of all the autoimmune dz's this one is the most likely one to have a "+" ANA (99% sensitivity). The Ab's you want to order to prove that its lupus are anti-Smith Ab (which has a 100% spec, therefore no false pos – therefore 100% PPV) for lupus, meaning that if you test "+" for this Ab, you have Lupus. The other Ab is anti –dsDNA – this not only indicates that you have lupus, but also that you have KIDNEY dz. That has a 98% spec, too. So, these are two good Ab's to confirm lupus. Morning stiffness is present in lupus (simulates Rh arthritis/photophobia), rash, pericarditis; LE cell prep – Anti – DNA Ab's are phagocytosed by neutrophils, and they have altered DNA. Not specific for lupus (waste of time).

Progressive Systemic Sclerosis/CREST
Tight face, telangiectasia, Raynauds, dysphagia (solids and liquids), dystrophic calcification, sclerodactly; if kidneys involved, it is progressive systemic sclerosis, NOT CREST (doesn't involved kidneys).

Dermatomyositis
Racoon eyes, elevated serum CK, rash over the PIP (goutren' patches), highest assoc with underlying cancer.

Sjogrens syndrome
Assoc with rh arthritis, autoimmune – Ab's destroy salivary glands leading to dry mouth, lacrimal glands leading to dry eyes.
Example: bx of lower lip which is a confirmatory test – its looking to see if there is destruction of the minor salivary glands – see lymphocytes (which is confirmatory dx). Ab's are anti-SSa (aka anti-Ro) and anti-SSb (aka anti-La) (SS = Sjogren's syndrome).
Anti-ro can also be in lupus pts, and can cross the placenta and disrupts the baby's conduction system (leads to complete heart block).

Skin

Basal cell carcinoma (upper lip)
Squamous cell carcinoma (lower lip)

Psoriasis – silvery lesion that is red and raised. Can involve the hands, scalp – pts think they have dandruff (aka seborreic dermatitis – from malasezia furfura), but they really have psoriasis. On black person won't see red lesion, will see silver one. Rash at pressure points – esp the elbow.

Atopic dermatitis – child with allergic diathesis starts dz; have eczema (aka atopic dermatitis); type I HPY.

Contact dermatitis – ie to metal (nickel); type IV HPY
Example: pathophys is equalant to what? "+" PPD, bc both are type IV HPY

Seborrheic Dermatitis
Due to *Malassezia furfur* (a fungus)
IC pt (ie AIDs)
This is a preAIDs lesion

Tinea capitis
Example: pt with bald spot on head, fluoureses and seen with black light blacklight (UV-A light)
Can cause Tinea capitis **(now Trichophyton tonsurans is MCC)**
Bc the fungus involves the inner portion of the shaft, there are no fluorescent metabolites, and is **Wood light negative**

All the other superficial dermatophyte infections including **Tinea corporis** (ring worm)
Example: red outer edge and clear center, what is first step in workup? Scrape outside and do KOH prep, and see hyphae and yeast forms. **All other superficial dermatophyte infections (except Tinea capitis) are due to trychophyton rubra.** What is the color around Tinea capitis? Red (= rubra) (how to remember it).

Molluscum contagiosum
Sandy like material in crater, children, self inoculate
Poxvirus makes these (DNA virus)
Volcano crater look, with sandy stuff in it

Pityriasis Rosea
Example: rash on butt – non pruritic rash, NON INFECTIOUS; oblong looking with red on outside and pale in middle. You think this is T corporis, but its oblong (and not circular). Do a KOH prep, find nothing; then put topical steroids and doesn't go away; 3 days later comes back with rash in the line of langer in Christmas tree like distribution; not an infectious dz, **like a herald rash; not a fungus**

Dysplastic Nevus syndrome
Example: precursor lesion for malignant melanoma; if you have over 100 nevi all over body, you have dysplastic nevus syndrome
Very common
Must go to dermatologist once a year bc need to look at dysplastic nevi.
Could be a precursor lesion for malignant melanoma.

4 diff types of malignant melanoma
What is first step in management? Excision
Example: superficial spreading malignant melanoma (MC)
Example: on face of older pt – Lentigo maligna melanoma; irregular border, corn colored, LEAST likely to met of all malignant melanomas.
Example: black pop'n do not get malignant melanomas bc the black pigment in the skin prevents UV light damage and propensity for cancer. however, there is one type of cancer they malignant melanoma they CAN get:
black pt with dyspnea, on xray find multiple mets all over body. Bx is done and pt has malignant melanoma, which part of the body would you examine to find the primary dz? Under the nails, palms or sole of the feet – this is Acrolentiginous malignant melanoma ('acro' means edge of/tip of) – this is the MOST AGGRESSIVE of all the melanomas. This has nothing to do with radiation. Pagets dz looks similar

Example: Nodular malignant melanoma – also very aggressive.

The most important thing affecting prognosis is depth of invasion (key to prognosis – magic # is .76 mm). If its less than .76, its not gonna met.

Toxins
2 poisonous spiders –
Black widow
Has a neurotoxin – causes spasm of the muscles in the upper thighs and abdomen so strong its almost like tetanus; pain muscle contractions, esp in the abdomen. There is an antivenom, painful bite

Example: person went down into their cellar, lifted boxes, felt sharp prick on finger, and developed contractures over a period of hrs – due to black widow bite.

Brown recluse spider (aka violin spider)
Painless bite, has a necrotoxin, leading to ulcer
So, neurotoxin for black widow, necrotoxin for brown reclous

Where is receptors to androgens? Sebaceous glands (this is why men get more zits than woman – testosterone will release lipid rich material which gets into the hair follicle. Then, if you have proprionum acnei (anaerobe) it has lipases that breakdown fat from the sebaceous gland and produces FA's that irritate the follicle and end up with acne. So, men more likely to get it bc they have acne
It all occurs in the erector pili muscle of the skin.
So, there are androgen receptors sebaceous glands and erector pili muscle.

Drug used to prevent hirsutism? Spironolactone (same drug used to block aldosterone); this drug is good bc it blocks androgen receptors and therefore prevents hirsutism. Can also lead to gynecomastia.

CNS

Spinal fluid – derives from choroid plexus in the ventricles. In the lateral, 3rd and 4th ventricles. Its an ultrafiltrate of plasma. What is the difference in serum and spinal fluid? Way more protein in spinal fluid bc it's an ultrafiltrate. Cell? Hardly any cells in spinal fluid (none). Glucose? Lower in spinal fluid – about 60% of what it is in serum (if the spinal fluid glucose level were low, then something is in there utilizing it for energy such as bacteria or fungus or cancer cells). Is there anything MORE in spinal fluid than serum? Chloride (way higher in spinal fluid than serum) - around 120. These are imp bc there are injuries to the head.

Example: baseball that hits the eye in an orbital blowout fracture – can potentially break cribriform plate, leading to dripping fluid out, which could be snot, serum, or spinal fluid. So, its imp to know diff's btwn the two.

Example: wacked in the head – fluid out of ear (otorrhea), hemorrhage leads to battle sign. This is a fracture of the basilar plate and there is spinal fluid there.

Most of the fluid comes out the aqueduct of sylvius – which is the MCC of hydrocephalus in children bc it gets blocked off until you get a build up of spinal fluid in the 3rd vent and lateral vent, which is a narrow area and leads to hydrocephalus. Then, it comes to the fourth vent and needs to get out bc it needs to get into the subarachnoid space. So, it goes through the foramen of Luschka and Magendie, so fluid goes out.

Dura means strong – it's tightly adherent to the periosteum. So, when pt has epidural hematoma (blood clot betwn bone and dura). The only pressure that can split the periosteum away from dura is arterial pressure. So, **this is the one when the middle mengial artery ruptures**, and can be done with arterial pressure (not venous).

It gets into the subarachnoid space (to protect us – a cushion against damage). Get rid of spinal fliud in arachonoid granulation. [A tumor can arise from the arachnoid granulations – meningioma.] It goes through the arachnoid granulations, (there are NO LYMPHATICS IN BRAIN) and the dural sinuses and conglomerate into the jugular vein, which is emptied into the right side of the heart.

So, when you do a valsalva and the neck veins distend, that pressure transmits all the way back to the dural sinuses, to the arachnoid granulations through the spinal fluid , and right down the the needle in the subarachnoid space at L4 and the pressure goes up. This is called quakens step maneuver. It is a great test for when you are doing a spinal tap to see if the entire subarachnoid space is patent. If you don't see that manometer go up, there is something blocking the spinal fluid more proximally.
Example: when you wt lift, you shouldn't hold your breath bc the pressure are huge and and lead to a herniated disk.

Tentorium Cerebelli
70% of brain tumors in adults are supratentorial (involve cerebral cortex)
70% of brain tumors in kids are infratentorial (cerebellar, cystic astrocytoma, medulloblastoma)

Hydrocephalus
Communicating vs Noncommunicating
Communication of spinal fluid in ventricles with subarchnoid space.

Noncommunicating
MC
Something is preventing spinal fluid in the ventricles from getting into the subarachnoid space
MCC = stenosed Aqueduct of Sylvius
Or something going in the 4th vent, ependymoma in kids will block it off, or meningitis in base of brain (TB), leads to scar tissue bc blocks foramen of magendie and luschka.

Communicating
Still communicating, but still a build up of pressure. One cause could be tumor of choroid plexus (papillary looking). So, if you have a tumor there, you have a greater ultrafiltrate of plasma and would be making more plasma. Also, would be making more spinal fluid. There would still be a communication with here, but the pressure would build up bc making more than you commonly do.
More commonly, what if you have a subarachnoid bleed or meningitis? Then pt has scarred off arachnoid granulations and have no way of draining it out. So, still have a communication, but cannot get rid of it (MC).

Arnold Chiari Malformation
Example: pull down spinal cord. This would bring the medulla into the cervical region and maybe a lil part of the cerebellum. Leads to hydrocephalus and platybasia (flattening of the base of the skull)

Dandy walker syndrome
Cerebellar vermis is not developed

Herniation
Why would we herniate in the brain? Bc there is cerebral edema and no other place to go. The famous ones are tonsillar herniation through the foramen magnum. (from the cerebellum) – cerebellar herniation – has been squeezed into the foramen magnum, and has constriction. Can cause immediate death.

Uncal herniation – medial portion of the temporal lobe herniates through the tentorium cerebelli and pressing against midbrain, leads to hemorrhage (duret's hemorrhage). Also an oculomotor nerve that is gonna be compressed. So, this will lead to opthalomoplegia (LR6SO4, 3), so everything innervated by CN III is paralyzed. With oculomotor nerve palsy, it is down and out. (down and in is CN 4 palsy – if CN 6 is paralyzed, will look cross eyed). Look at pupil.

Example: MRI of oribit, name muscles
Parasympathetic constrict the pupil (normally) , sympathetics dilate (normally)
So, if you mess up the parasympathetics, which normally constrict, it will lead to mydriasis.
The first sign of uncal herniation is mydriasis of pupil on side of herniation (so it dilates on that side). Also, posterior cerebral artery can get blocked with uncal herniation, leading to post lobe infarction.
Know brainstem and CN's and how it related to herniation

Papilledema
Any cause of increased incranial pressure
Vit A tox
Lead poisoning – delta-aminolevulinic acid – leads to increased permeability

Audio file Day5 #6 CNS

Hydrocephalus
MCC = stenosis of the aqueduct of sylvius
Noncommunicating.
Get hydrocephalus bc the sutures have not fused
if you miss hydrocephalus in adult and sutures have fused, will lead to dilatation of the ventricles and eventually over years, the pressure will turn back to normal bc the increased pressures keep the choroid plexus from making so much
Dementia, ataxia, urinary incontinence.
Aka normal pressure hydrocephalus (bc pressures normalize)

Tuberous Sclerosis
AD
Hamartomas (noneoplastic proliferation of things)
Ventricles have bumps called tubercles – which are hamartomas which have proliferation of astrocytes. They produce hamartomas that bulge into the ventricle, called candle stick dripping. Hemartomas of the kidney called angiomyolipomas, MR, cardiac tumors (rhabdomyomas), shagreen patches, areas of hypopigmentation, woods light shine out
Anencephaly
Worst of neural tube defects
Absent brain

Vertebral arch defects
Spina bifida occulta – tufts of hair come out, vert arches do not touch, no meninges come
Meningoceole – meninges come out
Meningomylocele – both meninges and spinal cord come out
High alpha feto protein levels in blood of mother; decreased in downs syndrome
Have to be on folate to prevent neural tube defects (neural tube finished forming by 30 days, so make sure she is on folate if she is trying to get pregnant).

Neurofibromatosis
Albright syndrome (precocious puberty, café au lait, bone zits)
Sturge weber
Café au lait (coffee colored non raised lesions) spot, plexiform neurofibromas, hyperpigmentation in the axilla (axillary freckling), neurofibromas
AD , therefore late manifestations (esp for neurofibromatosis), penetrance, variable expressivity (you are expressing the dz, but diff levels of how severe the dz is)
Example: pt with **HTN** and pic, what test would you get? Relationship of neurofibroma with pheochromocytoma, therefore get a 24 hr urine for VMA and metanephrine.

Acoustic schwannoma
Example: pt with sensorinerual hearining loss – b9 tumor of Schwann cells around CN 8

Meningiomas
Optic nerve gliomas

Syringomyelia
Example: pt that works in factory and one of workers says you are burning your hand and pt didn't notice this, on exam loss of musculature (loss of LMN) in intrinsic muscles of the hand, loss of pain and temp in cape like distribution across back.
Can't feel pain (not ALS – in ALS, first place of development of loss of muscles is here, so don't confuse; but ALS is UMN and LMN loss, PURE MOTOR , so if pt has pain, ie, this is sensory and not ALS)
Big cystic cavity knocking off spinothalamic knocking off pain and temp. can knock off the corticospinal tract and anterior horn cells, so it will be a COMBO of sensory AND motor loss for syringiomyelia.

Infections

Meningitis vs encephalitis
Meningitis – inflammation of meninges and nuchal rigidity; if you move your head or extend your knee, you will stretch the meniges, leading to pain (stretching inflamed meninges).
Encephalitis – sleeping sickness – they are always sleeping and drowsy; they have mental status abnormalities (not nuchal rigidity)

Pus at the base of the brain – can possibly block lushka and majendie, leading to obstructive hydrocephaly and noncommunicating
When you Rx meningitis, use steroids and Abs. why? Steroids prevent scar tissue formation and complications that arise with it (ie hydrocephalus).
This is standard TB meningitis Rx (TB in brain causes vasculitis and scarring)
Deafness is a complication of meningitis.

Rabies
Example:: meningitis, cerebral abcess, Rabies (MCC in States = skunks, dogs in 3rd world)
Negri bodies (perkinje cell inclusion)

CMV
Periventricular calicifications
Example: section of kid (brain) - see white stuff going around ventricles
MC congental infection = CMV
What body fluid is best to culture from? Urine

Meningitis
What is MC meningitis/sepis in first month of life? Group B strep – strep agalactae – bc many women have this organism in their vagina, so they are carriers. Premature ruptured membranes lets the organism get up, get an chorioamnionitis and into the bloodstream.
2nd MCC is E coli
3rd MCC is listeria monocytogenes (gram + rod with tumbling motility – as does Trichomonas vaginalis)

What food should pregnant women avoid? Soft cheeses (ie feta cheese, but listeria is present).
MC in 1 month – 18 yo = N meningitides
(not H influenza bc vaccination)
MC in 18+ = Strep pn
Example: 52 yo man, nuchal rigidity, tap shows increased protein, increased neutrophils and decreased glucose – dx? Strep pn. what is the gram stain? Gram + diploccus

Cryptococcus
India ink – see narrow based bud for Cryptococcus
Who do you think this is in? IC'd pts
What is MC immunodef in USA? AIDs
MCC meningitis in AIDs pts? Cryptococcus

Mucormycosis
In frontal lobe, therefore from a diabetic in ketoacidosis

Example: special stain on AIDs pt with CD 4 ct of 50, CT showed space occupying lesion
Dx? **Toxoplasmosis**

Example: pig herder, and long time problem with focal epileptic seizures (dilating therapy) – multiple calcified and cystic lesions in brain – dx? **Cysticercosis**

Example: Jacob Cruetzfeltds from prions (mad cow) – who is most likely to get? Neuropathologists, neurosurgeons, beef, lettuce from Arizona (cow manure on it)

Traumatic lesions
Epidural hematoma (above dura) – hit in head middle meningeal – have to fracture bone (under arterial pressures, can separate dura from periosteum). When you get 50 mls of blood, you get uncal herniation and die. Ie get him, say they are ok, 6 hrs later epidural hematoma and death

Subdural hematoma – rupture of bridging veins betwn dura and arachonoid membrane. If you have cerebral atrophy, then the space bwtn the dura and arachnoid membranes is bigger. Bridging veins dangling, break and get a hematoma. Fluctuating levels of consciousness. Left untreated lead to dementia. Do CT to r/o epi and subdural hematoma (also for strokes – if its a hemorrhagic stroke)

Strokes
Slide: Brain: one side is bigger. Atherosclerotic stroke; pale infarct of brain. At bifurcation, there is an atherosclerotic plaque and thrombus. No blood flow to brain and it infracted, starts breaking down, no reperfusion, so it remains a pale infarct. If the thrombus did break apart, and reperfusse the brain, the blood in the goes into the area of infarction and is called a hemorrhagic infarct. However, this usually doesn't occur and pale infarcts more common. If no blood, and there is infarction, pt is a candidate for heparin therapy. Over time, if pt survives, ends up with cystic space where there was infarction and this is called liquefactive necrosis--pale infarct, liquefactive necrosis.

Slide: hemorrhagic infarct – blood is to edge of brain – this is an embolic infarct, usually from left side of the heart. The vessel it always goes to is middle cerebral artery. It gets into the Circle of Willis and into the middle cerebral. If you embolize down, will go into the superior mesenteric
The reason it is hemorrhagic is bc pt will get breakdown of fibrinolytic system of the embolus and leads to reperfusion. Instead of being a pale infarct, it's a hemorrhagic infarct. So, both a atherosclerotic stroke and hemorrhagic stroke are both infarcts – one is pale and the other is hemorrhagic.

Slide: **HTN**, pressures cause lenticulostriate vessels to come up and supply this area of the brain. Derive from the middle cerebral aneurysms, called Charcot Bouchard aneurysm and it ruptures, leading to giant hematoma and blood clot. Horrible prognosis.
So, embolic stroke goes to surface of the brain and if it's in the basal ganglia, **it's always an intracebral bleed from HTN.**

Example: **subarachnoid hemorrhage** mostly due to rupture congenital berry aneurysm. MC at the junction ant comm branch of ant cerebral artery
Less common cause of SAH:
AV malformation
Sturge Weber – on same side as skin lesion of the face, there is an AV malformation

Lacunar infarcts – small areas on the brain; unusual bc they hit areas of the brain. Depending on where in the internal capsule, can have a pure motor stroke or pure sensory. MC due to HTN

Multiple Sclerosis (MS)
MC demyelinating Dz (autoimmune) – MS

Slide:demylinated: white matter has myelin it, grey doesn't. If you are destroying white matter, then you'll see grey underneath. **Plaques of MS**.

2 ways to demylinate
1) knock off cell that makes myelin in the brain (oligodendrocytes in brain, schwann cell in PNS) – viruses do this – subacute sclerosis, progressive multifocal leukoencephalopathy, HPV – they affect the oligodendrocyte;

2) can also have Ab's against myelin and not the oligodendrocyte, which is MS paresthesias
Nystagmus, ataxia, optic neuritis with blurry vision (**MCC of Optic Neuritis= MS** bc demylination of optic nerve)

Internuclear opthalmaplegia (demylination of MLF) - pathognomonic

Spinal tap will show increased protein, normal glucose, increase lymphs

Hydrocephalus Ex Vacuo
Severe atrophy of brain and ventricles look bigger than they should be
Dementia

Alzheimer's Dz
Classic lesion: senile plaque, neurit's, amyloid (Beta!!) – so beta amyloid is toxic and the more you have the more toxic – pathognomonic of alzheimers, on c'some 21, therefore seen in down's, neurofib tangles (in any dementia and HD)
Alz – probs in higer levels – dementia
Only way to dx is autopsy (confirmation) – see senile plaques

Parkinson's Dz
Resting tremor