RAPID REVIEW NOTES

DONNIE | GUNBOSS

Vitamins

Vitamin A

- Retinoic Acid is important in Rod and cone cells for vision
- Hair, skin, eyes = impt in night vision and blindness
- **Necessary in PTH function → cofactor**
- **Impt. Component of CSF**
- Deficiency:
  - **Night Blindness**
  - **↓ Ca^{2+} ↑ P = hypothyroidism**
- **Vitamin A Excess**
  - ↑↑ PTH Effect
    - **Moans, Groans → Pancreatitis**
    - **Bones → PTH leaching bone**
    - **Stones → Ca^{2+}**
  - **Excess production of CSF → pseudotumor cerebri = only cause of ICP that causes no herniation**
    - Presents with Headache and papilledema
    - CT → Ventricle enlargement
    - LP → ↑↑ pressure
    - Treatment:
      - Serial LP's to siphon excess CSF

Vitamin B1 (Thiamine) → TTP

- Pyruvate dehydrogenase
- α - keto glutarate dehydrogenase
- Branched Chain amino acid dehydrogenase
- Transketolase

Vitamin B1 Deficiecy:

- Wet Beri Beri = High output cardiac failure
- Dry beri beri = w/o heart failure
- Alcoholic = Wernicke's encephalopathy (temporal lobe) - ataxia, nystagmus
  - Korsakoff (Mammilary bodies) - confabulation, psychosis

Vitamin B2 (Riboflavin, FADH2)

- **Angular cheliosis/stomatitis**
- Best source = **Milk**, vegetables
- Sun can breakdown riboflavin → reason why milk is no longer stored in glass bottles
- Magenta colored tongue

Vitamin B3 = NIACIN

- **NAD**/NADH

Niacin Deficiency

- **Pellagra = 3 D's = Dementia, Diarrhea, Dermatitis, Death**
- Hartnup's Disease presents very similar
  - A problem with the transport of Tryptophan → which is needed to make niacin

Trytophan
- needed to make Niacin
- Source = corn
- Hartnup's Disease = defective renal transport, similar to Pellagra

Vitamin B4 = Lipoic acid
Vitamin B5 = Pantothenic acid → CoA

Vitamin B6 = Pyridoxine
- **Cofactor for all TRANSAMINASES (AST/ALT)**
- INH pulls B_6 out of the body
- Deficiency → neuropathy

Vitamin B12 = Cyanocobalamin
- Use:
  - Methyl malonyl CoA Mutase = needed in prevention of myelin neuropathy
  - Homocysteine methyl transferase
- Water soluble although absorbed in proximal ileum
- Deficiency:
  - Dorsal column/Corticalspinal Tracts will be affect because they are the longest tracts therefore, need the most
  - Megaloblastic Anemia

Folate
- Thymidine synthesis, purine synthesis.
- **1st vitamin to run out in association with rapidly dividing cells**
- Deficiency:
  - Megaloblastic Anemia without neuropathy
  - Deficiency in pregnancy can cause neural tube defects in the fetus
  - Homocystienemia with risk of DVT and atherosclerosis
- MCC
  - Alcoholics and pregnancy - body stores can be depleted in 3 months

Vitamin C
- Scurvy - **bleeding gums/hair follicles**
  - Needed in:
    - **Proline and lysl hydroxylase - collagen synthesis**
    - **Dopamine hydroxylase - catecholamine synthesis**
    - **Absorption of iron in GI tract**

Vitamin D
- Calcium absorption in Gut
- Reabsorption of Ca^{2+} from kidneys
- **Osteoblastic activity → ↑ both Ca^{2+} and P**
- Decreased in Rickets
  - Children
  - **Lateral Bowing of legs**

- Decreased in Osteomalacia = Soft bones
- Vitamin D resistance Rickets
    - **X-linked dominant (Father → daughter)**
    - Kidney is leaking phosphorus, so calcium goes with it

Vitamin E

- anti-oxidant (absorbs free radicals)
- Skin, eyes, hair
- Decreased in Retinopathy
- Decreased in Alzheimer's

Vitamin K

- **Clotting Factors 2,7,9,10, (1972) proteins C (shortest half life) & S**
- γ-carboxylation of these factors

Biotin

- **Cofactor for all CARBOXYLASES**
- Pyruvate carboxylase (Gluconeogenesis/FA Syn)

Minerals:

Fe^{2+}

- Hemoglobin → O2 Transport
- Supports electron transport chain → Complex III/IV
- When decreased = Possible mental retardation in children

Ca^{2+}

- Necessary for muscle contraction
    - **All muscles need INTRACELLULAR Ca^{2+}**
    - **Cardiac & Smooth Muscle need EXTRACELLULAR Ca^{2+}**
        - **Needed for atrial contraction**
- IP3/DAG Second messenger system

Mg^{2+}

- Co-factor for ALL KINASES and PTH

Cu^{2+}

- **Need for the hydroxylation of lysine**
- Deficiency
    - **Minky's kinky hair**
        - Orange hair
        - Feels like copper wiring
- **Excess = Wilson's Disease = hepatolenticular degeneration**
    - Lenticular → Basal ganglia
    - Hepato → liver
    - Keisher-fleisher rings in iris
    - Ceruloplasmin deficiency

Zn

- Hair, taste buds, **dysgusia**, sperm

Trace Elements:
Chromium - neede in Insulin action
Selenium - necessary for heart
Manganese - xanthine oxidase

Biochemistry:

CONCEPT:

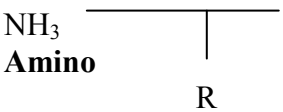
Low Energy State= the default illness state affecting all organ systems.

- Organs:
  - **CNS ➔ mental retardation**
  - **Muscle ➔ weakness**
  - **CV ➔ Heart Failure**
  - **Cilia ➔ Respiratory infection, shortness of breath**
  - **GI ➔ diarrhea initially due to malabsorption, then followed by constipation due to lack of motility**
  - **Hair ➔ falls out**
  - **Cuticles ➔ brittle**
  - **Skin ➔ dry**
  - **Vascular endothelium ➔ breaks down**
  - **Bone marrow:**
    - **RBC ➔ anemia**
    - **WBC ➔ agranulocytosis**
    - **Platelet ➔ bleeding disorder**
  - **Renal ➔ Proximal convoluted tubules**
  - **Reproductive ➔ low sperm count**
  - **Bladder ➔ slows down → hemorrhagic cystitis**
  - **Endometrium ➔ no menstruation**
  - **Germ cells ➔ CA**
- Signs and Symptoms:
  - **Most Common Symptom = weakness and SOB**
  - **Most Common Sign = Tachypnea and Dyspnea**
  - **Most Common infection = UTI and respiratory infections**
  - **Most Common cause of death = Heart Failure**

Proteins:

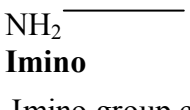
- Body is made up of mostly proteins.
  - Recall that enzymes are proteins
- But body likes to hang on to FAT (9 Kcal/1g)
- SUGARS and AMINO ACIDS (4 kcal/ 1g)

Structure of Amino Acids:



(determines structure of AA)

Exception: Proline:



Imino group creates **kinks** and **bends**
Found in: hair, muscle, skin, collagen, cartilage,

Buffers:
Proteins are the most important intracellular buffers
Bicarbonate is the most important extracellular buffer

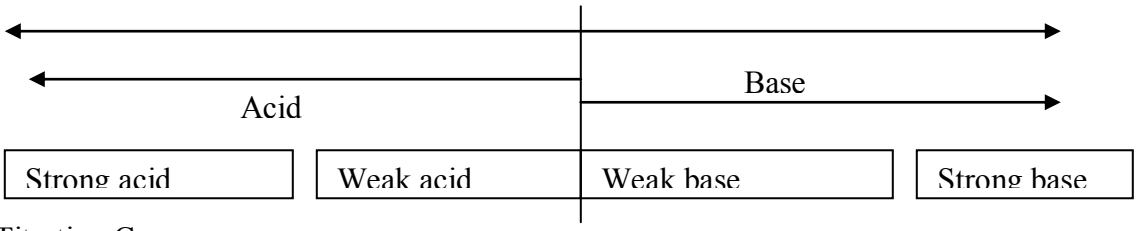
- Every acid group starts without a charge.
- Ex: As an amino acid group dissociates it becomes less soluble

- Dissociation= loss of H+
- Soluble = has charge and will attract H_2O → Can not cross Blood Brain Barrier
- Bioavailable = neutral, can cross a fat soluble membrane.
  - **When talking about Bioavailability think about Volume of distribution or t ½**

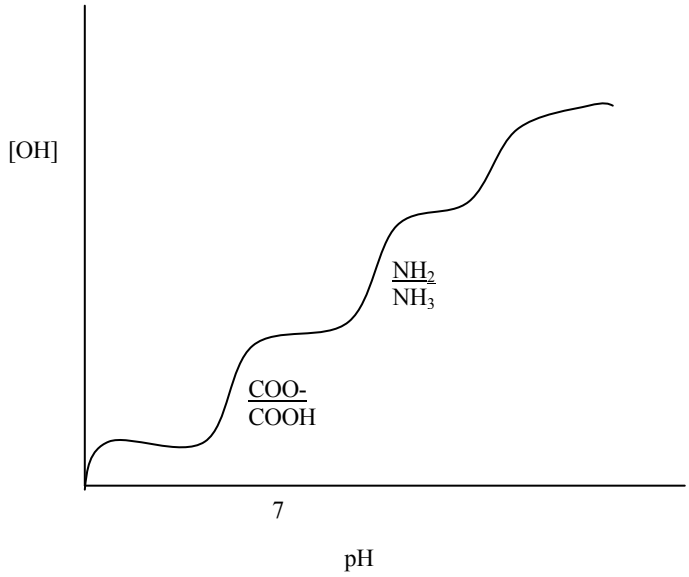
Example:
- **NH_3^+ → NH_2 = ↓ Solubility (by losing a charge); ↑ Bioavailability (by making it neutral)**
- **COOH → COO^- = ↑ Solubility (by adding charge); ↓ Bioavailability (b/c no longer neutral)**

pKa:

1 2 3 4 5 6 7 8 9 10 11 →14



Titration Curve:



Buffer = ability to absorb acid/

$$pH = pK - \log\frac{[HA]}{[A^-]}$$

In a buffer [HA] = [A] so pH=pK which means it is 50% dissociated.

Histadine **has pK = 6.7 which is closest to pH of 7.4 ➔ it is the best buffer in humans.**

* Liver handles fat-soluble content

Dissociation relationship:

pH = pK + 2 ➔ 99% dissociated	=99% soluble ➔ 1% bioavailable
pH = pK + 1 ➔ 90% dissociated	=90%soluble ➔ 10% bioavailable
pH = pK ➔ 50% dissociated Best Buffer	
pH = pK - 1 ➔ 10% dissociated	=10% soluble➔90% bioavailable
pH = pK - 2 ➔ 1% dissociated	=1% soluble➔99% bioavailable

In order to absorb molecules they need to remain **neutral = bioavailable**. Follow these rules to keep molecules neutral.

- **To absorb more acid need to place in a stronger acid**
  - **Acid + Strong Acid = Behaves as a BASE**
- **To absorb more base place in a stronger base**
  - **Base + Strong Base = Behaves as a ACID**
- **Understand that the body makes 20x more HCO_3^- than acid**
  - **Because we ingest primarily acidic substances**

Example:

1. Crossing the Blood Brain Barrier need to remain neutral.
2. If ingest acid → need to keep it charged so it will not be absorbed → give base (**$NaHCO_3$**)
   a. Recall Activated Charcoal in the ER
3. If ingest base → keep charged by giving acid (**coke, juice**) → will absorb less base.
4. Patient taking Aspirin and eating acidic food can cause increased dissociation of ASA and then ASA poisoning.

Common pHs:
Stomach → pH = 1-2
Duodenum → pH = 3-5
Early Jejunum → pH = 5-7
Late Jejunum → pH = 7-9
Ileum → pH > 9

Common Acids: ASA, Myoglobin (d/t crush injury), phenobarbiltal.
Common Bases: Amphetamines

Example: ASA has pK = 4.3 (like other NSAIDs), therefore it would be absorbed best in stomach pH of 1-2, when 1% will be dissociated and 99% will be bioavailable for absorption.

Key Concept: Acid + Base will decrease absorption.

Example: When muscle breaks down releasing myoglobin, give bicarbonate to prevent secretion and further loss of myoglobin.

Isoelectric Point:

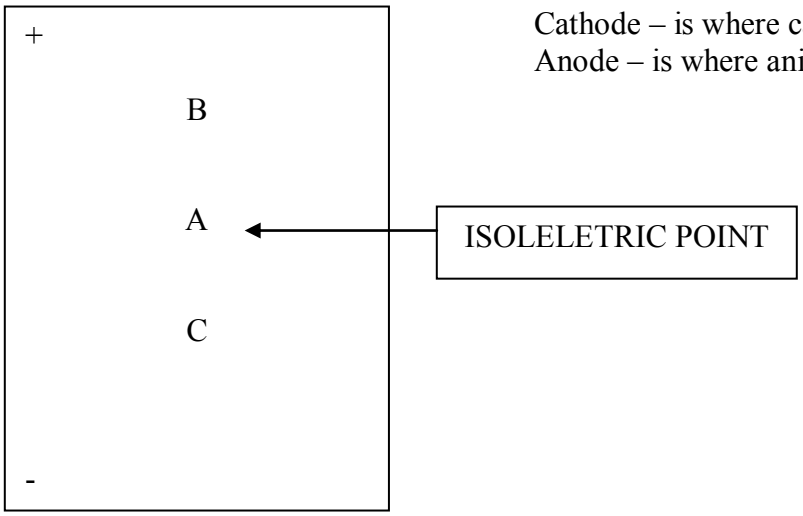
pI = Zwiterion = NO NET charge.

$$pI = \frac{pk_1 + pK_2}{2}$$

- When you have more than two groups:
  - "like" groups will have isoelectric point that will balance out opposite "like" group isoelectric point.

$$\frac{\frac{pK_1 + pK_2}{2} + \frac{pK_1 + pK_2 + pK_3}{3}}{2}$$

Gel Electrophoresis



Cathode – is where cations GO
Anode – is where anions GO

Amino Acids:
Groups

Amino Acid	Abbreviation
Alanine	Ala
Glycine	Gly
Leucine	Leu
Proline	Pro
Threonine	Thr
Cysteine	Cys
Histidine	His
Isoleucine	Ile
Methionine	Met
Serine	Ser
Valine	Val
Arginine	Arg
Asparagine	Asn
Aspartate	Asp
Glutamate	Glu
Glutamine	Gln
Phenylalanine	Phe
Tyrosine	Tyr
Tryptophan	Trp
Lysine	Lys

Acidic Groups = Asp, Glu
Basic Groups = Arg, Lys
Sulfur = Cys, Met
O-Bonds = Ser, Thr, Trp
N-Bonds = Asp, Gln
Branched aa = Leu, Ile, Val
Bulky (aromatic) =Phe, Thr, Trp
Small =Gly
Kinky =Pro

Ketogenic = Lys, Leu
(made and broken down to acetyl Co-A)
Glucogenic + Ketogenic = Phe, Iso, Thr, Trp
Glucogenic = All the rest.

GABA concept:

$$NH_4 + \alpha KG \rightarrow Glu \rightarrow GABA(\text{sup}\,pressor)$$
$$\swarrow \quad \searrow$$
$$NH_3 + H^+$$

GABA is a suppressor causing:
Bradycardia, Lethargy, Constipation, Impotence

Essential Amino Acids:

- Body will break down protein to look for essential amino acids if not provided by **the diet**.
- **PVT TIM HALL**

Phenylalanine
Valine
Tryptophan

Threonine
Isoleucine
Methionine

Histidine
Arginine
Leucine
Lysine

Disorders:

Childhood screening:
PKU, galactosemia, hypothyroidism, congenital adrenal hypoplasia, biotindase.

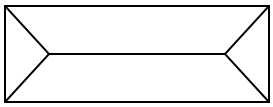
- **PKU**:
  - Phenylalanine hydroxylase is deficient
  - It is needed to make tyrosine
    - Therefore Tyrosine becomes an essential amino acid.
  - Signs and Symptoms:
    - Tyrosine is used to make:
      - Dopamine, Epinephrine and Norepinephrine→ mental retardation

- PKU cont.
    - Melanin for pigment → pale, blond, blue eyes
    - Build up of → phenylacetate + phenylpyruvate = musty odor

Screened in childhood ➔ GUTHIRE testing.

- **Maple Syrup Urine Disease:**
    - Deficiency in **branched amino acids** → Leu, Iso, Valine
    - Defective transport of branched amino acids in kidney collecting ducts will cause amino acids to "leak out".

- **Cystinuria: Autosomal Dominant**
    - Cystathione synthase enzyme is missing.
    - 4 Amino Acids show up in Urine
        - ***C***ysteine
        - ***O***rnithine
        - ***L***ysine
        - ***A***rginine



    - Develop Cysteine stones that have a crystal/envelope shape.

Protein Structure:

1° AA sequence including the peptide bonds:

1. All Bonds are planar = flat
2. Restricted mobility
3. R groups face away from each other

L R

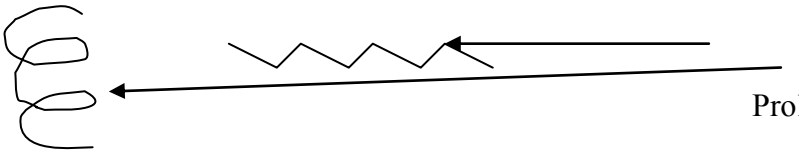
R

N—C—N—C

R

Transfiguration

2° α-helix vs. β- pleated sheet



Proline

GI, vessels, hair flat bones, skin

Humans have L-amino acids → will attack the D-amino acids

Adipose layers have the least amount of blood supply→ will take longer to heal.

3° 3D- determined by:

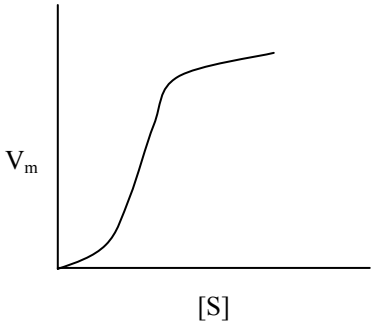
- Hydrophobic
- Hydrophilic interactions.

Covalent bonds begin to form.

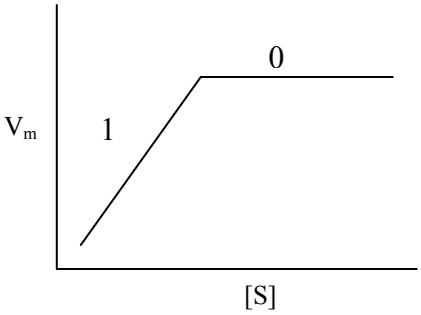
4° ≥2 proteins interact with enzymes

- Cooperativity
- Allosterism (one site will affect another site)
- **HEMOGLOBIN**

Ex. Hemoglobin



Allosterism



Cooperativity

1st order = [S] increases with V_m

0 order = change in [S] has no effect on V_m

- **The most effective way to monitor drug intake → PEAK & TROUGH Measurements**
  - Peak → taken 4 hours after dose → If Peak is ↑↑ = the dosage is too high
  - Trough → taken 1 hour after dose → If Trough is ↑↑ = Give the drug less often

Meds: usually exhibit 1st order kinetics

- As ↑ [drug], ↑degradation ⇒ less toxic

Chemo drugs exhibit 0 order kinetics

- Same amount of drug metabolized over time regardless of concentration ⇒ more toxic

Acid Hydrolysis:

- Dip protein in acid → acid denatured protein.
    - Glutamine → glutamate
    - Aspargine → aspartate

Gel Electrophoresis:

- Separated protein based on size
    - Smallest will move the farthest
    - Then separate by charge.

Ninhydrin Reaction:

- Separate out proline
    - Proline will stain yellow
    - All others will stain purple.

Edmund's Degradation

- Degradation that needs **Propylisothiocyanate (PITC)**
    - Will react with one amino acid at a time
        - From the **L amino terminal**
    - Used in spectrophotometry
    - Good for only **100 amino acids.accuracy**

Restriction Peptidase:

Amino Acids Sequencing

_ _ _ _ _

(lys, ala) (ser, met, phe)

You need to know which was amino acid was sequenced first!!!

If you cut with **trypsin**, where does it cut?

Trypsin cuts to the RIGHT of of lys and arginine!!!

_ lys/___ = Therefore, in a question, find the answer that already contains lys in the second position

KNOW WHERE THE ENZYME CUTS

Restriction Peptidases:

ALL CUT TO THE RIGHT

- Trypsin I - cuts arginine or lysine (basic groups)
- Elastase - gly, ala, ser
- CNBr - met
- Amino peptidase - repeatedly cleaves N-terminal from glycopeptides
- Chymyotrypsin - phe, thr, trp
- Mercaptoethanol - dissolves disulfide bonds

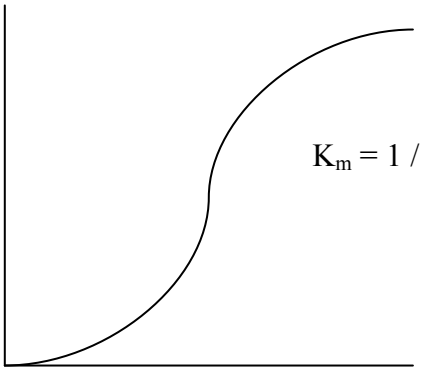
EXCEPTION:

Carboxy peptidase - cuts to the LEFT of any amino acid on carboxy terminal

Allosterism

- **Rate limiting Enzyme**
  - Always the slowest

V_{MAX}



K_m = 1 / Affinity (Potency)

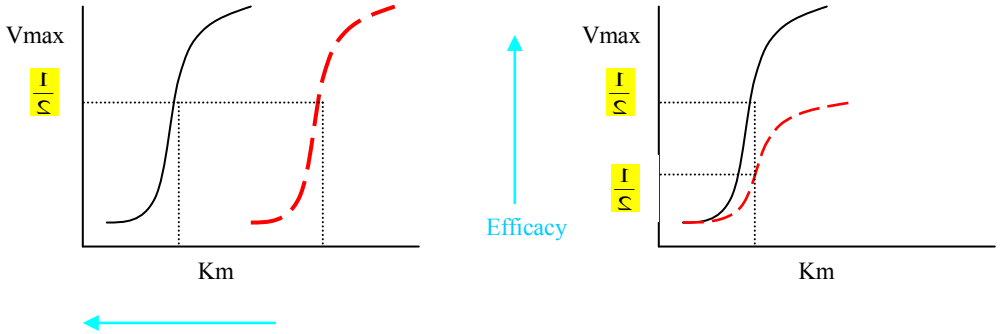
- **Inhibition:**
  - Competitive vs. Non-Competitive.
- Competitive ➔ looks like substrate fights for active site [S]

$\uparrow K_m = \frac{1}{affinity \downarrow}$

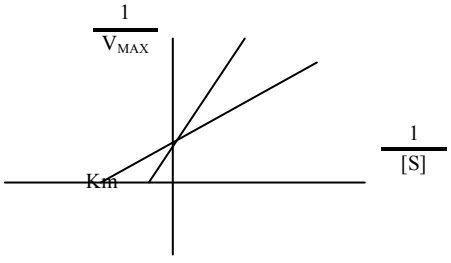
$V_{max} = V_{max}$

- Non-competitive ➔ competing for regulatory site.
  - No Δ in K_m or affinity
  - ⇓ V_{max}

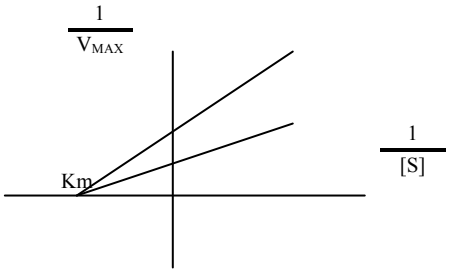
- **Competitive vs. Non Competitive inhibitors:**



Competitive Inhibition	Non-competitive Inhibition
Efficacy stays the same while potency decreases Fights for the active site	Potency remains the same while efficacy decreases.



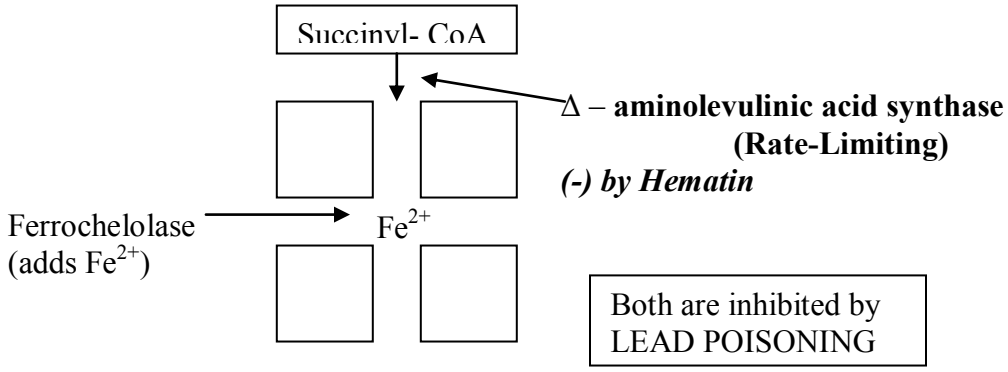
Change in Km NOT Vmax



Change in Vmax NOT Km

Hemoglobin:

Hg	HbA ➔ 98%	HbA_2 ➔ 2%	HbF
Genes	$\alpha_2\beta_2$	$\alpha_2\Delta_2$	$\alpha_2\gamma_2$



Anemias:

Microcytic Hypochromic anemia:

- Fe- deficiency anemia
- Anemia of Chronic disease (no Fe)
- Lead poisoning
- Thalasemias
- Hemoglobinopathies

Sideroblastic Anemia:

Macrophages that eat iron:

- Parasitic infection
- Impaired iron absorption
- Liver disease (live stores Fe)

Porphyrias:

Enzyme deficiencies causing inability to break up heme → Degradation problem
Symptoms: Red urine indicating hemolytic anemia.

Acute Intermittent Porphyria (most common)

- Recurrent acute abdominal pain and **neuropathy (remember this can be anything..headaches, ↑ ICP, etc…)**
- **MCC = STRESS**
  - Can be set off by menses
- MC Drugs that can cause this
  - Sulfa
  - Anti – Malarial
  - Metroniazole
  - Barbituates
- Treatment:
  - Hematin → stop Δaminolevulinic acid synthase → decrease further production of porphyrin.
  - Fluids → to flush it out
  - Sugar → helps draw the excess porphyrins out

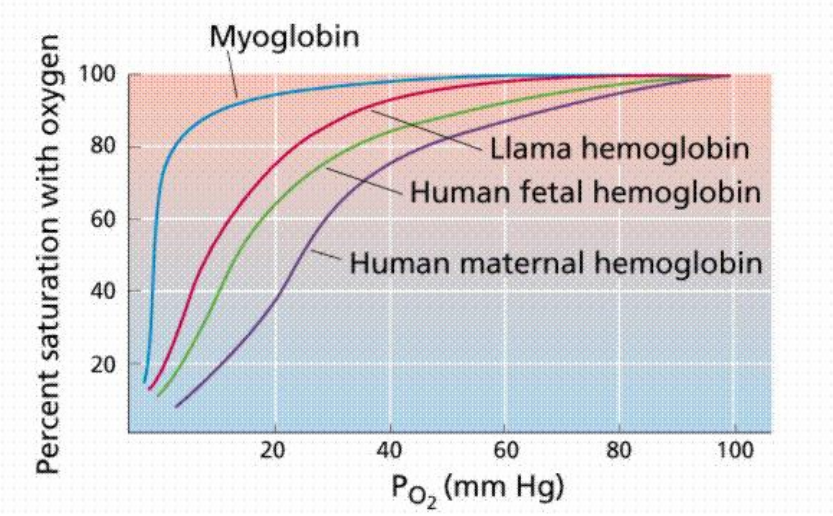
Porphyria Cutanea Tarda

-Sun blisters skin
-Starts in late childhood > 5 years old

Erythrocytic Protoporphyria

-Early childhood < 1 years old
-Blister in the su

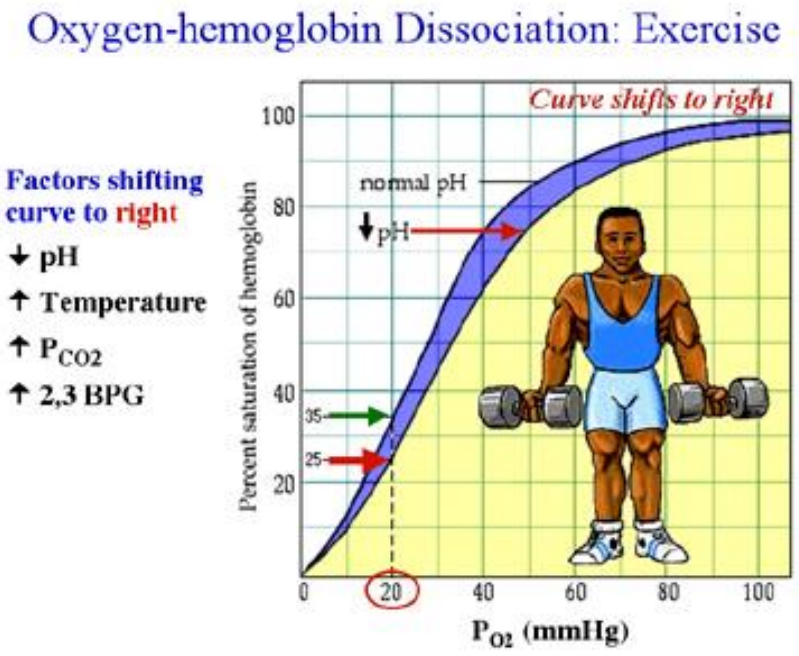
Myoglobin vs. Hemoglobin



Fetal Hb:

- Highest pO_2 in umbilical vein coming from placenta (coming from mom)
  - $pO_2 = 80$
- After liver $pO_2 \downarrow$ to 60%
- After brain $pO_2 \downarrow$ to 50%
- In extremities $pO_2 \downarrow$ to 40%
- Through Foramen Ovale and Left side $pO_2 = 90\%$
- $S_aO_2 = 90\% \rightarrow pO_2 = 60$

Hemoglobin
Normal values: Hg=15, Hct=45
1g of Hg has 4 Heme sites.



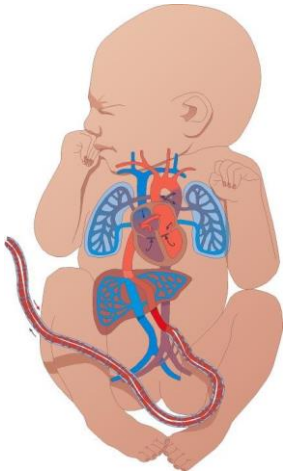
Athletes
pO_2 between 40 → 60 = Hypoxic period
Begin anaerobic → ↑ lactic acidosis
The 2nd Wind Theory
An athlete must out last this hypoxic period so that Myoglobin can begin to drop oxygen

Ex; **Normal pO_2 in the body is between 60-90** so O_2 sat will be > 90%
If pO_2< 60, free Hg to de saturate and curve shift to Right
Hg lets go of O_2 and shift to Left → Hg holding on to O_2

Erythropoiesis

- begins in the Yolk Sac at 4 months gestation.
- 6 months → liver, spleen and flat bones → close at 1 year
- 8 months → long bones
- After 1 year of age long bones are in charge of erythropoesis.

If long bones are damaged, ↓ in bone marrow > 1 year → spleen will take over again = splenomegaly



Inhibitors to Hb:

Carbons Monoxide:

- ***Competitive inhibitor of O_2***
  - Treatment = O_2
- **Cyanide**
  - ***Non-competitive inhibitor of O_2***
  - K_m doesn't change
  - V_{max} will decrease
  - Treatment with O_2 will not make saturation go up

Hemaglobenopathies:

Sickle Cell Disease:

- Autosomal recessive, HbS
- Protect Against Malaria
- Amino Acid substitution: **Val → Glu @ position 6 of β chain**
  - **Valine = Neutral → goes inside**
  - **Glutamic acid = Negative (charged) → goes outside**
  - **THIS PROVIDES THE MECHANISM FOR SICKLING**
- When O_2 decreases, the Val on opposite sides (positions 1 and 6) attract each other and change shape

SICKLE CELL = VASOOCLUSION

- Symptoms:
  - Begin to feel cold, lightheaded, and experience syncope
  - Dactylitis – painful and swollen fingers and toes in new born
- Present at 4-6 months of age when Hg F switches to Hg S
- At 6 years → SPLENECTOMY

Sickle Cell Trait (SA)

- Asymptomatic, but barred from extreme hypoxic situations or jobs
  - Fireman, pilot, diver

Hg C:

- Autosomal recessive
- Amino Acid substitution: Lys → Glutamic acid @ position 6 of β unit. → NO SICKLING
  - Lys – (+) = outside
  - Glutamic acid – (-) = outside
  - BOTH STAY ON THE SURFACE = no sickling
- Lys is charged so it remains hydrophilic even after lets go of O2

Methemaglobanemia

- Fe^{3+} → can't pick up O_2 = Ferric (oxidized)
  - 1° methemaglobanemia- inborn
  - MCC = 2° methemaglobanemia- drug induced (sulfa) can oxidize Fe^{2+}/Infections d/t free radicals
  - **Low O_2 saturation BUT pO_2 will be normal**
- Treatment:
  - **Methylene Blue – "Give them something blue to turn them pink"**
    - Anyl Nitrite- will convert Hg to Fe^{3+} not allowing CN to act.
    - Sodium Thiosulfate will bind CN and recant thiocyanate
    - Blood transfusion

Thalassemias:
Hg made up of:
- α subunit - 4 genes
- β subunit – 2 genes

Thalassemia	# of Genes missing	% Hb Left	Hb	Symptoms
α – minor	1	75%	11.25	No symptoms
	2	50%	7.5	? symptoms
	3	25%	3.75	(+) symptoms, basophilic stippling
α – major	**4**	**0%**	**0**	**Hydrops Fetalis**
β – minor	1	50%	7.5	Always have ↑ HbA_2 and HbF +/- symptoms based on lifestyle
β – Major	**2**	**0%**	**0**	**No HbA, asymptomatic until 6 mos. b/c time when HbF → HbA; All erythropoietic organs reopen**

Cooley's Anemia (Type of β Thalassemia)
- Ineffective erythropoiesis → making useless RBC
- Baby making blood from everywhere:
  - Frontal Bossing
  - Large sternum/ clavicles
  - Hepatosplenomegaly
  - Long tender extremities
  - **HCT ↑↑↑, but Hb ↓↓↓**
- Treatment:
  - Total body transfusion every 60-90 days → TRANSFUSION DEPENDENT
    - Recall that a RBC only lives 120 days
  - 1 unit of PRBC =
    - **↑ Hg by 1-2g**
    - **↑ Fe by 3-4g**
    - **Will die within I 10 years of transfusion related infections**
    - **Can die d/t Iron overload = Hemochromatosis**

Hemosiderosis:
- Bone marrow overwhelmed with Fe due to frequent transfusions.
  - **Sideroblastic anemia**

Hemochromatosis: Deposit Fe into organs.
- 1^0 Hemochromatosis:
  - Congenital – rare autosomal recessive, **HLA_3** + Chr 6
  - Duodenum absorbing too much Fe leading to:
    - Hemosiderosis
    - Hemochromatosis
- Hemochromatosis:
  - Acquired
  - Due to transfusions:
    - Bronzing accumulates in skin
  - Will die of:
    - 1^{st} decade of life ➔ transfusion related infections
    - 2^{nd} decade of life ➔ HF

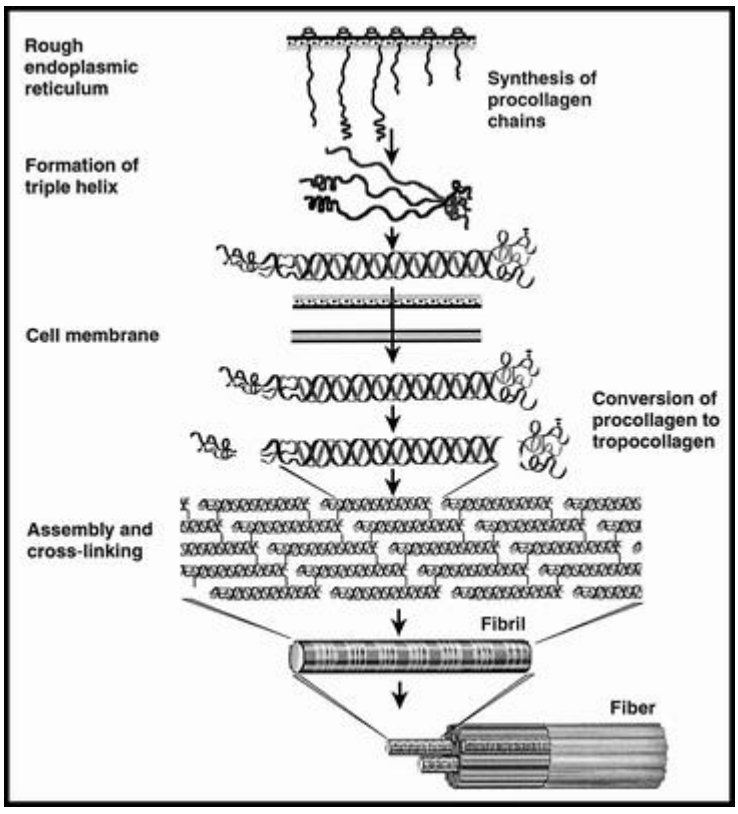
Transfusion Infections
Hep B
Hep C
HIV
CMV
EBV
West Nile
Hep D
Malaria
Bacteria
Babesosis
Syphuliis

Proteins:

Collagen

- Most abundant type
- 4 types of collagen → **SCAB**
    I. **S**kin and bone
    II. **C**onnective tissue –
        - Support for skin and bones
        - Tendons, ligaments, cartilage, all jelly-like material, aqueous humor, interstitium, synovial fluid
    III. **A**rteries
    IV. **B**asement membrane
    - Amino Acid Makeup:
        - Gly (→ compact)
        - Pro
        - Lys
        - OH- Pro (= proline hydroxylase)
            - **Need Vitamin C**
        - OH- Lys (= lysine hydroxilase)
            - **Need Copper**
            - **Inhibited by Homocysteine in diet.**
    - Type III collagen abnormalities are the most dangerous.
        - Coronary arteries are always the 1st to be affected in vasculitis.

- **Collagen made in the RER**
    - Comes out as **Pre Pro** Collagen
        - **Pre = guides to ER and gets cut off**
    - Collagen in the **ONLY** protein to get modified in ER
        - All other proteins get modified in the **Golgi**
        - **Pro = guides to Golgi for packaging.**
    - Comes out of Golgi a
        - **Tropocollagen:**
- Tropocollagen then gets secreted
    - ONLY protein secreted out of the cell **unfinished**
    - It is completed at the site of action →
    - Tightened up by Plasma Peptidases.



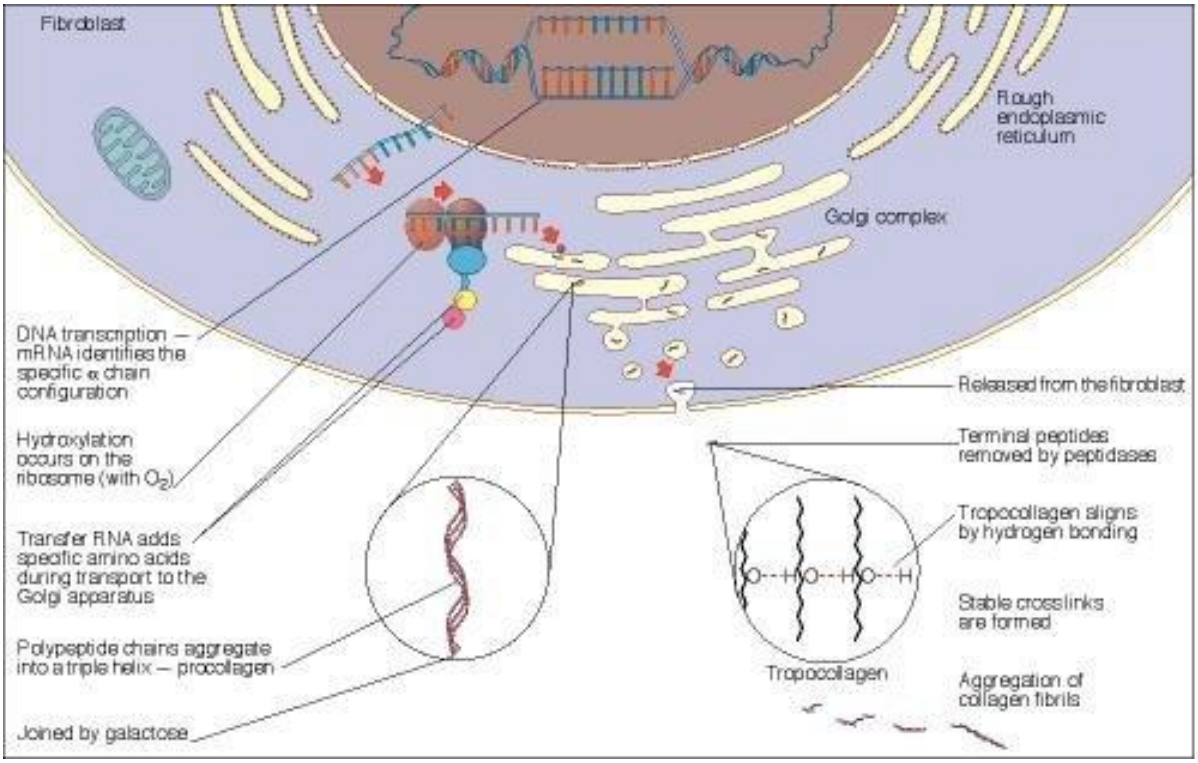
→ Occasionally in Blacks and Hispanics **fibroblasts release too much collaged forming a Keloid = Hamartoma (too much tissue)**

Post Translation

- O – glycosylation
    - Ser, Thr, Trp
- N – acetylation
    - Asparagine, Gly

Fibroblasts

- **Short amino terminal sequence will guide it to the mitochondria**
    - **Hsp 70 will unravel the protein as it enters the mitochondria**
- Mannose 6 – Phosphate label is added for redirection to lysosome
    - Done at the Golgi
    - If missing enzymes = Acid hydrolases are loose in the plasma = I Cell Disease



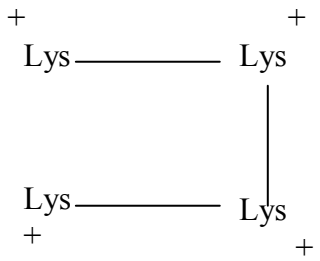
Collagen Diseases:

Symptoms based on type of collagen affected:
I) Thin skin, ecchymosis, striae, skin infections, bone infections, soft bones.
II) Tendons, compression fractures, joint infections, rotator cuff injuries, vision problems
III) Vasculitis (bleed and clot)

- **Marfan's**
  - Autosomal Dominant
  - Type II and III collagen involved.
  - **Hyper extensibility of joints and blood vessels**
  - **Wing span is longer than height**
  - **Arachnodactyly = spider like fingers**
  - **Dislocated lens from bottom of eye → always looking up**
    - "Like curtain coming down"
  - **Die from aortic root dilatation**
  - **Increased incidence of mitral valve prolapse.**
- **Ehlers Danlos**
  - Type I and III collagen involved → hyperextensible skin
    - Skin and blood vessels.
- **Scurvy**
  - **Vitamin C deficiency (OH-pro problems)**
  - Type III affected
  - **Bleeding gums**
  - **Follicular hemorrhages (=bleeding into hair follicles)**
  - Die of Coronary artery disease.
- **Homocysteinuria**
  - Caused from high fat diet
  - Interferes with lysine hydroxilase
  - **Lens will detach from top → always looking down**
  - **High levels of Methionine**
- **Scleroderma**
  - Type I and III collagen involved
  - **Anti smooth muscle antibody**
  - **Anti SCL70 antibody**
  - Tightened skin
  - Blood vessel problems
- **Osteogenesis Imperfecta**
  - All 4 types involved
  - **Blue Sclera**
  - **Especially Type I → Brittle Bone disease.**
  - Mild type is always confused with child abuse
    - Look out for "bone shattered" to differentiate.
- **Syphilis**
  - Obliterative endarteritis → tree bark appearance
- **Takayasu**
  - Pulseless aortitis
- **Minky Kinky Hair Syndrome**
  - **Copper deficiency (OH –lys affected)** → Hair looks like Cu^{2+} wire.

Elastin:

- Made of:
  - Gly
  - Pro
  - Lys
  - OH-Proline (proline hydroxylase)
    - **No OH-Lys**
  - **Desmosine = gives elastic properties**
    - ⊕ Repel each other making it elastic.



Desmosine

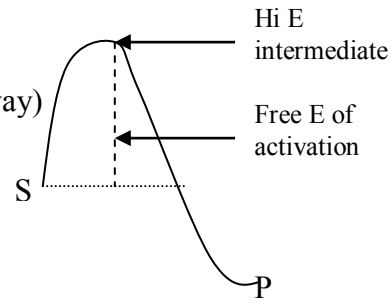
- Compliance:
  - $\text{Compliance} = \frac{\Delta V}{\Delta P}$
    - **Ability to keep pressure constant with change in volume.**
  - With age compliance decreases → increased pressure (…arteries)
- Elastase breaks up elastin.
  - **α-1-antitrypsin → inhibits elastase**
    - Bacteria that are elastase ⊕
      - Staph aureus = 90%
      - Pseudomonas = 10%
      - Will digest elastin in the lungs →
        - Bullous (pneumoatocele) emphysema = air bubbles.
  - **Emphysema**:
    - Problems with compliance.
    - **Bullous (pneumatocele) emphysema** ➔ elastase ⊕ Bacteria
    - **Panacinar Emphysema (all of lung)** ➔ α-1 antitrypsin deficiency
      - Involves the lung and liver (hepatitis)
      - Autosomal recessive inheritance.
    - **Centroacinar Emphysema** ➔ smoking
    - **Distal - acinar emphysema** ➔ aging (periphery)

Keratin

- **Made of Cys → disulfide bonds ➔ tensile strength**
  - Heat makes disulfide bonds
  - Water is it's worst enemy because it ruins disulfide bonds
    - How a Curling Iron works
- **Mercaptoethanol dissolves disulfide bonds.**

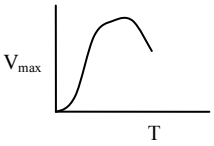
Enzymes:

- Helps catalyze a reaction
- Bring substrates together in space and time
- Lower Free Energy of activation (does NOT change it in any way)
- Stabilize HI energy intermediate
- Is NEVER consumed in the reaction
- **K_m =[substrate] @** $\frac{1}{2}$**V_{max}=** $\frac{1}{affinity}$
- V_m = efficacy



Free Energy of Reaction:

- $-\Delta G = \Delta H - T\Delta S$
- ΔG = determines favorability and spontaneity
- ΔG is additive:
  - Ex.
    - A ⟶ C, $\Delta G = -7$
    - C ⟶ B, $\Delta G = +5$
    - A ⟶ B, total $\Delta G = -2$ → favorable spontaneous reaction
- **90% of reactions in body have a ⊕ ΔG → NOT favorable or spontaneous**
  - ATP → ADP + Pi $\Delta G = -7.3$ Kcal (-7300 cal)
  - Most reactions don't need more than 5000 cal for reaction, that's why we have a lot of Energy left over.
- Enthalpy (heat), ΔH
  - Endothermic = endergonic → add heat
  - Exothermic = exergonic → gives off heat ➔ spontaneous, favorable
    - Silver Sulfadiazine for burn victims:
      - Heat sucked out and sulfur breaks off in skin to protect from bacteria.
      - ENDOTHERMIC REACTION
- Entropy (degree of randomness) , ΔS
  - Positive Δ in degree of randomness,
  - reaction will go from high energy/randomness to low energy/rando
- Temperature, T
  - **As T↑ ➔ V_{max} ↑**
  - **As T increases too much, proteins denature and V_{max} will drop.**

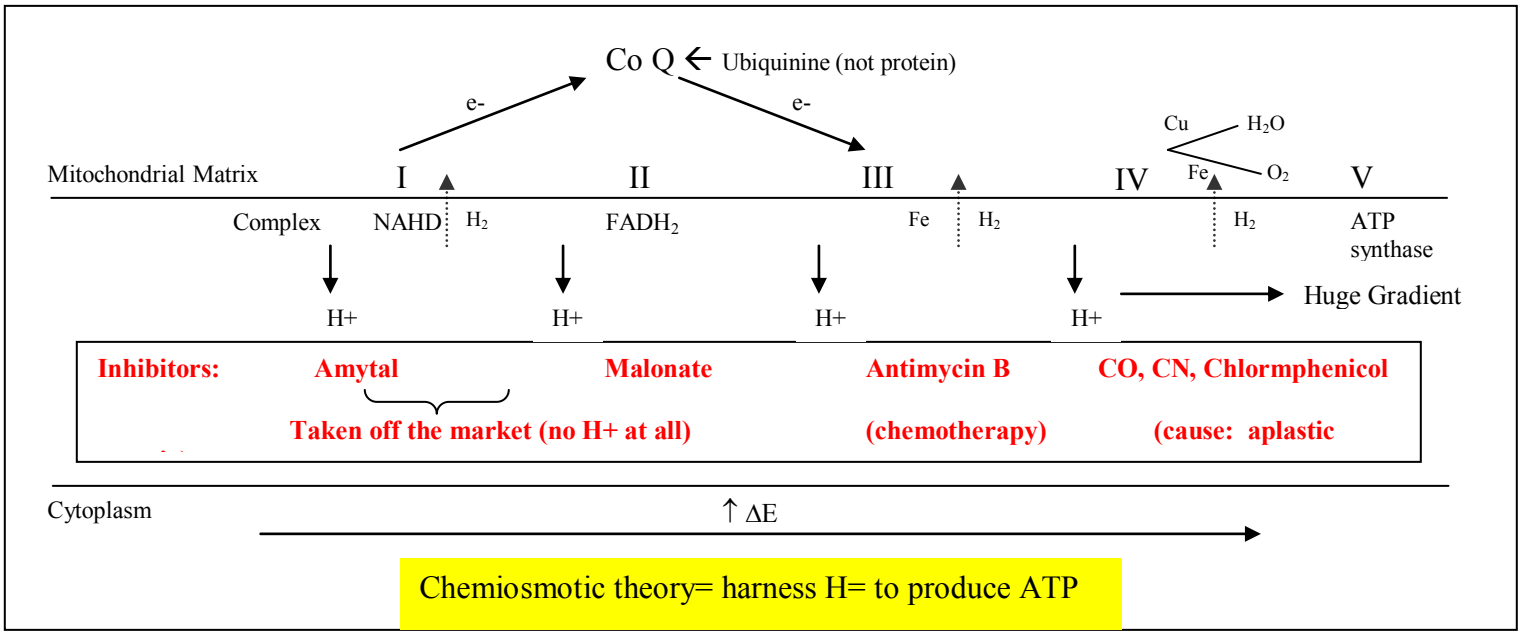


- Redox Potential, ΔE
  - $-\Delta E$ → wants to give away e-
    - ⇒ reducing agent
    - It is being oxidized
  - ΔE → want to accept e-
    - ⇒ oxidation agent
    - It is being reduced
  - Electron transport will move e-'s down the chain.

OiL RiG
Oxygenation is Loss of electrons
→ Reducing Agent
Redcution is a gain of electrons
→ Oxidizing agent

Electron Transport

- Occurs in the Mitochondria
  - Mitochondrial DNA and RNA get from mother



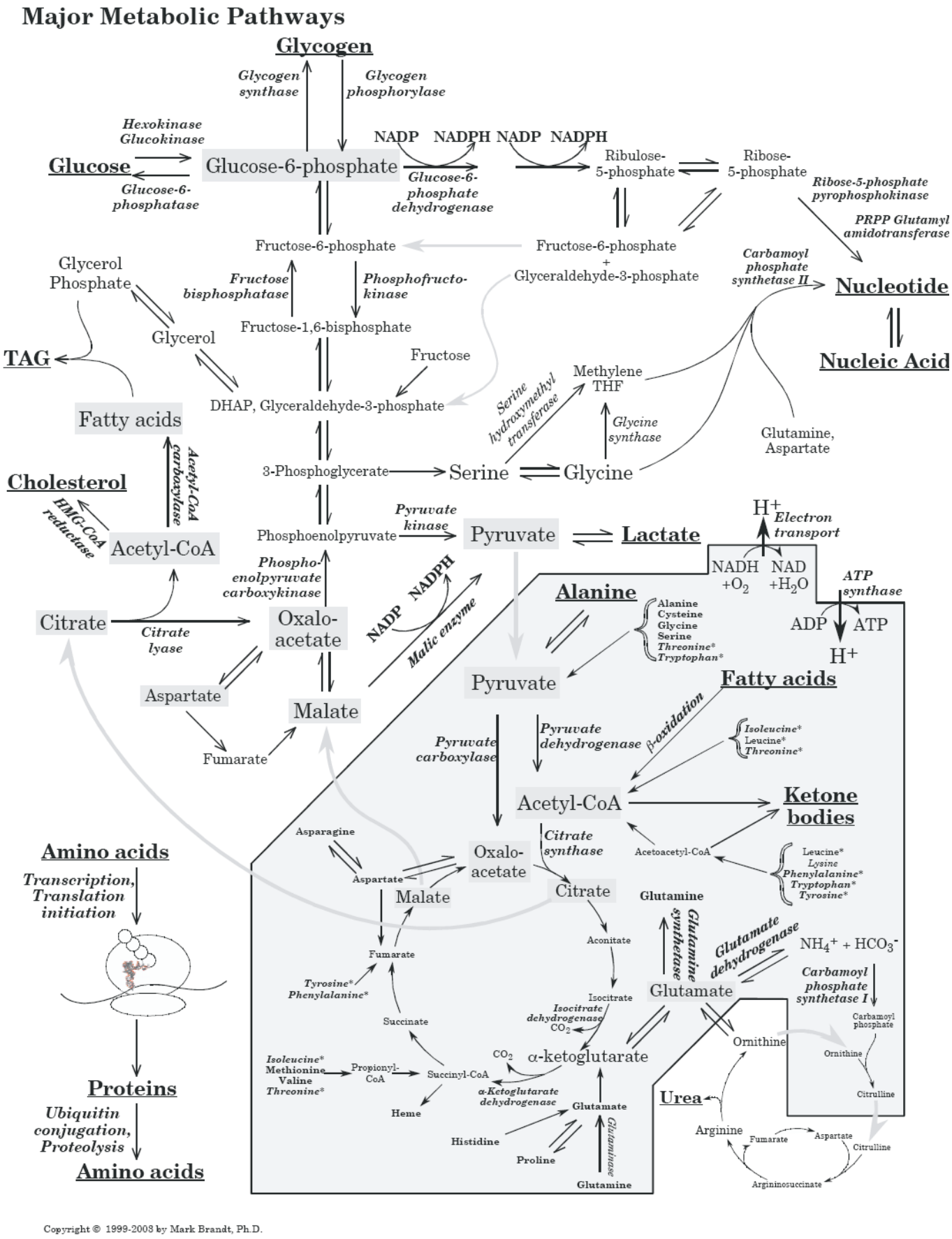
- **NADH = 3 H ➔ 3 ATPs**
- **$FADH_2$ = 2 H ➔ 2 ATPs**
- NADH and $FADH_2$ are cofactors with high affinity to H+, therefore there is high ΔE.
- Complex IV- has the most ⊕ΔE which is why e- gets driven toward it.
- Need O_2, Cu, and Fe- without, will have low E state.

Inhibitors:

- **Uncoupler – will eliminate the proton gradient so that the entire E is released as heat as e- keeps moving** down.
  1. ASA can accidentally cause uncoupling
     - Overdose will cause high temperature
     - Most effective Platelet inhibitor
     - Useful in 1st time MI and 2nd time stroke. (NOT 1st stroke)
     - Three metabolic effects:
       - Low Dose = 1º respiratory alkalosis→ ↓pCO_2 → ↑pH (7.51)
       - 2º Metabolic acidosis (compensation)= ↓CO_2 →↓HCO_3→↑pH (7.42)
       - Toxic Dose= ↑CO_2, ↓HCO_3 → respiratory acidosis and metabolic acidosis ➔ patient will be comatose/ obtunded
     - **Reye's syndrome**: ASA with virus will uncouple patient's e- transport.
       - ↑ body temp → "burn out liver" in children
       - Uncouple e- transport in liver faster → **Acute liver failure**
       - Follow NH_4^+ levels to avoid GABA → low E state.
     - **DNP (Dinitrophenol)** :
       - Insecticide
       - Will burn on inside because uncoupler will make heat rather than ATP
     - **Free FA**:
       - Can act as uncouplers → ↑ body temperature

- **Remember Heat will still be the first to denature proteins and cause death.**

Microsteatosis (small fatty deposits in liver)	Macrosteatosis (big fatty deposits in liver)
Reye's	EtOH
Acetaminophen intoxication	
Pregnancy	



METABOLISM

- **Name enzymes**
  - **Name of Substrate = 1st name**
  - **What was done to substrate = 2nd part**

- Endings
  - ***Kinase***
    - Use ATP to phosphorylate
    - **Mg^{2+} cofactor**
  - ***Phosphorylase***
    - Used free Phosphate to phosphorylate
  - ***Isomerase***
    - Create isomer
    - Think fructose & glucose
  - ***Epimerase***
    - Same chemical make-up, but differ at one chiral carbon
  - ***Mutase***
    - Move phosphate from one carbon to another
  - ***Transferase***
    - Interchain movement of side chains between 2 structure
  - ***Carboxylase***
    - Uses CO_2 to add CARBON
    - Uses ATP
    - Biotin
  - ***Dehydrogenase***
    - COFACTORS
  - ***Lyase***
    - Cutting a carbon – carbon bond
  - ***Thio…***
    - Used with SULFUR bond involvement
  - ***Synthase***
    - 2 substrates consumed in reaction
  - ***Synthetase***
    - Requires ATP

GLYCOLYSIS

- Glucose lasts for 2 hours
- Glycogen lasts for 20 Hours
- After that protein and fat breakdown begins
    - Think about ↑ levels of ketones also

- Insulin
    - Activates glucose transport (GLUT Receptors)
        - Proteins that allow glucose entry

4 types of Glucose Transporters

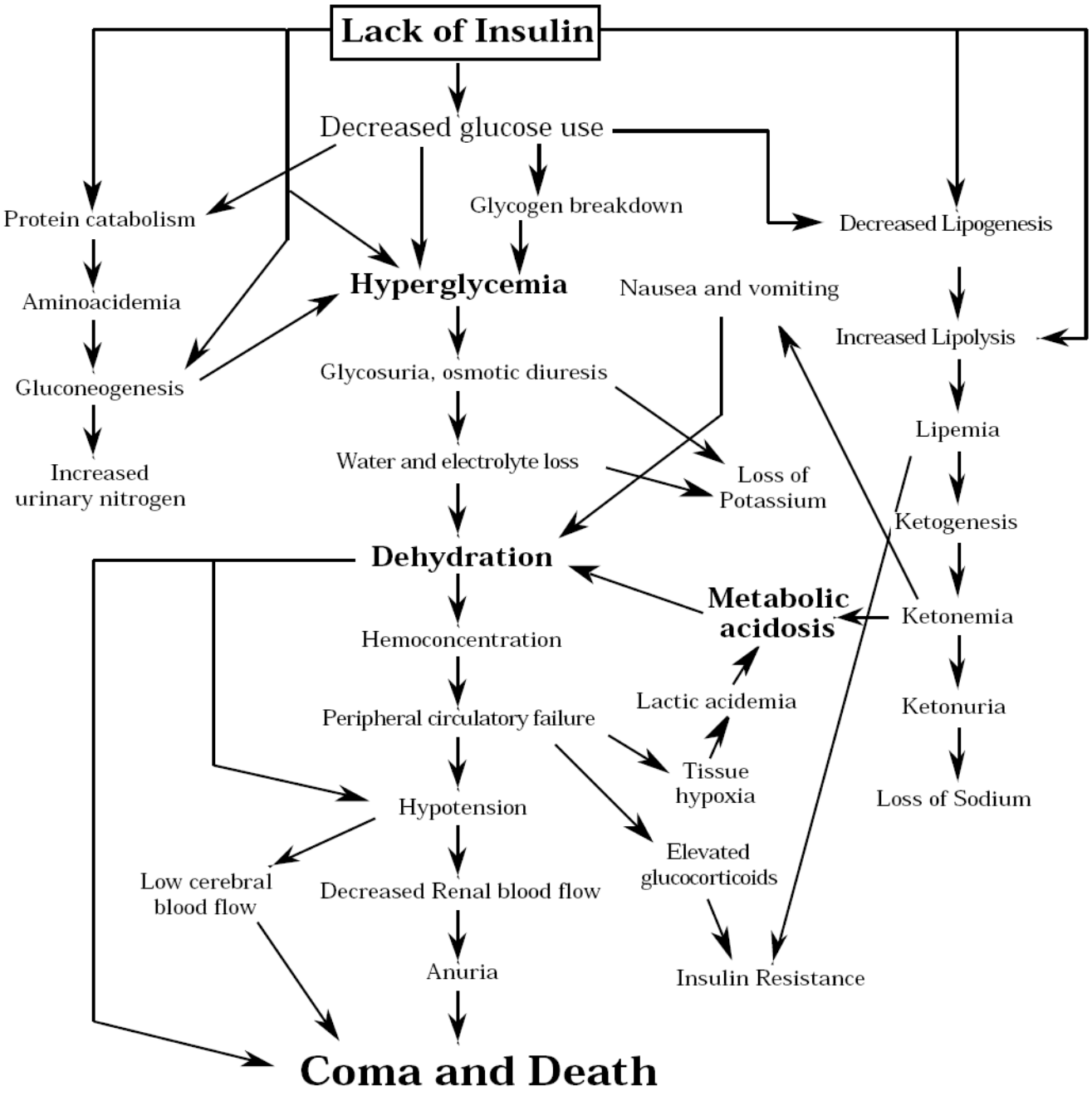
- GLUT 1 & 3
    - Found in most tissues → HIGH AFFINITY for Glucose
    - Allow for basal uptake
- GLUT 2
    - Found in the LIVER & β Cells of PANCREAS → LOW AFFINITY
        - A low affinity makes sure that glucose will bypass LIVER and go to the systemic circulation to the necessary organs
- GLUT 4
    - Found in MUSCLE & ADIPOSE TISSUE
    - Insulin regulated!!!
        - Makes sure glucose gets INTO muscle and adipose tissue
    - ↓ Insulin
        - Endocytosed GLUT 4 transporters that are bound to cytoplasmic vesicles
    - ↑ Insulin
        - Exocytosis of GLUT 4, places them on membrane = Maximum uptake of glucose

TISSUES THAT DO NOT REQUIRE INSULIN = BRICKLE

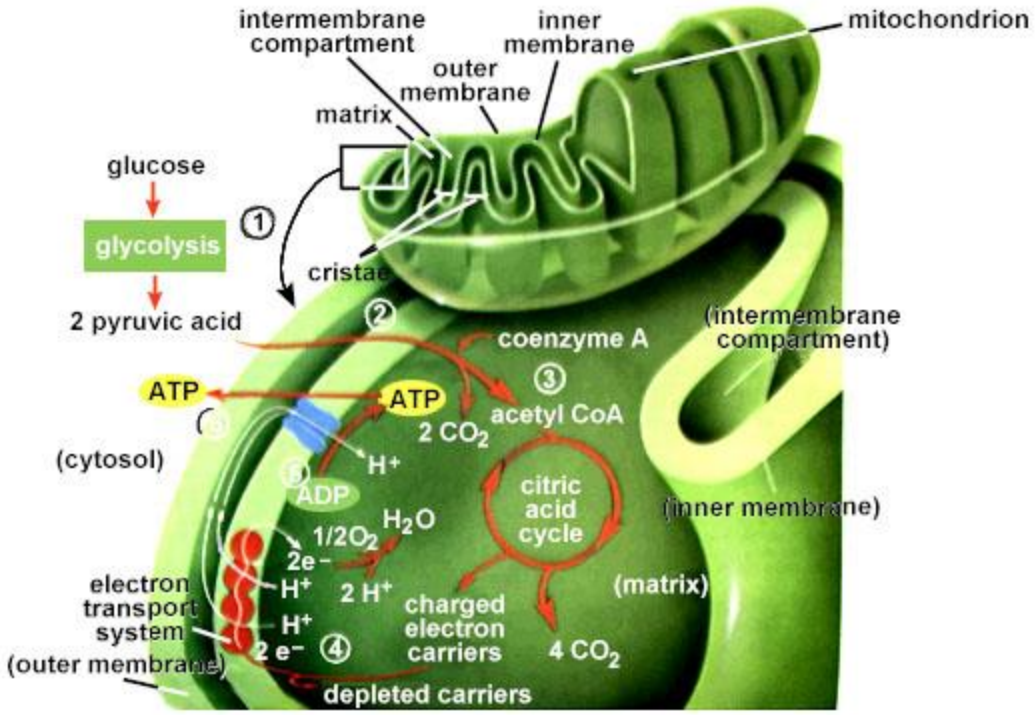
- **B**rain → neuropathy
- **R**BC → hemolysis
- **I**ntestinal wall → absorption
- **C**ardiac
- **K**idney → nephropathy
- **L**iver
- **E**xercising muscle

ORGANS OF IMPORTANCE:
BRAIN >> HEART >> KIDNEY

- ***REMEMBER:***
    - RBC uses glucose exclusively
    - ↓ in glucose = LOW ENERGY STATE
        - Therefore, RBC will die 1st → HEMOLYTIC ANEMIA
        - Think any disease affecting glucose can stimulate hemolysis

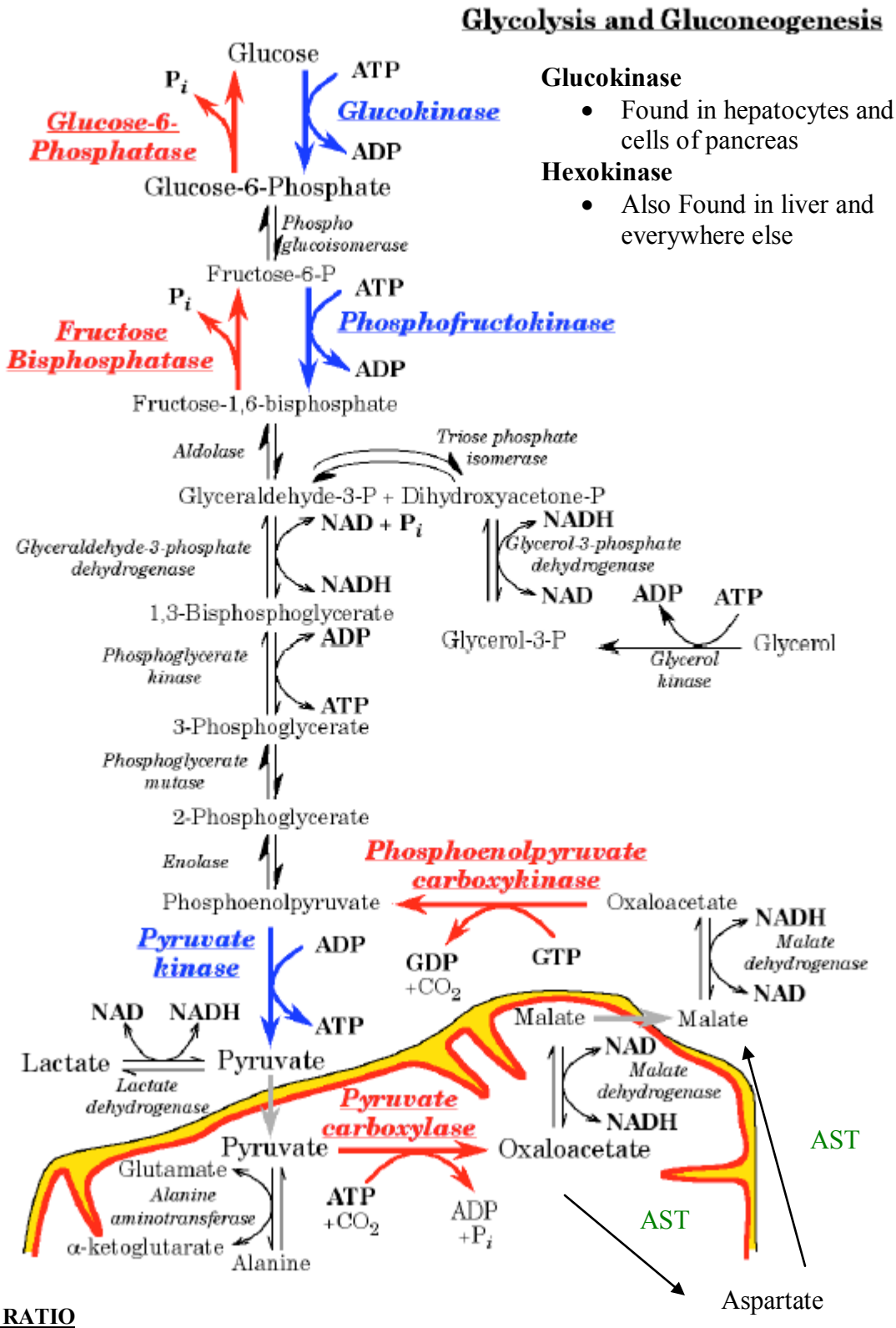

Lack of Insulin
Decreased glucose use
Protein catabolism
Glycogen breakdown
Decreased Lipogenesis
Aminoacidemia
Hyperglycemia
Nausea and vomiting
Increased Lipolysis
Gluconeogenesis
Glycosuria, osmotic diuresis
Lipemia
Water and electrolyte loss
Loss of Potassium
Increased urinary nitrogen
Ketogenesis
Dehydration
Metabolic acidosis
Ketonemia
Hemoconcentration
Lactic acidemia
Ketonuria
Peripheral circulatory failure
Tissue hypoxia
Loss of Sodium
Hypotension
Elevated glucocorticoids
Low cerebral blood flow
Decreased Renal blood flow
Anuria
Insulin Resistance
Coma and Death

LOCATIONS



Fatty acid metabolism sites	Fatty acid synthesis = cytosol. Fatty acid degradation = mitochondria. Fatty acid entry into mitochondrion is via carnitine shuttle (inhibited by cytoplasmic malonyl-CoA). Fatty acid entry into cytosol is via citrate shuttle.	Fatty acid degradation occurs where its products will be consumed—in the mitochondrion.

GLYCOLYSIS



Glucokinase

- Found in hepatocytes and β cells of pancreas

Hexokinase

- Also Found in liver and everywhere else

AST:ALT RATIO

- VIRUSES (HEPATITIS) WILL BREAKDOWN ONLY THE CELL WALL AND LET AST & ALT TO SPILL OUT
  - **AST/ALT < 2:1**
- ALCOHOL WILL DISSOLVE BOTH THE CELL MEMBRANE AND THE MITOCHONRIDAL MEMBRANE AND LET ↑AST ALT OUT
  - **AST/ALT > 2:1**

Glycolysis

Hexokinase versus glucokinase

Hexokinase is found throughout body.

Glucokinase (lower affinity [↑K_m] but higher capacity [↑V_{max}]) is predominantly found in the liver.

Only hexokinase is feedback inhibited by G6P.

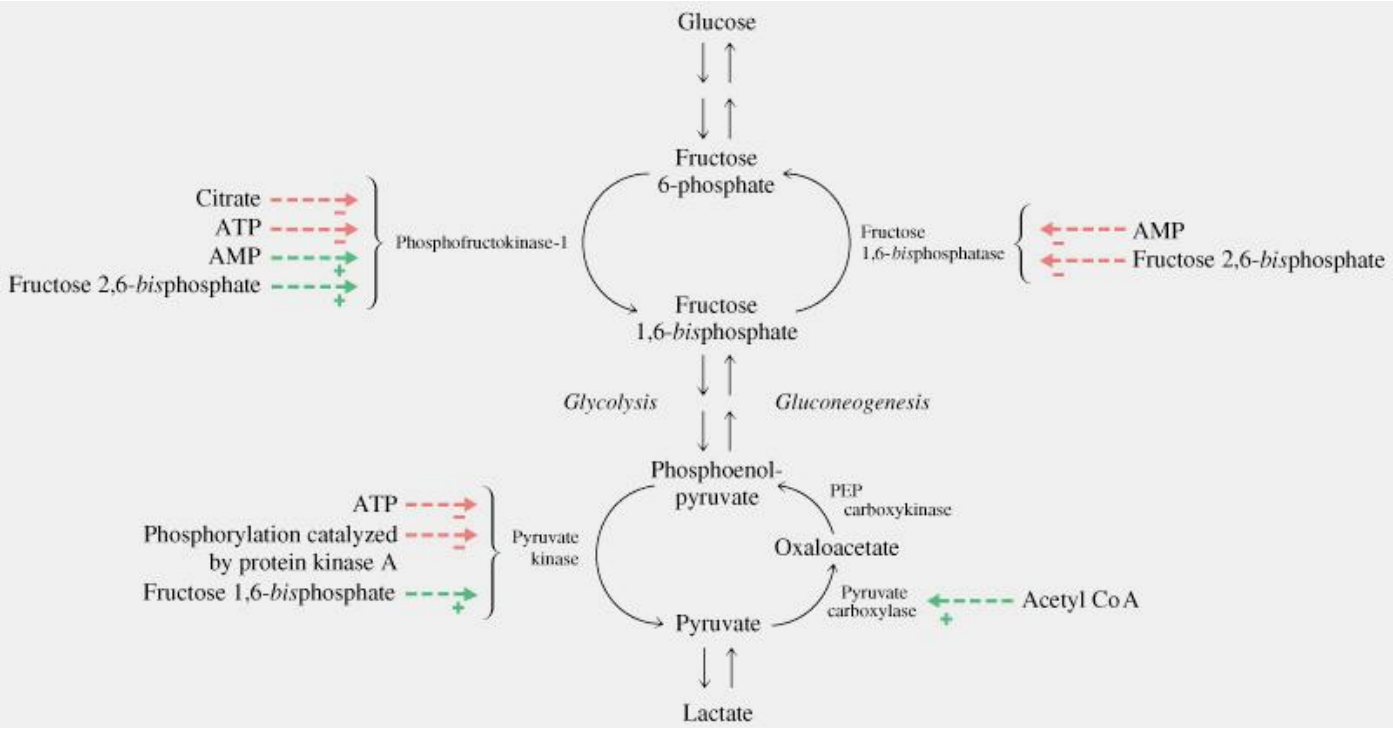
Glycolysis regulation, irreversible enzymes

D-glucose → Glucose-6-phosphate (Hexokinase/glucokinase*)	Glucose-6-P ⊖	
Fructose-6-P → Fructose-1,6-BP (Phosphofructokinase (rate-limiting step))	ATP ⊖ , AMP⊕, citrate ⊖ fructose 2, 6-BP⊕	
Phosphoenolpyruvate → Pyruvate (Pyruvate kinase)	ATP ⊖ , alanine ⊖ , fructose-1,6-BP⊕	
Pyruvate → Acetyl-CoA (Pyruvate dehydrogenase)	ATP ⊖ , NADH ⊖ , acetyl-CoA ⊖	

* Glucokinase in liver; hexokinase in all other tissues.

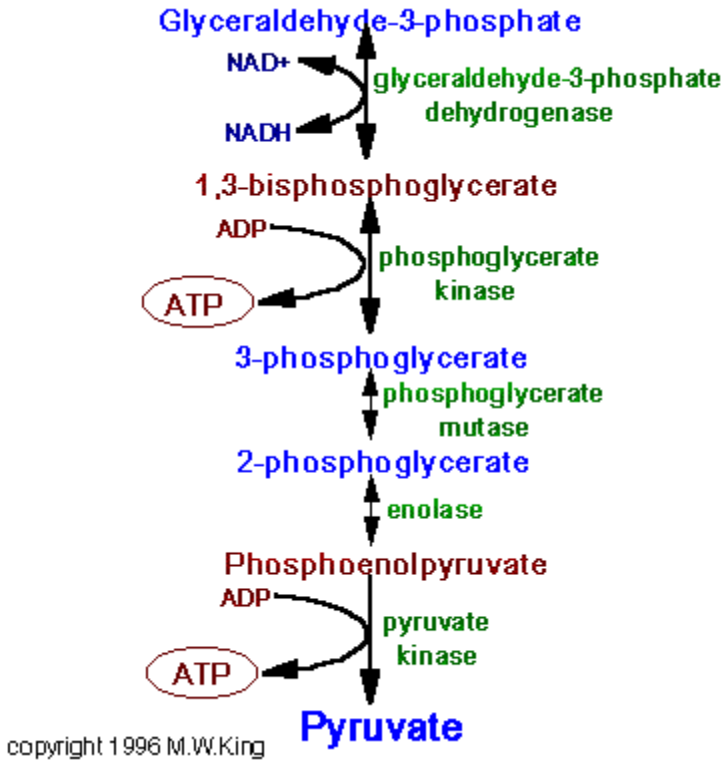
- ATP production and Electron Shuttles
  - NADH
    - Malate Shuttle
    - 3 ATP
  - $FADH_2$
    - Glycerol-3P Shuttle
    - 2 ATP

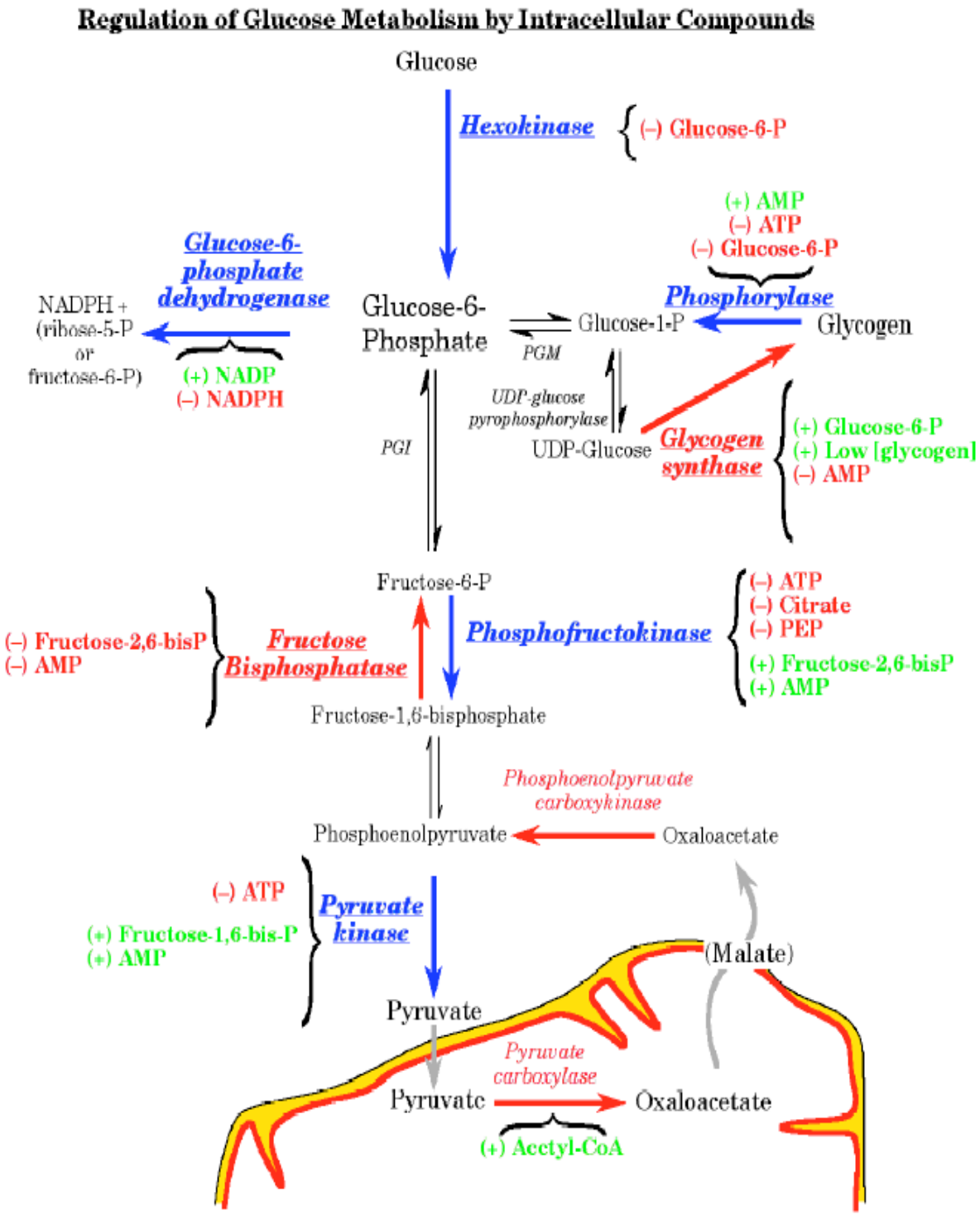
- ***CLINICAL***
- Primary Lactose intolerance
  - Hereditary deficiency of LACTASE
  - Symptoms:
    - Vomiting
    - Bloating
    - Explosive/Watery diarrhea
    - Cramps
    - Dehydration
  - Symptoms can be attributed to bacterial fermentation of lactose
  - Dx. based on positive hydrogen breath test after an oral load of lactose
  - Tx.
    - Dietary restriction



GLYCOLYSIS REGULATION

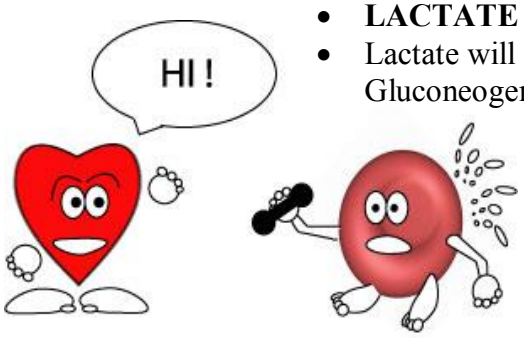
- ***PFK -1***
  - Rate-limiting Enzyme of Glycolysis
- ***Fructose 2,6 – biphosphate***
  - **Allosteric activator of PFK – 1**
    - If there is a build-up of Fructose 6-phosphate F 2,6-biP will make PFK "work harder"
- ***Glyceraldehyde 3 – Phosphate***
  - Has **disulfide bonds** which can be disrupted by alcohol
  - **Mercury Poisoning**
    - **Inhibits sulfur group of enzyme**
- ***Phosphoglycerate kinase***
  - **Substrate level phosphorylation**
    - Potential for energy
- ***Enolase***
  - Inhibited by Fluoride
  - **CLUE = Shiny white teeth**
- **1,3 Bisphosphoglycerate**
  - With RBC mutase can be converted to 2 – BPG
  - 2 – BPG
    - ↓ Hb Affinity for O_2




Regulation of Glucose Metabolism by Intracellular Compounds
Glucose
Hexokinase
(–) Glucose-6-P
(+) AMP
(–) ATP
(–) Glucose-6-P
Phosphorylase
Glycogen
Glucose-6-phosphate dehydrogenase
NADPH + (ribose-5-P or fructose-6-P)
(+) NADP
(–) NADPH
Glucose-6-Phosphate
PGM
Glucose-1-P
UDP-glucose pyrophosphorylase
UDP-Glucose
Glycogen synthase
(+) Glucose-6-P
(+) Low [glycogen]
(–) AMP
PGI
Fructose-6-P
(–) Fructose-2,6-bisP
(–) AMP
Fructose Bisphosphatase
Phosphofructokinase
(–) ATP
(–) Citrate
(–) PEP
(+) Fructose-2,6-bisP
(+) AMP
Fructose-1,6-bisphosphate
Phosphoenolpyruvate carboxykinase
Phosphoenolpyruvate
Oxaloacetate
(–) ATP
(+) Fructose-1,6-bis-P
(+) AMP
Pyruvate kinase
(Malate)
Pyruvate
Pyruvate carboxylase
Pyruvate
Oxaloacetate
(+) Acetyl-CoA

CONNECTIONS

- **RBC**
  - **Glycolysis is the only source of energy**
  - Relies on Substrate level phophorylation for ATP production and the Cori Cycle
  - **The cell can eventually run out of NAD**
    - It must be reoxidized in ETC, **BUT RBC does not have mitochondria**
      - Therefore, can't replenish NAD
    - **What's the solution?**
      - **LACTATE DEHYDROGENASE**
      - Lactate will be turned into pyruvate and sent to the liver to induce Gluconeogenesis and supply more glucose of the RBC



Mr. RBC working hard for the heart to get him more O_2

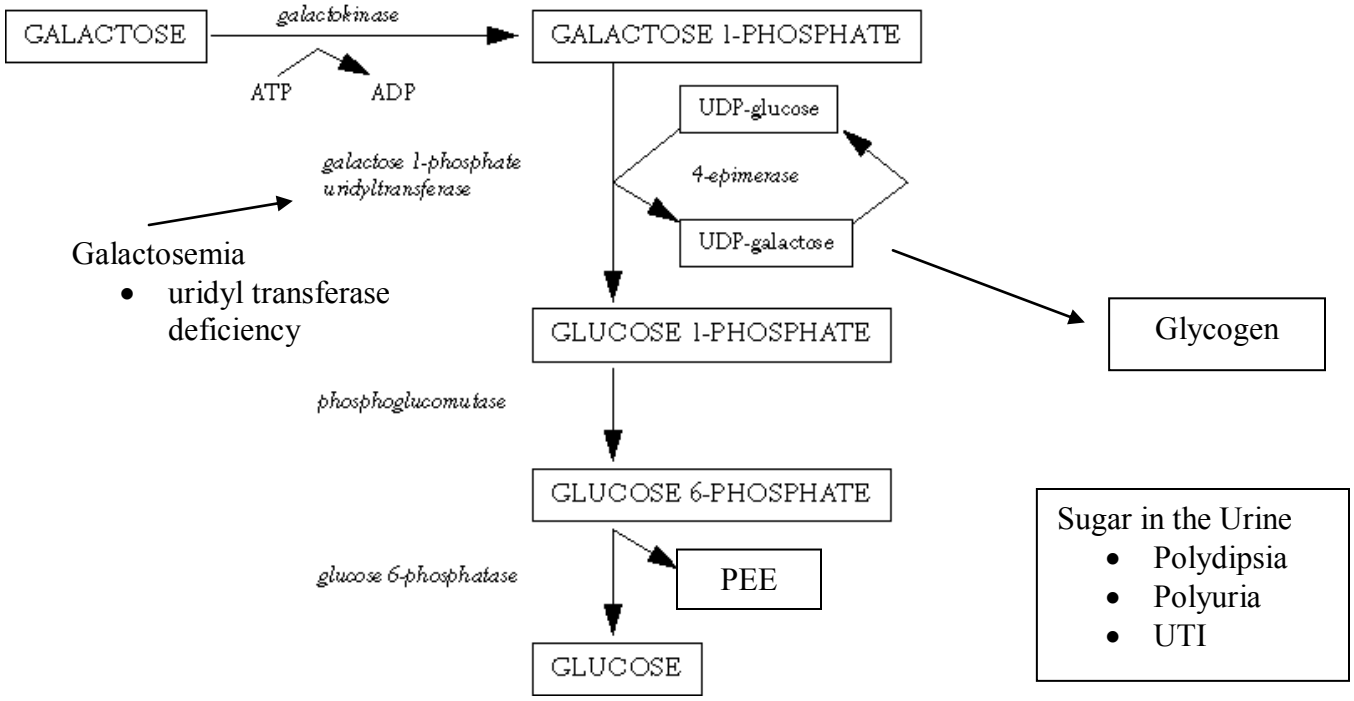
- **Lactate Dehydrogenase**
  - **Anaerobic function**
    - May be in a hypoxic state
  - Any enzyme of Glycolysis can be ↑↑↑ during hypoxia
  - **Recall that in a MI LDH levels are measured!!!**

Pathophysiology Bridge

- **IF there is a loss of ATP production = Na^+/K^+ pump dysfunction**
  - **Loss of gradient = Cell will swell**

GALACTOSE METABOLISM

Galactosuria
- **Galactokinase deficiency**
- Galactosuria > galactosemia b/c of HEXOKINASE activity, but will still have excess galactose in urine



Sugar in the Urine
- Polydipsia
- Polyuria
- UTI

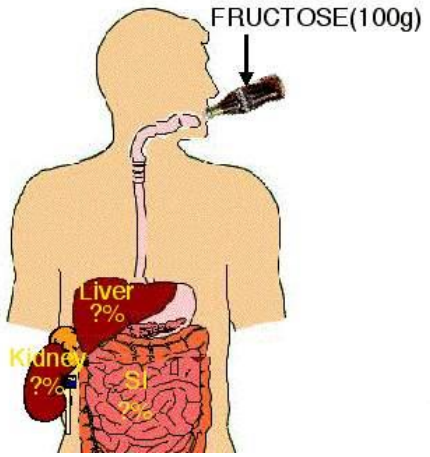
1 Galactose = 2 Glucose

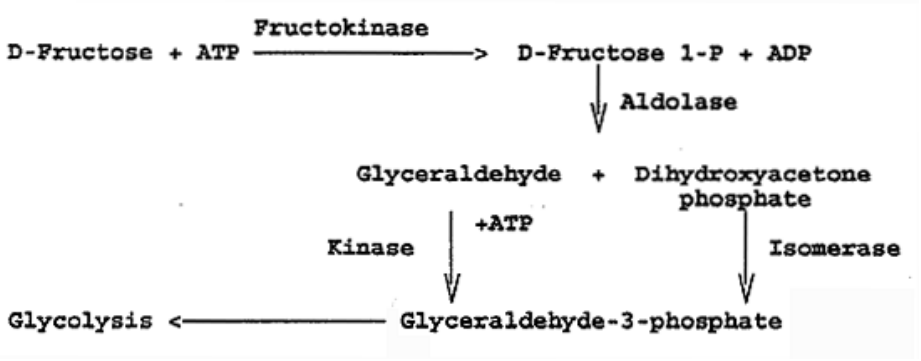
- Babies need a lot of milk/formula b/c of the baby uncoupling it's ETC
  - Therefore, baby needs a lot of Energy replacement from milk (glucose resource)
  - Soy is a good source also if lactose intolerant

Required at Birth Screening
"**P**lease **C**heck **B**efore **G**oing **H**ome"
- **PKU**
- **CAH**
- **Biotinidase**
- **Hypothyroidism**

Also, Addison's Disease

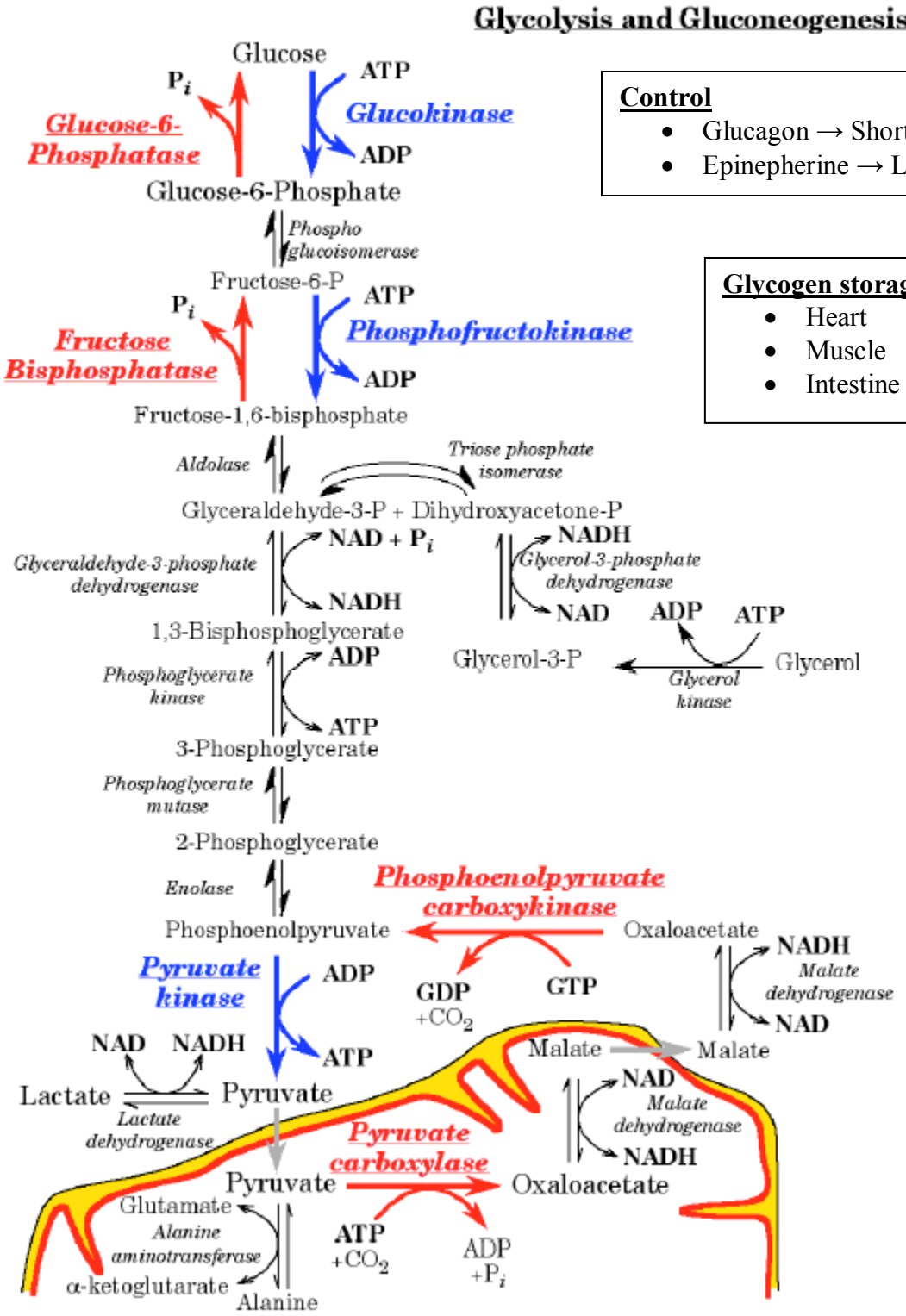
FRUCTOSE





- **Fructosuria**
  - Polydipsia
  - Polyuria
  - UTI
  - **Asymptomatic, benign condition**

GLUCONEOGENESIS



Control

- Glucagon → Short term
- Epinepherine → Long term

Glycogen storage Sites

- Heart
- Muscle
- Intestine

Acetyl-CoA is the **allosteric activator**

- **<u>Gluconeogenesis</u>**
  - IMPT. Substrates
    - **Gluconeogenic amino acids**
    - **Protein from muscle**
      - ALANINE!!!
        - Alanine transaminase (recall liver fxn enzyme)
    - **Lactate**
      - Anaerobic glycolysis
      - Lactose dehydrogenase (LDH)
    - **Glycerol 3-phosphate**
      - From triacylglycerol in adipose tissue
  - Gluconeogenesis requires that the irreversible steps be side-stepped!!!

Gluconeogenesis, irreversible enzymes

Pyruvate carboxylase	In mitochondria. Pyruvate → oxaloacetate.	Requires biotin, ATP. Activated by acetyl-CoA.
PEP carboxykinase	In cytosol. Oxaloacetate → phosphoenolpyruvate.	Requires GTP.
Fructose-1,6-bisphosphatase	In cytosol. Fructose-1,6-bisphosphate → fructose-6-P	**P**athway **P**roduces **F**resh Glucose.
Glucose-6-phosphatase	In cytosol. Glucose-6-P → glucose	

Above enzymes found only in liver, kidney, intestinal epithelium. Muscle cannot participate in gluconeogenesis.

Hypoglycemia is caused by a deficiency of these key gluconeogenic enzymes listed above (e.g., von Gierke's disease, which is caused by a lack of glucose-6-phosphatase in the liver). *Bio.82*

UCV

- Pyruvate carboxlase
  - Activated by acetyl-CoA (from β oxidation)
  - Malate Shuttle provides means to begin Gluconeogenesis
- Phosphoenolpyruvate carboxykinase
  - Induced by *glucagon and cortisol*
- Fructose 1,6 – bisphosphatase
  - Key control point
  - Activated by ATP
  - Impedes on formation of Fructose 2,6 busphosphate which will then favor gluconeogenesis

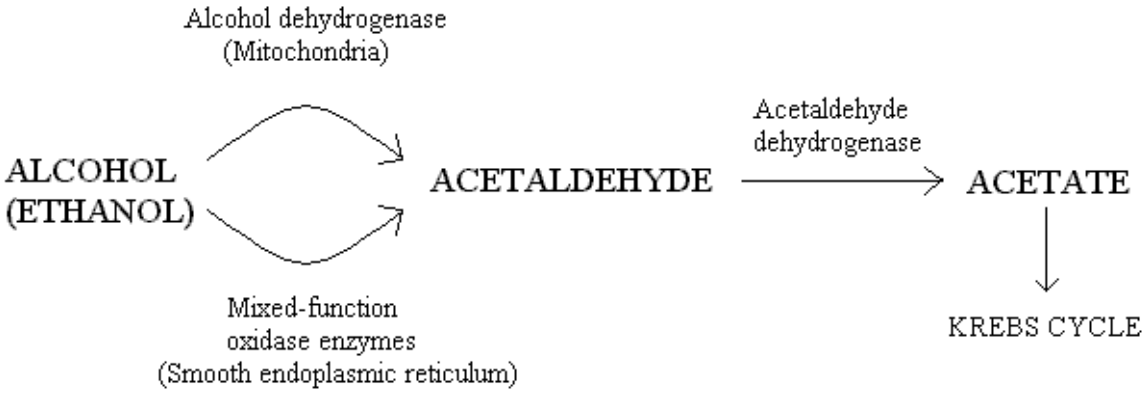
Pathway	Major regulatory enzyme(s)	Activator	Inhibitor	Effector hormone	Remarks
Gluconeogenesis	Pyruvate carboxylase Phosphoenolpyruvate carboxykinase	Acetyl-CoA cAMP?	ADP	Glucagon?	Induced by glucocorticoids, glucagon, cAMP
	Fructose-1,6-bisphosphatase	cAMP	AMP, fructose 2,6-bisphosphate	Glucagon	Suppressed by insulin

Coordinate regulation of Pyruvate Carboxylase and pyruvate dehydrogenase by Acetyl-CoA

- Between meals → ↑acetyl-CoA activates Pyruvate carboxylase in order to produce energy and prevent conversion of lactate and alanine to acetyl CoA
- Well fed state → ↑ acetyl CoA is shuttled to Cytoplasm for FA syn and storage

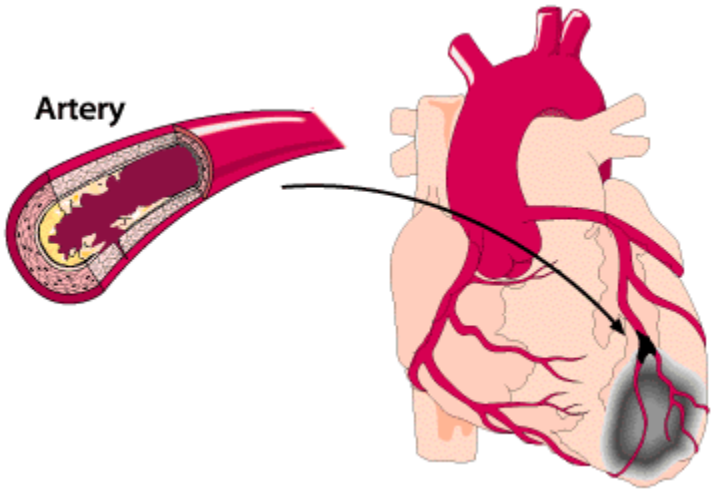
CLINICAL:

- Alcoholism and Hypoglycemia
  - High amounts of cytoplasmic NADH is produced via alcohol dehydrogenase and acetaldehyde dehydrogenase (alcohol metabolism) → Interference of GLUCONEOGENESIS
  - ↑↑↑ NADH
    - (+) Lactate → pyruvate
    - (+) Malate from OAA
    - (+) Glycerol 3-P from DHAP → FATTY LIVER!!!



Myocardial Infarction Work – Up

- 1st perform a EKG
  - It will be positive in less than 10 seconds
- Initially = ST Wave depression
  - Partial occlusion
  - 70% stenosis
- Later…
  - ST wave elevation
  - Total occlusion

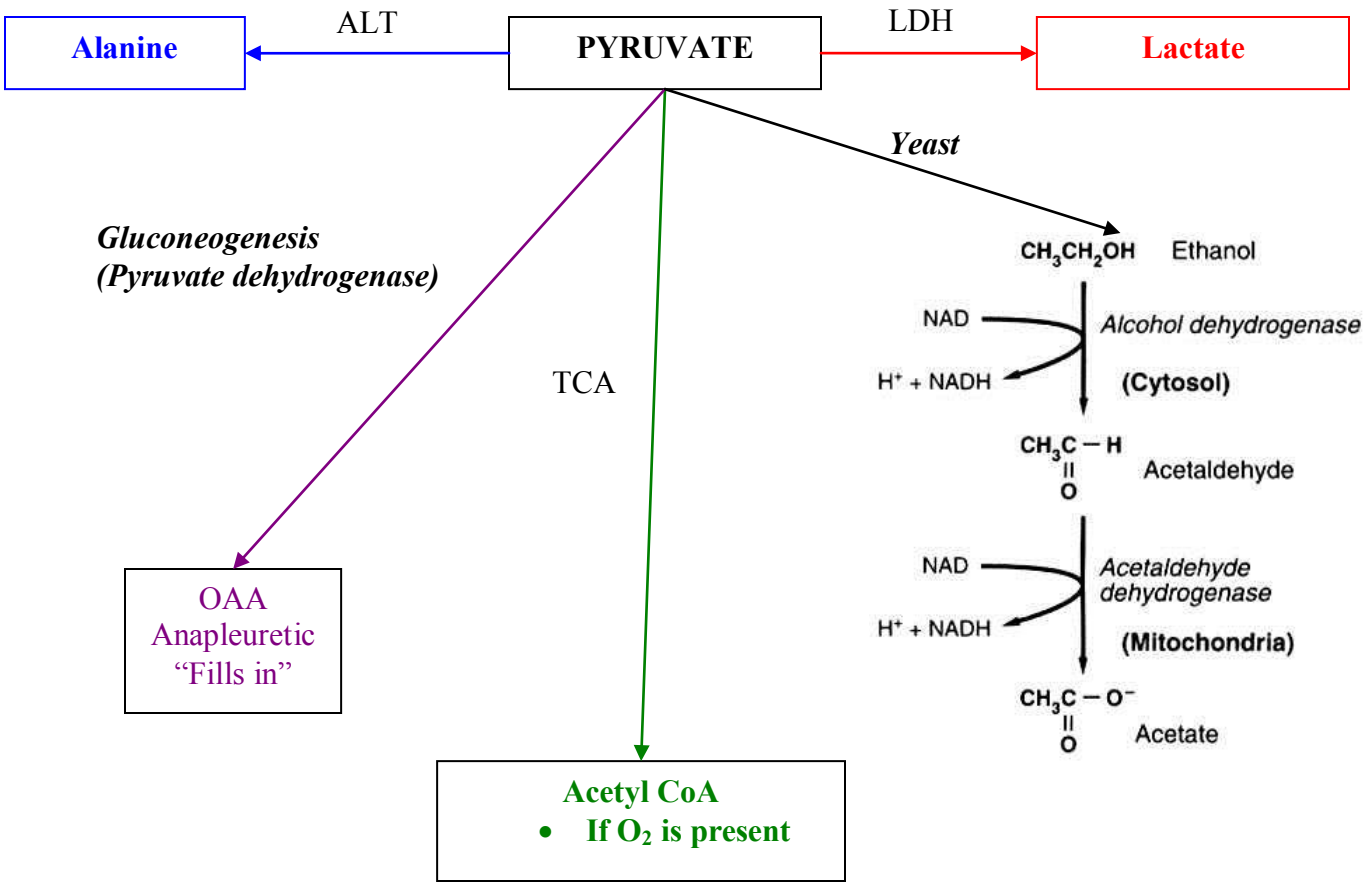


Enzyme	Rises	Peaks	Gone
Troponin I	2 hours	2 days	Stays positive for 7 days MOST SPECIFIC
CK – MB	6 hours	12 Hours	24 hours
LDH_1	24 hours = 1 day	48 hours – 2 days	72 hours – 3 days

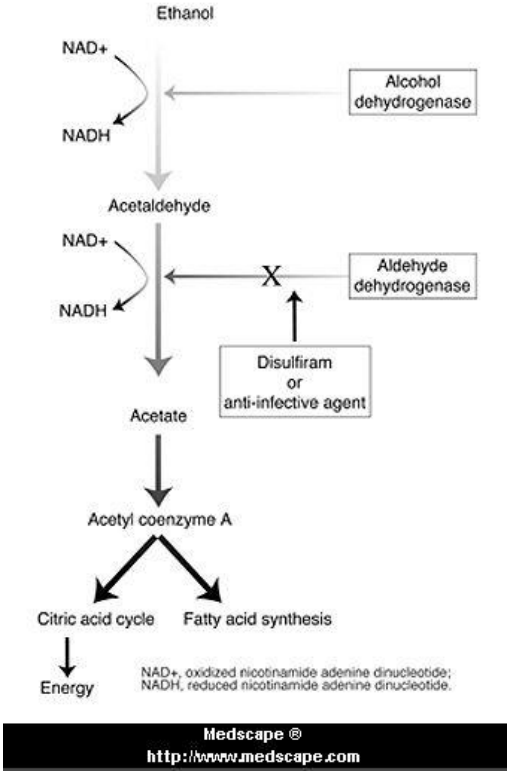
LD5

- There are 5 isoenzymes
- **LDH – 1 is specific for the heart**
  - It should be < the others normally
  - **If LDH – 1 is increased = CARDIAC TISSUE DAMAGE**

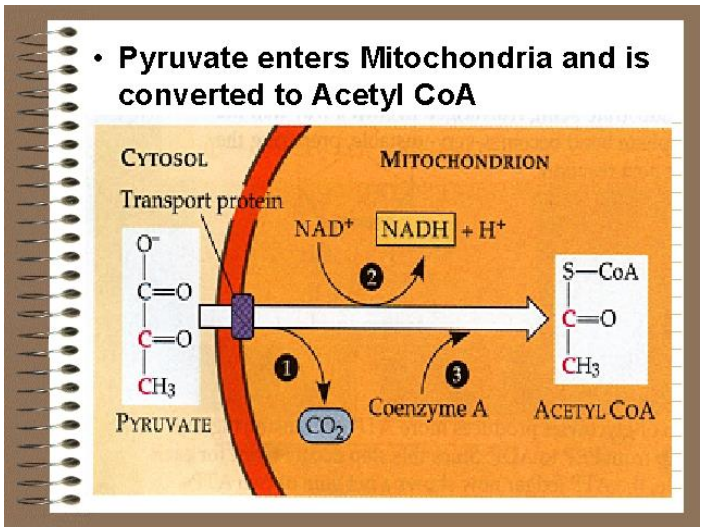
DESTINIES OF PYRUVATE

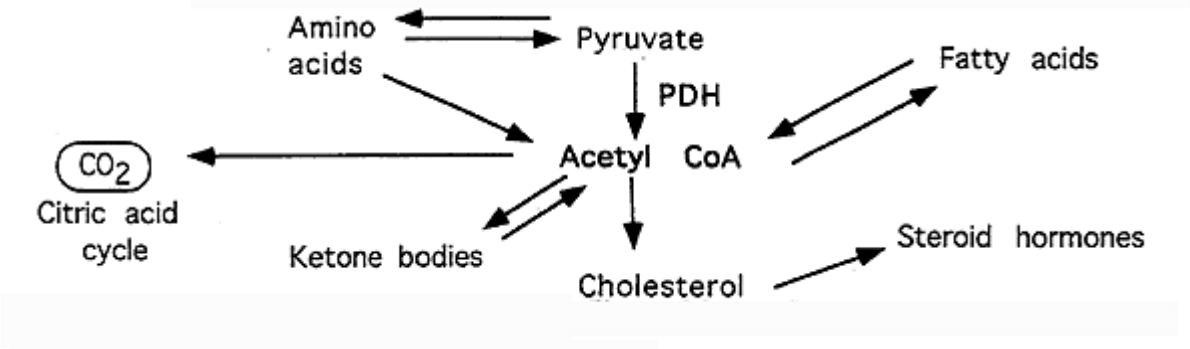


- Why are alcoholics hypoglycemic?
  - Because they will interfere with Gluconeogenesis NADH
- The ↑ in NADH will stimulate the reactions that use it
  - Sites where they produce the most NADH
    - Lactate → pyruvate
    - Malate → FROM OAA
    - DHAP → Glycerol 3 – Phosphate
      - This will produce the fatty liver
- Because the ↑↑↑ NADH and it's sent to the ETC and will produce increased amounts of ATP at a fast rate and the body will begin to use the excess ATP and deplete glucose stores
  - Will interfere with gluconeogenesis more readily



Cofactors





Pyruvate dehydrogenase
α-ketoglutarate dehydrogenase
Branched chain amino acid dehydrogenase

- Use **"PLAN F"**

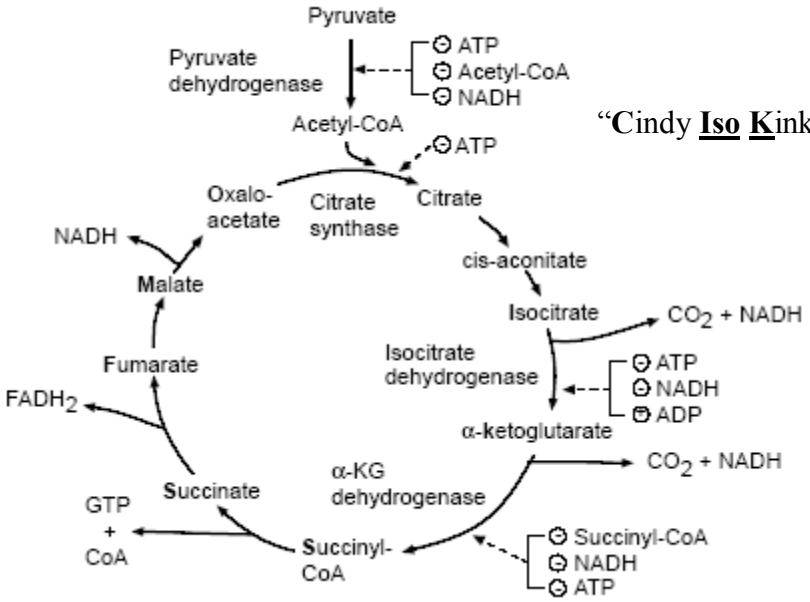
COFACTORS	***ACTION***	***Vitamin Derivatives***
TP**P**	Decarboxylates enzyme	Thiamine (B_1)
Lipoic acid	Accepts acetyl group	Lipoic acid
Co**A**	Final acceptor	Panthenoic acid (B_5)
NAD	Oxidization	Niacin (B_3)
FAD	Oxidizes lipoic acid	Riboflavin(B_2)

The order in which they occur = TLC For Nancy

- Thiamine (B_1) – Tender
- Lipoic Acid – Loving
- CoA (B_5) – Care
- FAD (B_2) – For
- NAD (B_3) –Nancy

TCA Cycle

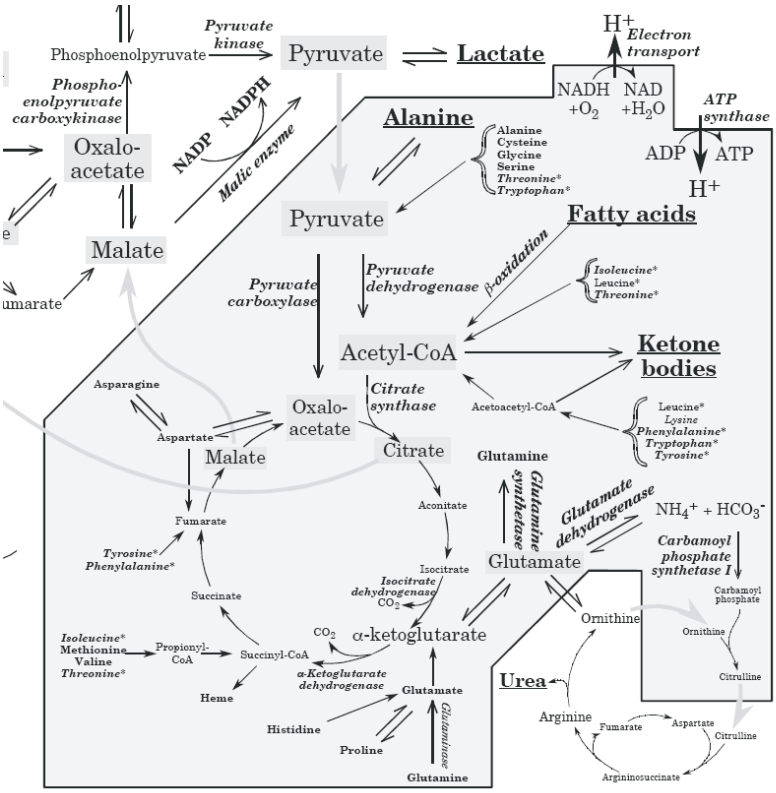
- Occurs in Mitochondria
- Primary function
  - Oxidation of acetyl CoA to CO_2



"**C**indy **Iso** **K**inky **S**o **S**he **F**ornicates **M**ore **O**ften"

Once there is enough glucose used/energy requirement fulfilled, Acetyl CoA will be used to produce Fat and Heme

- Isocitrate dehydrogenase
  - MAJOR CONTROL ENZYME
  - Inhibited by NADH & ATP
- α-ketoglutarate dehydrogenase

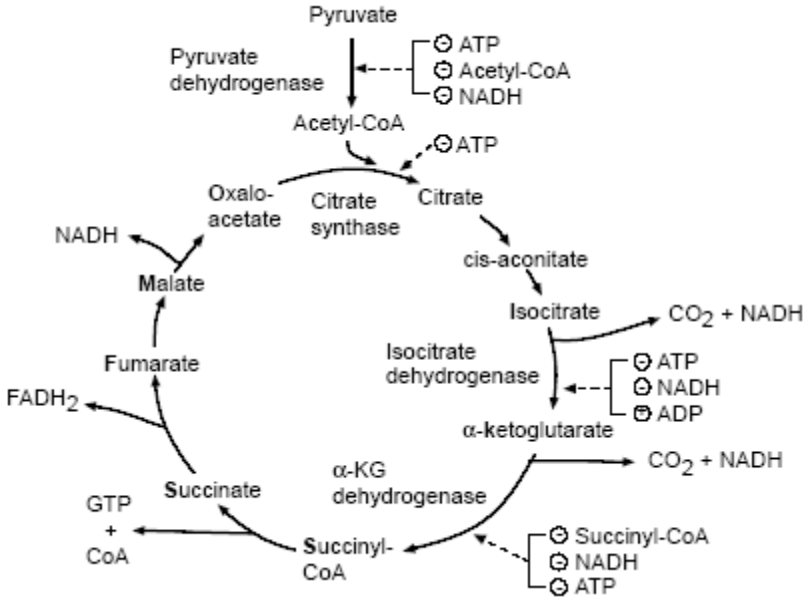


Other fxns of TCA intermediates

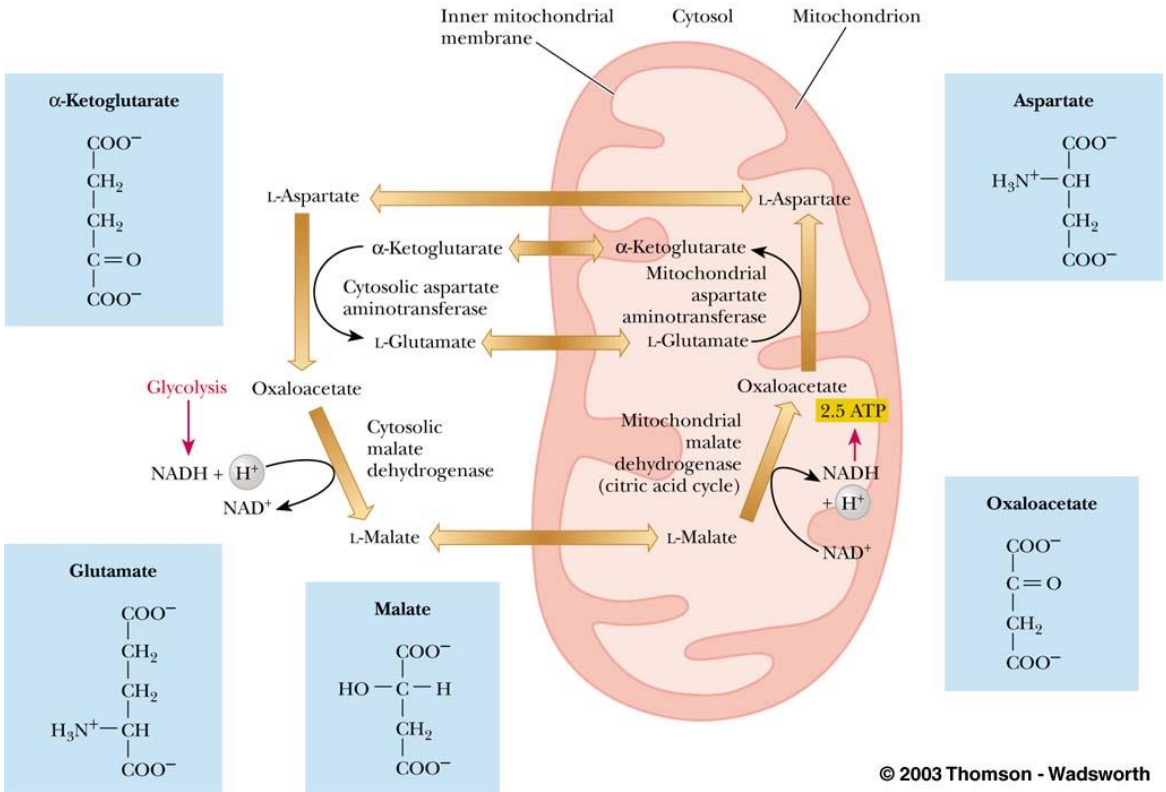
- ***Citrate***
  - Citrate Shuttle → **delivery of acetyl-CoA for Fatty acid synthesis**
  - **Allosteric inhibitor of PFK1**
- ***α-ketoglutarate***
  - Intermediate for **ALL TRANSAMINASES** (ALT/AST)
- ***Succinyl CoA***
  - Heme Synthesis
  - Ringed structure production
  - Ketone body activation
  - Odd chained Fatty acids will feed into here
    - **Proprionic-CoA**
  - ***Malate***
    - Malate Shuttle & Gluconeogenesis
  - ***Fumarate***
    - Urea cycle

TCA and Energy

- 1 Acetyl CoA =
  - 3 NADH = 9 ATP
    - 1 NADH = 3 ATP
  - 1 FADH = 2 ATP
  - 1 GTP = 1 ATP
- **Therefore, for every turn of the TCA cycle = 12 ATPS**

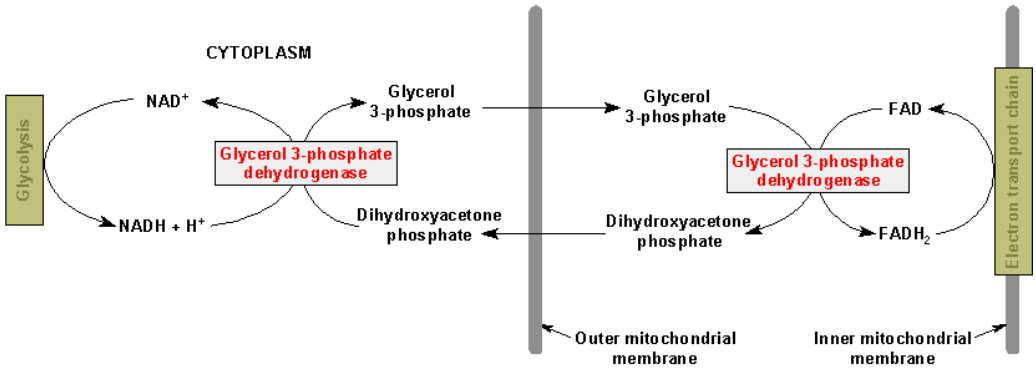


Malate – Aspartate Shuttle



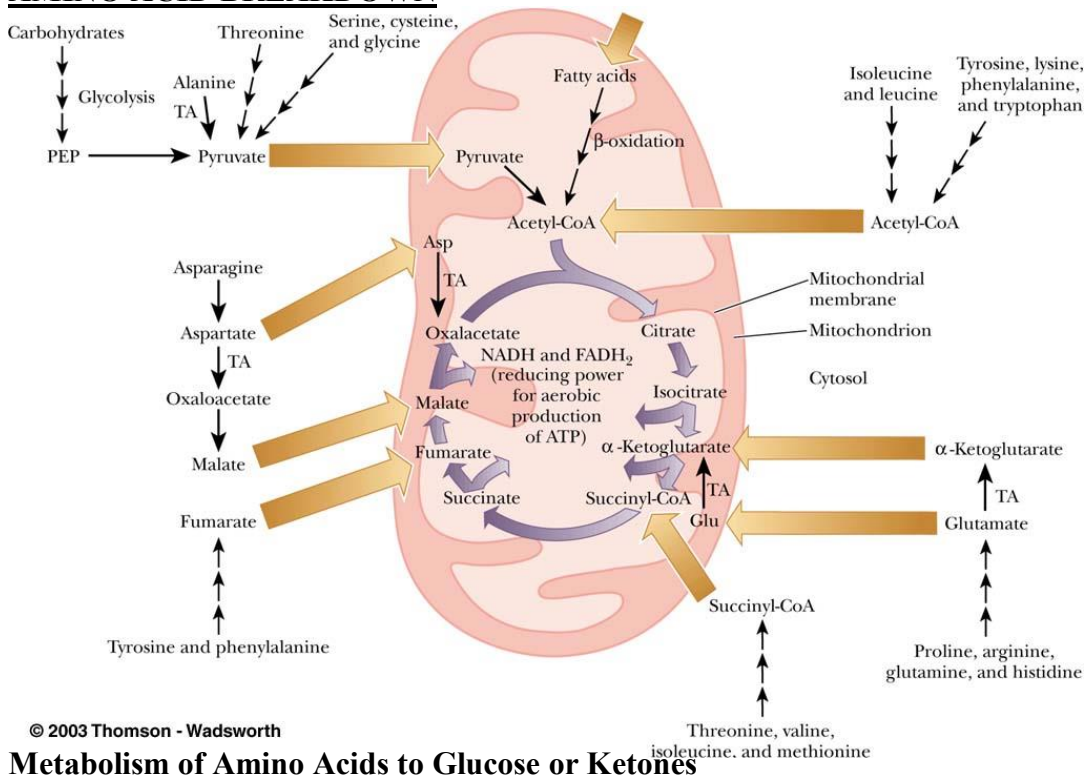
Glycerol 3 – Phophate Shuttle

- **Glycerol Phosphate Shuttle:** converts NADH to $FADH_2$ in the cytosol then the $FADH_2$ enters the chain at Complex II producing 2 ATP
    - **But this uses 2 ATP in it's process**



- When the body is rapidly dividing is when the shuttles work the most
    - Recall stages of development
        - 0 – 2 years
        - 4 – 7 years
        - Puberty
        - Misc.
            - Pregnancy
            - Cancer
            - Burns

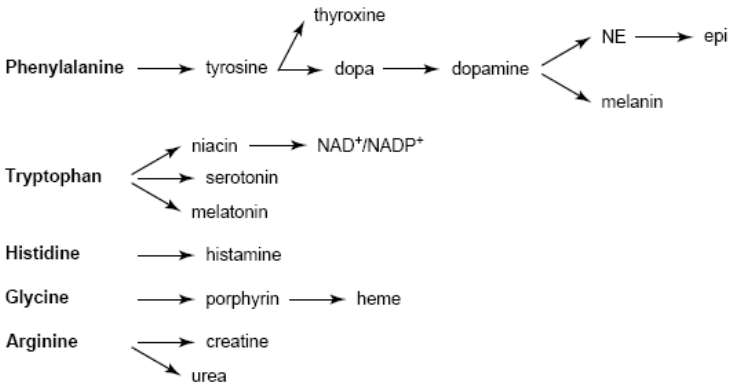
AMINO ACID BREAKDOWN



Metabolism of Amino Acids to Glucose or Ketones

- Ketogenic
  - Leu
  - Lys
- Ketogenic & Glucogenic
  - Phe
  - Iso
  - Tyr
  - Tryp
  - Thre
- Glucogenic
  - All others

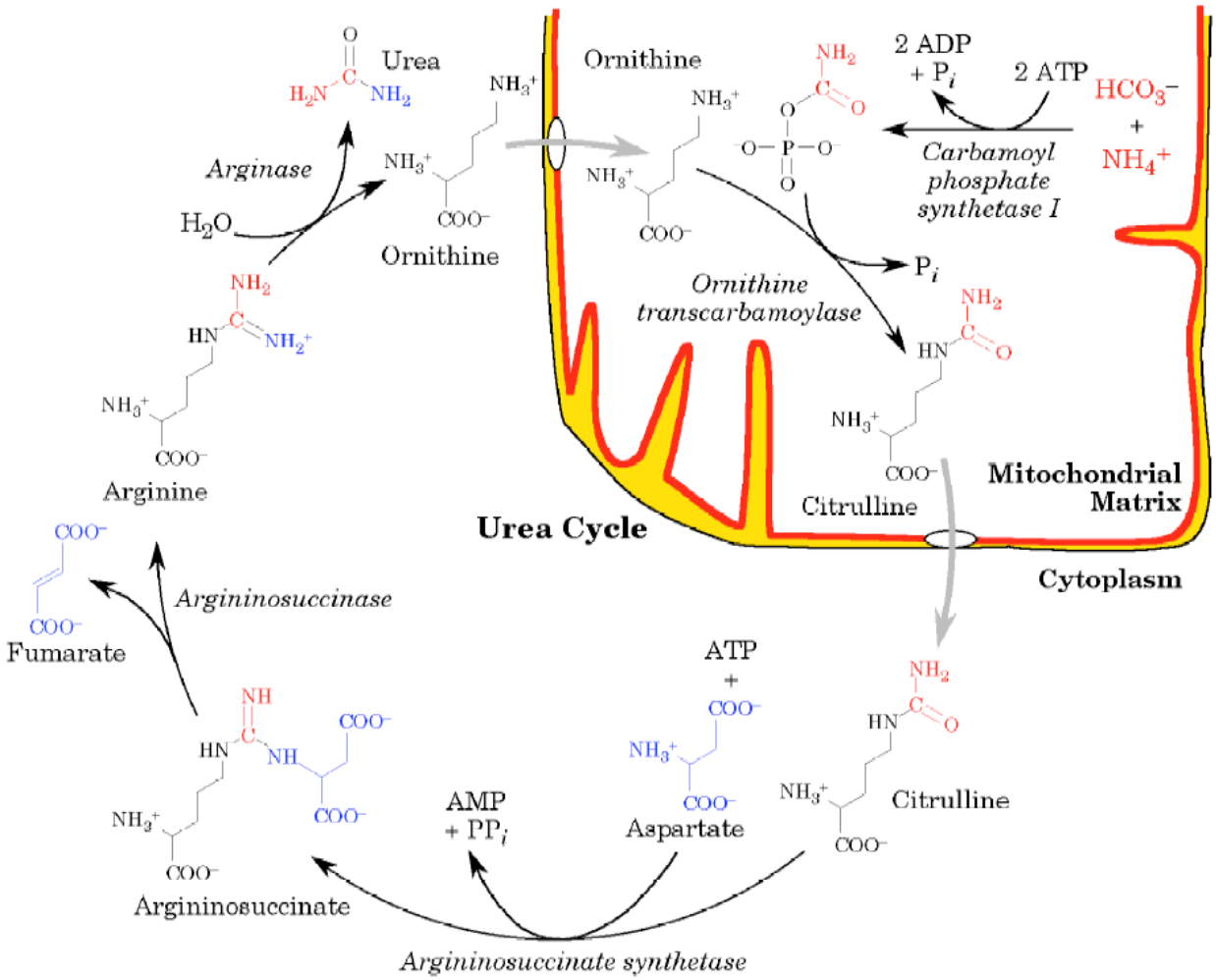
Amino acid derivatives



- **Requirements of Amino Acid Breakdown:**
  - Transaminase
  - Vitamin B_6
- Amino acid breakdown will ↑ **buildup of GLUTAMIC ACID**
  - Need to get rid of the stuff.…How?
    - **UREA CYCLE**
- **Recall the disorders of amino acid breakdown**

UREA CYCLE

- **Allosteric Activator = N – acetyl glutamate**
  - Because there is an ↑ in acetyl CoA and α-ketoglutarate = Formation of N-acetylglutamate
    - This signals the cycle to speed up!!!
- **Rate – Limiting Step**
  - **Carbamoyl phophatate synthase I (CPS-I)**
    - Vmax = 2 g of protein per day
      - Patient with cirrhosis, must try to ut down NH_4^+
      - Treatment :
        - Restrict diet to only 2 g protein/day
        - Neomycin – kill NH_4^+ producing bacteria in the GI tract
        - Lactulose pills (sugar pills) will pull water and NH_4^+ out
- **The urea produced will enter the blood stream for excretion via the kidney**
- Locations
  - 90% in liver
  - 10% in Collecting duct of kidney



Glycogen Synthesis

- Anabolic process
- Related to the well – fed state
  - Time to store

Recall
- UDP carries 1 sugar
- Dolichol carries multiple sugars

Glycogenin – OH

↓

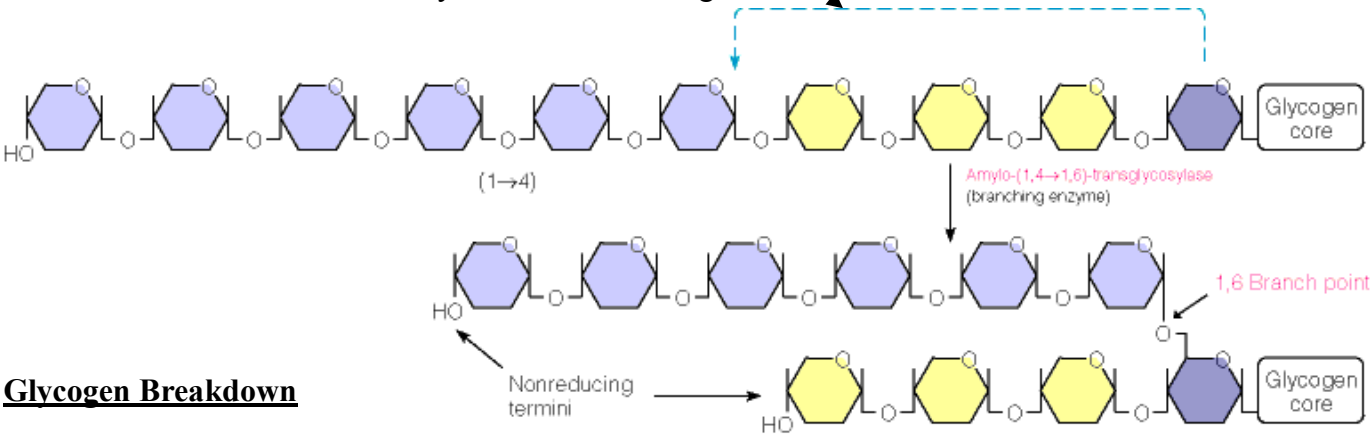
Glycogenin-O-Phos. + UDP – Glu

↓

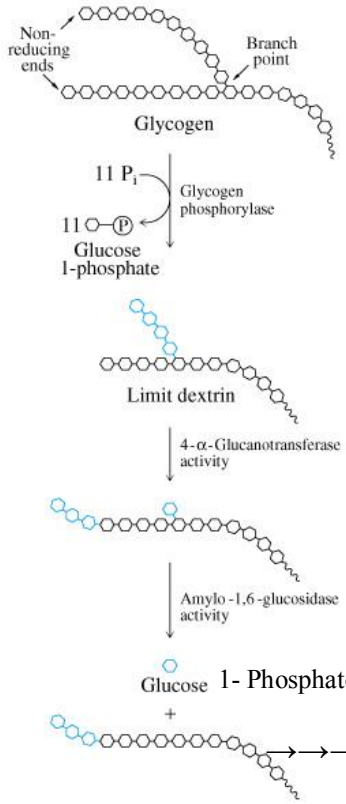
Glycogenin-O-Glu

Glycogen Synthase

1 gram of glycogen drags with it 3 gram s of water
- This the reason why our livers are so big



Glycogen Breakdown

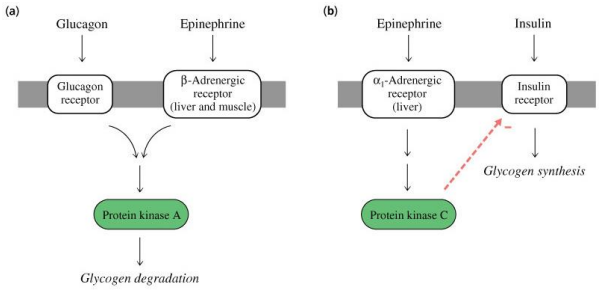


Breakdown of α 1-4 linkages via Hydroxylases = DEBRANCHING ENZYME
Debranching enzyme stops when 4 residues remain

→ removes 1 branch point

→→→→→ Glucose 6 – Phosphatase in the liver → Glucose

Hormones involved:



- Glycogen Synthesis
  - **Rate limiting step = Glycogen synthase**
    - LIVER → Insulin & Glucose → (+) Glycogen synthase
    - Muscle → Insulin → (+) Glycogen synthase
    - LIVER → Glucagon & Epinephrine → (-) Glycogen synthase
    - Muscle → Epinephrine → (-) Glycogen synthase
- Glycogenolysis
  - Glycogen phosphorylase – Debranching enzyme
    - LIVER → Epinepherine & Glucagon → (+) Glycogen phosphorylase = THINK FASTING need more energy = release glycogen
    - LIVER & Muscle → Epinephrine →(+) Glycogen phosphorylase = STRESS Situations → Scared and Running needs energy
    - Muscle → AMP /Ca 2+ → (+) Glycogen phosphorylase = Decreased energy states (between meals or fasting)
    - LIVER → Insulin → (-) Glycogen phosphorylase
    - Skeletal muscle → Insulin/ ↑ ATP → (-) Glycogen phosphorylase

Glycogen storage diseases	12 types, all resulting in abnormal glycogen metabolism and an accumulation of glycogen within cells.	
Type I	Von Gierke's disease = glucose-6-phosphatase deficiency. Findings: severe fasting hypoglycemia, ↑↑ glycogen in liver. *Bio. 82*	
Type II	Pompe's disease = lysosomal α-1,4-glucosidase deficiency. Findings: cardiomegaly and systemic findings, leading to early death. *Bio.79*	Pompe's trashes the Pump (heart, liver, and muscle).
Type III	Cori's = deficiency of debranching enzyme α-1,6-glucosidase.	
Type V	McArdle's disease = skeletal muscle glycogen phosphorylase deficiency. Findings: ↑ glycogen in muscle but cannot break it down, leading to painful cramps, myoglobinuria with strenuous exercise.	McArdle's: Muscle. Very Poor Carbohydrate Metabolism.

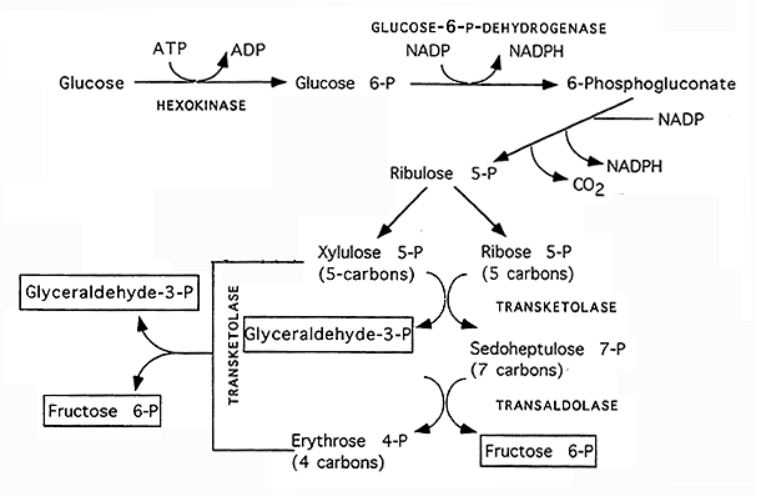
UCV

Type IV **Anderson's Disease = Only Glycogen synthase – Glycogen synthesis problem!!! No branching occurs = linear chain**

Type VI **HERS → Hepatic Glycogen Phosphoylase Deficiency**

Pentose Phosphate Pathway

Function:



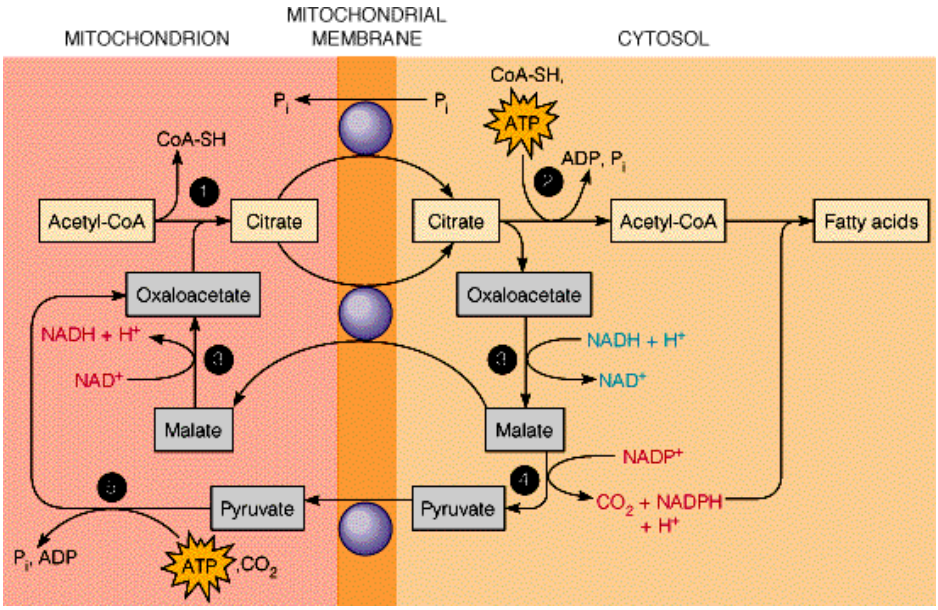
- **NADPH production**
  - Used in FA synthesis
  - **Glutathione (helps in RBC repair)**
  - Bacterial activity in PMN
- **Production of ribose 5-P for nucleotide synthesis**
  - Important for rapidly dividing cells
  - If this is not activated, rapidly dividing cells can be damaged b/c Ribose 5-P provides DNA
    - Think about why Diabetic's have **skin lesions**
  - Activated in the well fed state
- **Rate limiting enzyme**
  - G6PDH
    - Induced by insulin
  - Allosteric activator = Glucose 6-phosphate
  - Allosteric inhibitor = Ribose 5-Phosphate
- **Transketolase (TTP)**
  - Contains thiamine → associate with decarboxylation
  - Think about Thiamine Deficiency
    - Wernicke's
      - Post temporal lobe is thiamine dependent, if deficient = no TTP
      - **Therefore, the affected area of the brain will have sugar build up which will suck up water = ENCEPHALOPATHY**
- **G6PD Deficiency**
  - Leads to chronic hemolysis due to poor RBC defense against oxidizing agents (fava beans, sulfa drugs)
    - ***Favism***
      - Common in:
        - Greece, Italy, Spain, Portugal, and Turkey **(Mediterranean)**
      - Presentation:
        - Pallor
        - Hemoglobinuria
        - Jaundice
        - Usually occurs 24 hrs after ingestion of beans
  - ***Chronic granulomatous disease***
    - Caused by genetic deficiency of NADPH oxidase
    - Succeptible to ***CATALASE (+) BUGS***
      - S. aureus
      - Klebsiella
      - E. coli
      - Candida
      - Aspergillus

Drugs causing hemolytic anemia:
PCN
α-methyldopa
Cephalsporins
Sulfa
PTU
Anti-malarials
Dapsone

- Test: A negative **nitroblue tetrazolium** test

CITRATE SHUTTLE → Fatty Acid Synthesis (occurs in cytoplasm)

- When ATP production gets too high → inhibits dehydrogenases
  - Therefore, **Citrate allosterically inhibits PFK – 1**
- **It will then turn to Fatty acid synthesis**



- **Citrate Shuttle and Malic enzyme**
  - Acetyl CoA transportation out to the cytoplasm for FA synthesis
    - Insulin and High energy status INDIRECTLY promote this process
  - Malic Enzyme
    - Source of cytoplasmic NADPH (supplements that from the HMP Shunt)

Fatty Acid Synthesis Rules

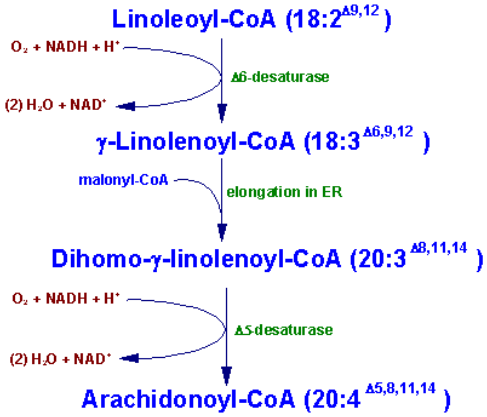
- **The body cannot make a FA > 16 carbons long (C_{16})**
- **C = C, must be located 3 carbons apart**
- **No C = C after C_{10}**

Exanple: C_{16}

- Calculations
  - **#C – 1 = # of ATPs needed**
    - ***16 – 1 = 15 ATPs need to make C16***
  - **[#C / 2] – 1 = # of rounds needed to make C16**
    - ***[16/2] – 1 = 7 rounds needed***
      - For every Round = adds 2 Carbons
  - **[(#C / 2) – 1] x 2 = number of NADPHs required to make C16**
    - ***14***

- **Fatty Acid Biosynthesis**
  - Major enzymes to remember:
    - **Acetyl CoA carboxylase (dephosphorylated)**
    - **Fatty acid synthase (induced)**
- **Acetyl Co-A carboxylase = Rate limiting**
- Fatty Acid synthase
  - Induced by liver AFTER A MEAL!!!
  - 8 acetyl CoA groups are required to produce Palmitate

- **<u>Fatty Acid Nomenclature</u>**
  - Saturated fatty acids
    - NO Double bonds
  - Unsaturated fatty acids
    - One or more double bonds
  - Palmitic acid
    - Primary end product of fatty acid synthesis
  - **Important ESSENTIAL fatty acids**
    - **Linolenic**
    - **Linoleic**
      - **Precursor to *Arachidonic acid* → Remember prostoglandins, thromboxanes, and leukotrienes**

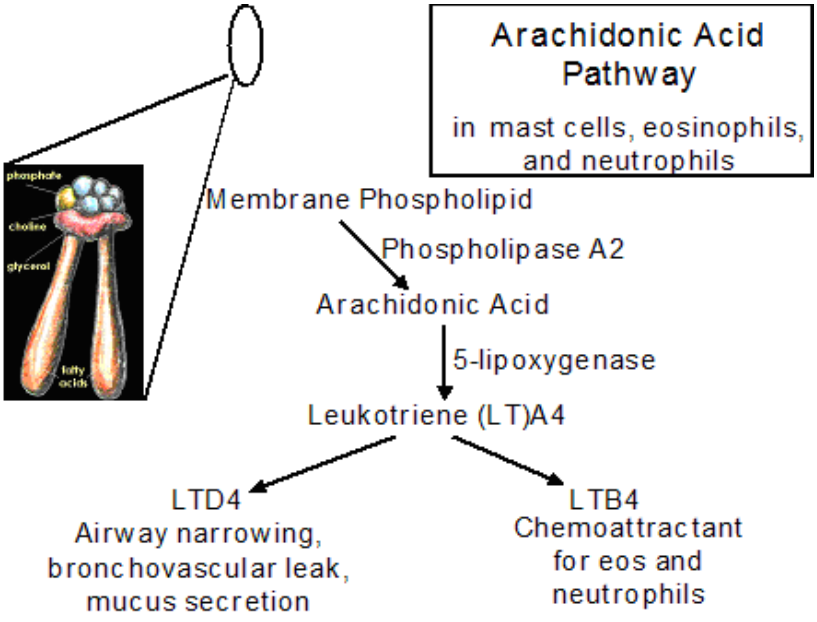


<u>PHARMACOLOGY Connection</u>

STEROIDS → 5 Actions (KIISS)

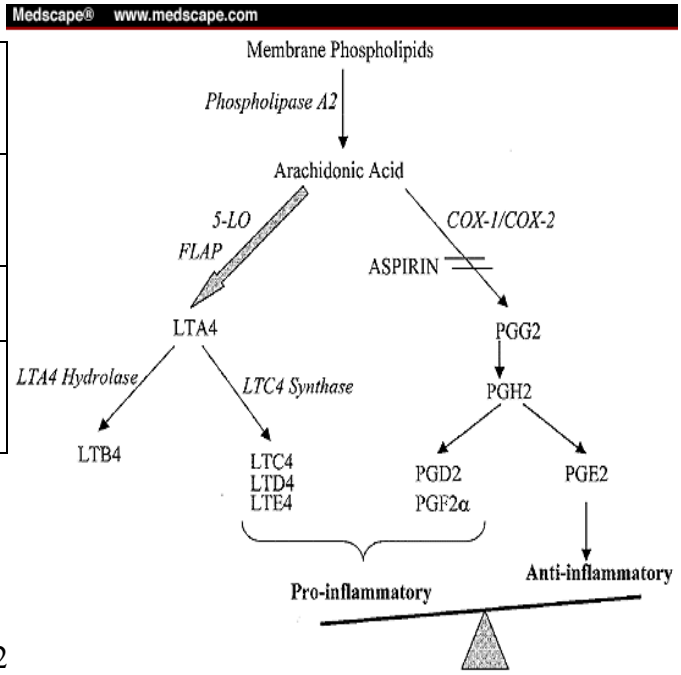
- **K**ills helper t-cells and eosinophils
- **I**nhibits Phospholipase A
- **I**nhibits Mast cell degranulation
- **S**tabalize endothelium
- **S**timulates protein synthesis

- Prednisone
  - MC oral form
- Hydrocortison
  - MC topical form
- Fludrocortisone
  - Used in aldosterone deficiency
- Bethmethasone/Beclamethasone
  - Stimulate surfactant production
- Triamcinalone
- Prednisalone/Solumedrol
  - IV for Asthma attack
- Dexamethasone
  - Diagnosis of Cushing's Syndrome

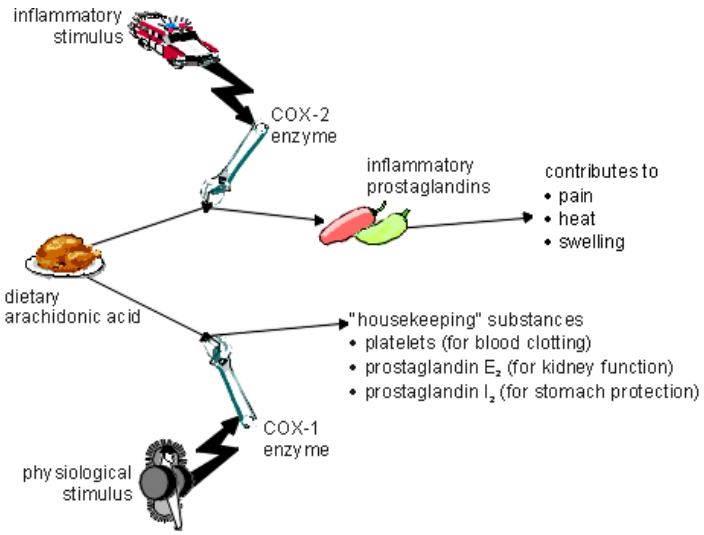


Cromyln → good for children/inhibits degranulation
LTB is a powerful bronchodilator

PGI_2	Prostacyclin produced by endothelium Inhibits platelet aggregation & Vasodilation Possible ↑ Bleeding Time
PGA_2	aka Thromboxane Stimulates platelet aggregation (+) Vasoconstriction
PGE	Vasodilation Keeps PDA open
PGF_2	(+) Vasoconstriction Responsible for painful menstrual cramps Seperates placenta → can be detected in urine



- ASA
  - Non competitive inhibitor
    - Irreversible
  - Blocks prostaglandins both COX-1/COX-2
  - @ > 81 mg
    - Thrombocytopenia
    - Tinnitus
    - ETC uncoupler
    - Hyperventilation
      - ASA induced asthma will present with nasal polyps
- COX – 1
  - Found in GI
- COX – 2
  - Found in inflammatory cells



- NSAID
  - Competitve inhibitor
    - Reversible
  - No anti-platelet function
  - Ibuprofen
    - MC OTC
  - Naproxen
    - MC for menstrual cramps
  - Indomethicin
    - Most potent NSAID
    - Close PDA
    - 2nd line for Gout
  - Phenylbutamine
    - Next potent NSAID
  - Baclofen
    - Back pain control
  - Cyclobenzaprine
    - Has anti-choinergic SE
  - Ketorelac
    - Morphine like!!!

Complex Lipids

- Phosphatidic acid is the precursor for all glycerolipids in eukaryotes
  - It is made into either DAG or CDP-DAG
  - CDP can bring along Serine, Ethanolamide, and choline
- These are used by NEURAL TISSUE
  - Brain/Spinal Cord
  - Adrenals
  - GANGLIA
- CDP – DAG
  - Is used to produce Cardiolipin
    - Think about SLE → anti Cardiolipin antibody
    - Cardiolipin promotes clots
    - vWF is inhibited by Cardiolipin AB
    - Cardiolipin AD Syndrome
      - (+) multiple spontaneous abortions
- DAG
  - Recall 2nd messenger system

Triglyceride/Triacylglycerol Synthesis

  - Liver sends triglycerides to adipose tissue as VLDLs
  - ↑↑ in tissues other than Adipose tissue → (+) PATHOLOGIC STATE ☹
- Sources of Glycerol 3-Phosohate for Synthesis of Triglycerides
  - DHAP reduction from glycolysis
    - Glycerol 3-P dehydrogenase in both liver and adipose tissue!!!
  - Phosphorylation of free glycerol by glycerol kinase
    - Glycerol kinase in liver, NOT ADIPOSE TISSUE
- Lipoprotein Metabolism
  - ↑ Density = ↑ amt of proteins

- Classes of Lipoproteins/Apoproteins
  - Chylomicrons
    - Transportation from INTESTINE (vascular endothelium)→ tissues
  - VLDL
    - Transport from LIVER → adipose tissue
    - ***apo B-100 = Binds to LDL receptor/secreted by liver***
    - ***apo C-II = cofactor for lipoprotein lipase***
      - **Induced by INSULIN**
  - LDL
    - Delivers cholesterol into cells
  - IDL
    - Picks up cholesterol from HDL to become LDL; Adipose → everywhere else
    - Picked up by liver

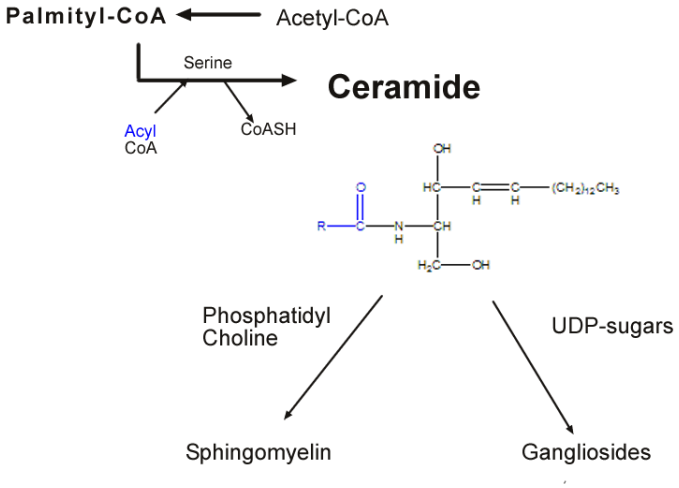
- HDL
  - Picks up cholesterol ACCUMULATING in blood vessels
  - ***a*poA- 1 = *a*ctivates LCAT (produces cholesterol esters)**

- LDL, HDL, and Athersclerosis
  - ***CLINICAL***
    - Elevated LDL, free radicals from smoking, diabetes, and HTN → Endothelial Cell Damage → Endothelial dysfunction = ↑adhesiveness and permeability of the endothelium for platelets and leukocytes → INFLAMMATION → recruitment of monocytes and macrophages containing oxidized LDL which become laden with Cholesterol (foam cells) → accumulation = Fatty Streaks → plaque with fibrous cap → possible rupture of cap → leading to thrombosis → HDL acts to pick up any excess cholesterol before an advanced lesion forms.

<u>Sphingolipids</u>

C_{16} – Acyl CoA + CDP-Serine = Sphingosine
Sphingosine + C_{16} =CERAMIDE

- Add UDP-Glucose to ceramide =Cerebroside
- Add Dolichol + "Gang of sugars" = Ganglioside



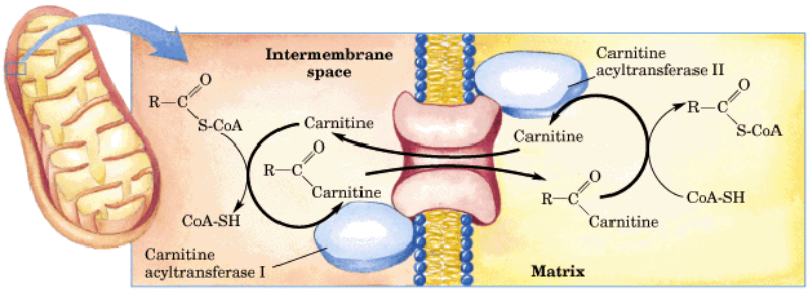
- **Lysosomal Storage diseases**
  - Wasted possible energy
  - (+) lysosomal inclusion bodies b/c lysosome just sitting there doing nothing
  - SEE CHART
  - **Remember that there is neural tissue in the cornea**
    - **Cherry red macula**

Disorder	Enzyme Deficiency	Accumulating Substance	Symptoms
Tay-Sachs disease	**Hexosaminidase A**	GM_2 ganglioside	**Jewish descent,** mental retardation, **blindness**
Gaucher's disease	**Glucocerebrosidase**	Glucocerebroside	**Jewish descent, gargoyle facies, "crinkled paper" MΦ, long bone degeneration**
Fabry's disease	**α-Galactosidase A**	Globotriaosylceramide; also called ceramide trihexoside (CTH)	**X-linked Recessive, catracts, renal failure**
Niemann-Pick	**Sphingomyelinase**	Sphingomyelin LDL-derived cholesterol LDL-derived cholesterol	**Cherry red macula, Zebra bodies**
Krabbe's disease; globoid leukodystrophy	**Galactocerebrosidase**	Galactocerebroside	mental retardation, myelin deficiency **Globoid cells in BM**
Sandhoff-Jatzkewitz disease	**Hexosaminidase A and B**	Globoside, GM_2 ganglioside	same symptoms as Tay-Sachs,**progresses more rapidly**
GM_1 gangliosidosis	GM_1 ganglioside: β - galactosidase	GM_1 ganglioside	mental retardation, skeletal abnormalities, hepatomegaly
metachromatic leukodystrophy	**Arylsulfatase A**	Sulfatide	presents like MS in a 5-10 y.o.

FAT BREAKDOWN = β Oxidation

- Lipid Mobilziation
  - Insulin ↓↓ = activates hormone sensitive lipase → (+) Glycerol (*Gluconeogenesis)*and Fatty acids (*β-oxidation)*
  - ↑↑ Epinepherine and Cortisol stimulate Fat breakdown

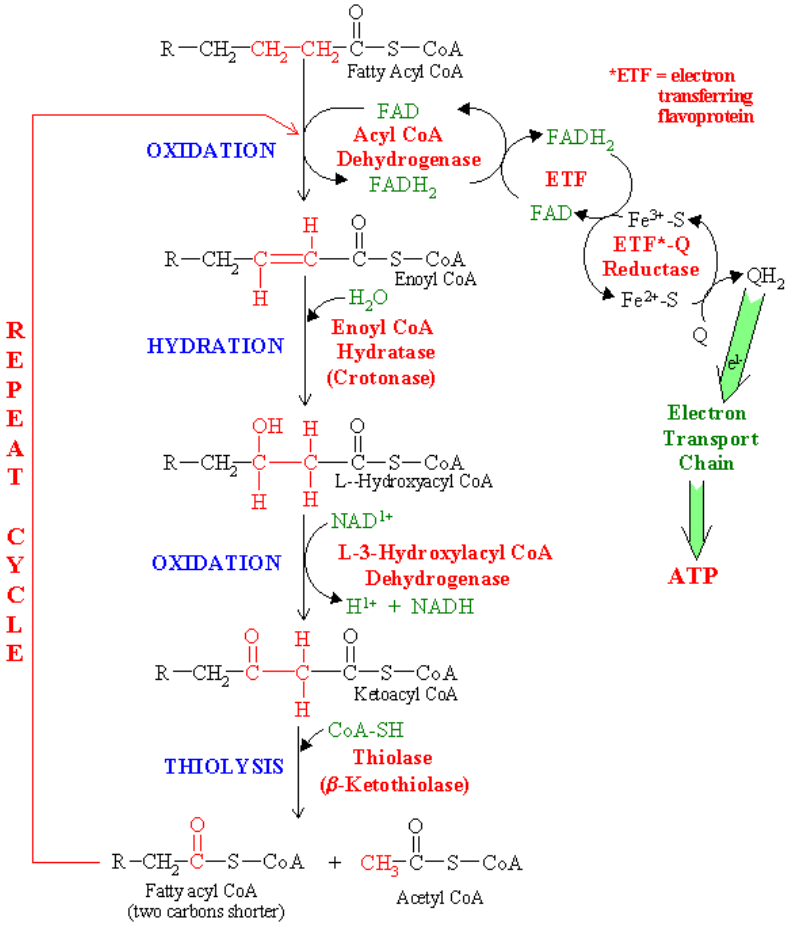
- Fatty Acid Oxidation
  - Brain and Erythrocytes do not use FA
  - Fatty Acid entry into Mitochondria via…
    - Carnitine Shuttle
      - Inhibited by cytoplasmic *malonyl-CoA* therefore preventing newly synthesized FA from entering the mitochondria



- **β-oxidation in Mitochondria**
  - Oxidizes and releases units of acetyl CoA
    - Ketogenesis (liver) or TCA Cycle (other tissues)
  - Reduction of NAD and FADH
    - Provides for the ETC!!!
  - **Adrenoleukodystrophy**
    - **Underlying problem = defective long chain FA**

"OHOT"

- **O**xidation → 7 NADH → goes to ETC (3 ATP:1NADH) = 21 ATP
- **H**ydate
- **O**xidation → 7 $FADH_2$ → goes to ETC (2 ATP:1 $FADH_2$) = 14 ATP
- **T**hiolysis → 8 Acetyl CoAs → goes to Kreb cycle (12 ATP: 1 Acetyl CoA) = 96 ATP
  - #C / 2 = ATPs
- **TOTAL = 131 ATP**

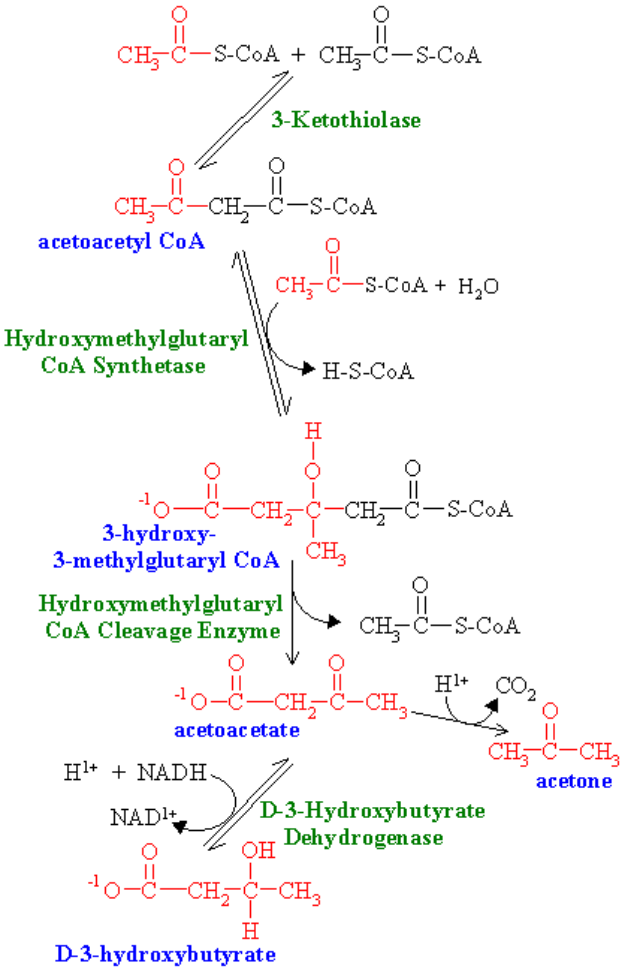


- Proprionic Acid Pathway
  - Odd Chain fatty acids
    - Vitamin B12
      - Megaloblastic anemia → production of a peripheral neuropathy b/c lack of FA incorporation into MYELIN!!!
      - Excretion of methylmalonic acid indicates Vitamin B12 Deficinecy versus Folate

Organ	Normal	Stress	Extreme Stress
CNS	Glucose	Glucose	Ketones
Muscle	Gluose	Free Fatty Acids	
CV	Free Fatty acids	Glucose	

KETONE METABOLISM

- **Ketogenesis**
  - **HMG-CoA synthase → impt. enzyme**
  - Occurs in the liver **when excess acetyl CoA accumulates during fasting**
  - Can cross the BB Barrier at times of need!!!
    - β-hydroxybutyrate
  - Acetone → **(+) breath**
- Ketoacidosis
  - Diabetes Type I (IDDM)
    - **If not treated with INSULIN, FA release from adipose tissue and ketone synthesis > the ability of other tissues to metabolism them = KETOACIDOSIS**
  - **Alcoholics**
    - ↑3-hydroxybutyrate due to the high NADH/NAD ratio
  - **Associated Symptoms**
    - **Polyuria, dehydration, thirst**
    - **CNS depression/coma**
    - **Potential depletion of K+**
    - **↓plasma bicarb**
    - **Fruity breath odor**



CONNECT BABY

- When you breathe fast you generate a lot of acid (Hyperventilation) → remember that acid DENATURES proteins → LOW ENERGY STATE
  - The build up of acid leads to ↑ of GABA → "Hey!!! Slow breathing down!!"
  - But body still needs to rid the body of the acid
    - Have two forces fighting each other = KUSSMAUL's BREATHING!!!
    - Diabetic Ketoacidosis
      - Remember that the K will be low in these patients
      - Must give K^+ to prevent depolarization → possible arrhythmia!!!

DIABETES TYPE I

- Insulin dependent
  - (+) anti – islet cell antibodies
- Affects children the most
  - Autoimmune
  - **HLA DR3/DR4**

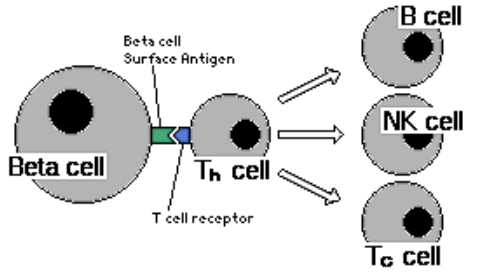
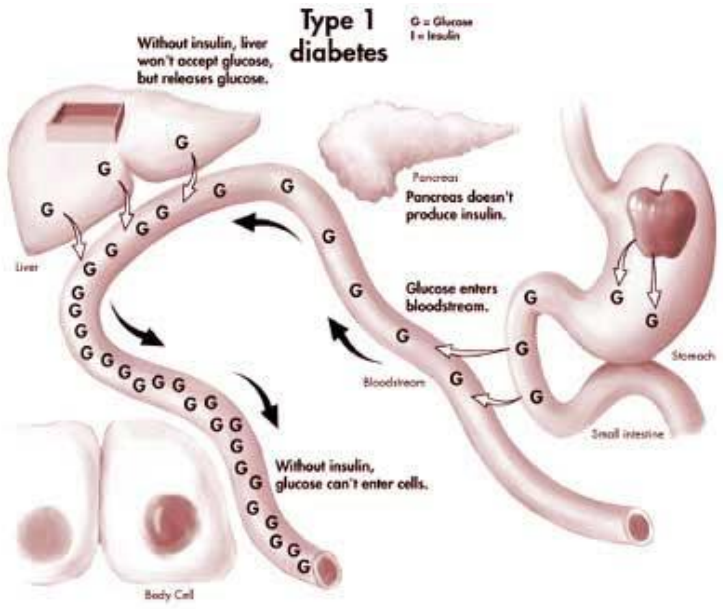


Fig D.07.01 – The T_h cell recognises a Beta cell antigen and activates B cells, NK cells, and T_c cells which in cooperation with Antibody, and complement destroy the Beta cell.

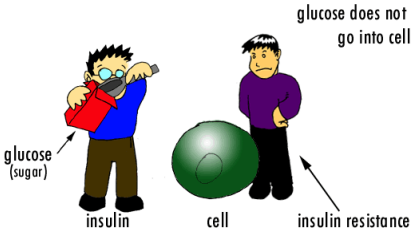
- Present with symptoms when …
  - 90% of islet cells are gone
  - 10% are in the "honeymoon period"
    - Hyperplasia of remaining islet cells can be off of insulin for a little bit
    - The child can eat what he/she wants ☺
    - But in 2-3 months must go back ☹
  - Aciduria, and Hyperglycaemia (High blood glucose) lead to dehydration, and vomiting. Eventually chronic lack of insulin will lead to damage to blood vessels, heart disease, stroke, blindness, and kidney failure. Eventually leading to coma and death.
  - MCC of Death = Cerebral Edema

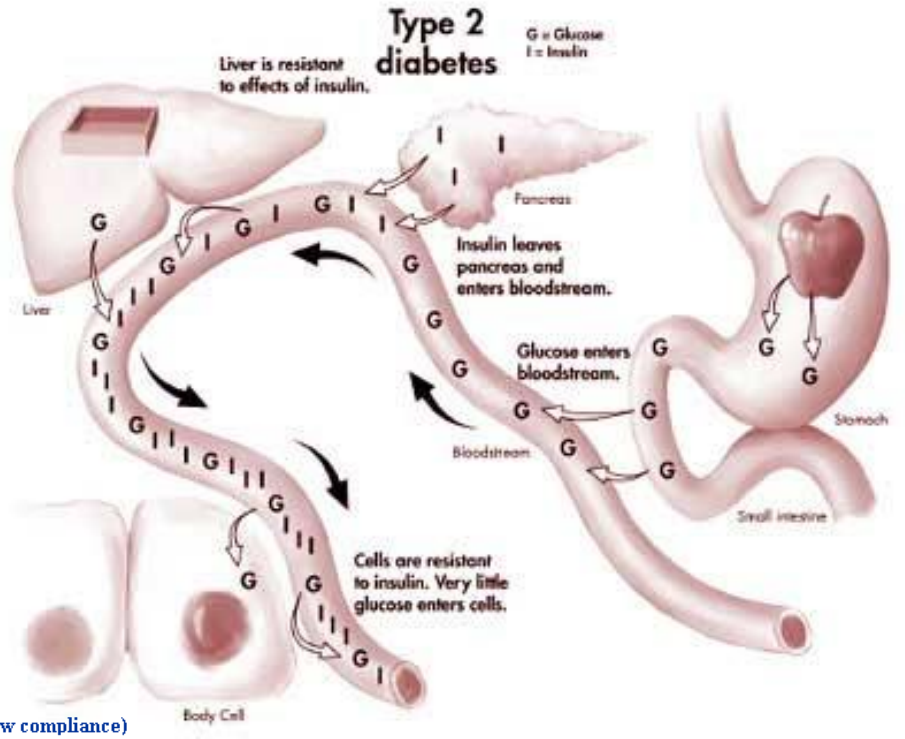
- Treatment
  - Insulin!!!
  - Give Fluids >> Insulin >> K^+/PO_4^{2-}
- Total body K^+ = Hypokalemic
- Serum K^+ = "False" hyperkalemia
- Complications
  - DKA
    - Occurs because of unopposed Glucagon release
    - Remember Glucagon promotes Fatty ACID breakdown = Acid know in the blood stream = ACIDOSIS
    - MCC = Infection
      - Always rule out infection → Do a Culture



DIABETES TYPE II

- Adult onset d/t obesity
- Insulin resistance





Treatment

- Weight loss
- Oral hypoglycemic drugs
- Insulin when all else fails

Exercise, diet, weight reduction

↓ (failure after 3 months: review compliance)

Sulphonylurea (or metformin)

↓ (failure after 3 months : review compliance)

Add metformin (or Sulphonylurea)

↓ (failure after 3 months : review compliance)

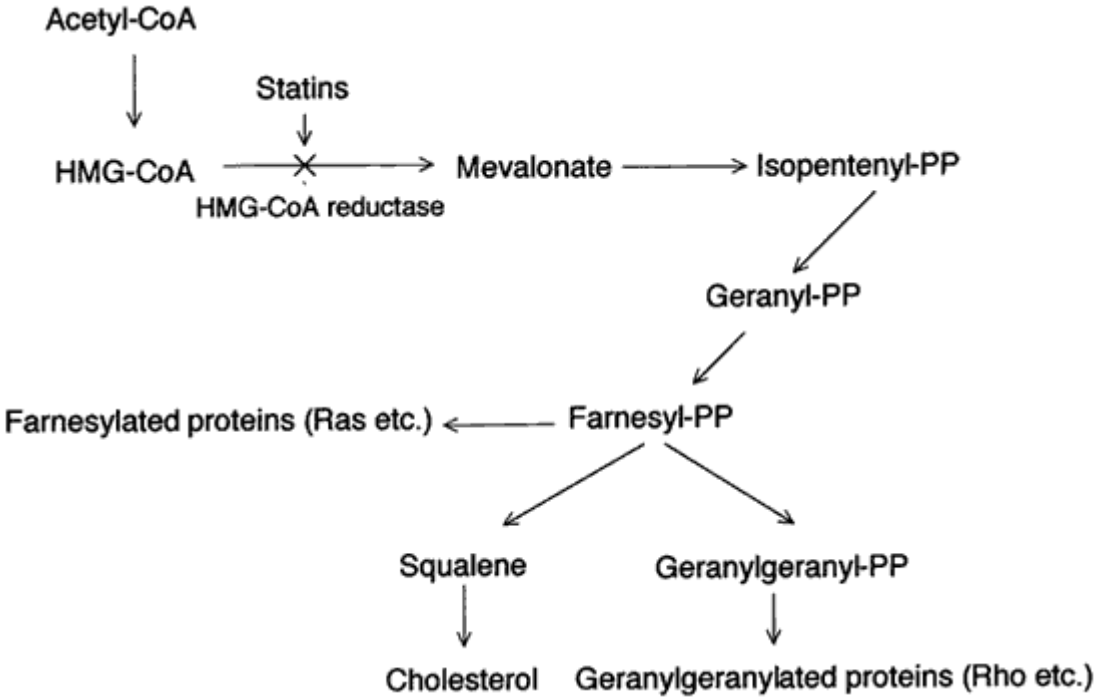
Insulin

PHARM CONNECTION

- Sulphonylurea
  - **Cause release of preformed insulin**
  - 1st Generation
    - Chlorpropamide
      - (+) SIADH !!!!
    - Tolbutamide
    - Tolezalide
  - 2nd Generation → also stimulate preformed insulin
    - Glipizid
      - **(-) gluconeogensis in liver**
    - Glyburide
      - **(+) Glucose transport to peripheral tissues**
- Ascarbose & Miglitol
  - **(-) GI absoption of sugar**
  - Indicated for post- prandial hyperglycemia
- Metformin
  - **(-) Gluconeogenesis in liver**
  - SE
    - DDIX with kidney damage
    - Severe metabolic acidosis
- Troglitazone
  - 1st line treatment
  - **Sensitive insulin receptors = ↓ hypoglycemia & ↓ atherosclerosis**
- Piaglitazone
- Roglitazone

CHOLESTEROL SYNTHESIS

- Cholesterol Metabolism
  - Needed for…
    - Membrane Synthesis
    - Steroid Synthesis
    - Bile acid synthesis (in the liver)
  - De novo synthesis
    - Occurs in the LIVER
      - From acetyl CoA in the cytoplasm via the Citrate shuttle



- HMG CoA Reductase is most active at 8:00 pm
  - Therefore, give Statin drugs at 8:00 pm!!!

PHARM CONNECTION

- STATINS
  - **MOA**
    - **Inihibit HMG-CoA reductase**
  - Provastatin
  - Lovastatin
  - Simvastatin
  - Alorvastatin
  - Side effects
    - Myositis
    - Hepatitis (b/c these are fat soluble)
  - Check liver enzyme

Hematology

- RBC
  - **120 day lifespan**
- Spleen
  - Function
    - Get rid of the dead RBC's
    - This is done gradually → begins to leak small RBC = Spherocytes
    - **Therefore, the MCC of spherocytes is AGING**
    - Link to Immunology
      - RES (MΦ) will check out the RBC and make sure they are correctly made or if they are too old
      - If something wrong with the RBC → Destroy them!!
- Reticulocyte
  - Immature RBC
  - If there is an ↑ **in Reticulocytes → indicates that the BM is at work**
    - Ret. Count < 1% = Normal
      - With anemias check the Ret. Count 1st

- **Is the anemia d/t a BM problem or something else in the periphery?**
  - **If Ret Count ↓ = BM problem**
  - **If Ret Count ↑ = Peripheral problem → (+) Splenomegaly**

- Coomb's Test
  - This test tells if an anti-body is killing the RBC → indication of Autoimmune attack against RBC
    - Direct Test → Antibodies are ON the RBC surface causing the hemolysis
    - Indirect Test → There are antibodies in the serum causing the hemolysis
      - ***Drugs that Cause AUTOIMMUNE HEMOLYTIC ANEMIA***
        - ***PCN***
        - ***α-methyldopa***
        - ***Cephalosporins***
        - ***Sulfa***
        - ***PTU***
        - ***Anti-malarials***
        - ***Dapsone***
- Hemolytic Anemias
  - Types of Hemolysis
    - Intravascular
      - RBC is destroyed within the blood vessels = **VASCULITIS**
      - **Clue: SHISTOCYTES (sheared RBC/Platelet)**
        - Burr Cells (TTP/HUS)
        - Helmet cells (DIC)
    - Extravascular
      - RBC is destroyed by the SPLEEN, when there is an abnormality of/in the RBC membrane (Abs. on surface)
      - Spleen will initiate RBC destruction
      - **Clue: SPLENOMEGALY**
      - Ret Count ↑ → Peripheral Problem!!!

- RBC Types
  - Elliptocytes
    - Hereditary elliptocytosis (AD)
  - Howell-Jowel Bodies
    - Nuclear remnants left over
    - Results from 2 problems
      - BM working to fast or
      - Spleen not working
    - Scenario: Child > 6 y.o. with Sickel Cell HbS
      - Recall that usually by the age of 6 autosplenectomy has occurred!!!
        - #1 cause of splenectomy → TRAUMA
  - Heinz bodies
    - Precipitated protein stuck on the side of RBC
    - MC in G6-PD
    - Basophilic stippling → d/t lead poisoning
  - Target Cell
    - Contains ↓↓ Hb than normal
    - Recall Heme synthesis
      - Succinyl-CoA is needed to make porphyrin rings
    - MC in Fe Deficiency, thallasemia, and hemoglobenopathies
  - Tear drop cell
    - Bone marrow pushes the RBC too quickly so it comes out in a tear shape
      - Hemolytic anemia causes the RBCs to be pushed out quickly in order to replace hemolyzed RBCs
        - High reticulocyte count
        - Cancer in bone marrow pushing it out
          - MC in Children → ALL
          - MC in Adult male → Prostate
          - MC in Adult female → Breast
  - Anisocytosis
    - Different SIZES of RBCs
      - Represents:
        - > 1 disease process occurring
        - 1 disease in it's 2nd phase (long standing)
  - Poikilocytosis
    - Different SHAPES on RBC
      - See Burr cells with normal cells in a smear

Anemia

- Disease in circulating RBC mass
  - ↓↓↓ hemoglobin = less O_2 carrying capacity
- Normal Hb = approx. 15g/dl
  - < 11 g/dl → Anemic
- **Anemia does not mean HYPOXIA/CYANOSIS occurring!!!**
  - Because it does not tell you anything about saturation
  - O_2 content = Hb + pO_2
    - Hb can drop but doesn't mean pO_2 drops with it!!!
  - O_2 Content and pO_2 can change together

- Not hypoxic because body will try to compensate for the anemia
    - **How to determine if compensation is occurring?**
        - **Resting Tachycardia can indicate an anemic state**
        - **↑AVO_2 Difference**
            - Tissue will extract more O_2 d/t lack of RBC and Hb available →
            - Therefore, patient will not appear SOB
                - **Heart has highest AVO_2 difference at rest only→ will extract the most** O_2
                - Muscle will have the highest AVO_2 after exercise
                - GI will have the highest AVO_2 after a meal
                - **Kidney has the lowest AVO_2 all the time.**
        - ↓ Mixed venous O_2
        - If AVO_2 ↓ → not much oxygen has been extracted!!!
            - Possible AV fistula → blood never got to the tissue therefore, O_2 is not extracted
            - Vasodilation → more blood comes in but extract the same amount
- Hb < 9 – moderate anemia
- Hb < 7 – Severe anemia
    - But transfusion is needed in relation to the signs and symptoms → ex. Cyanosis!!!
- Cyanosis
    - **Occurs when 5g of Hb is FULLY de-saturated at one time**
    - Example
        - 5g/25g Hb = 20 % → easier to desaturate → Cyanosis
        - 5g/8g Hb = 6% → more difficult to desaturate → no cyanosis
            - Polycythemic rubra vera- are usually cyanotic b/c an ↑↑ in RBC makes it easier to desaturate 5 g of Hb at one time

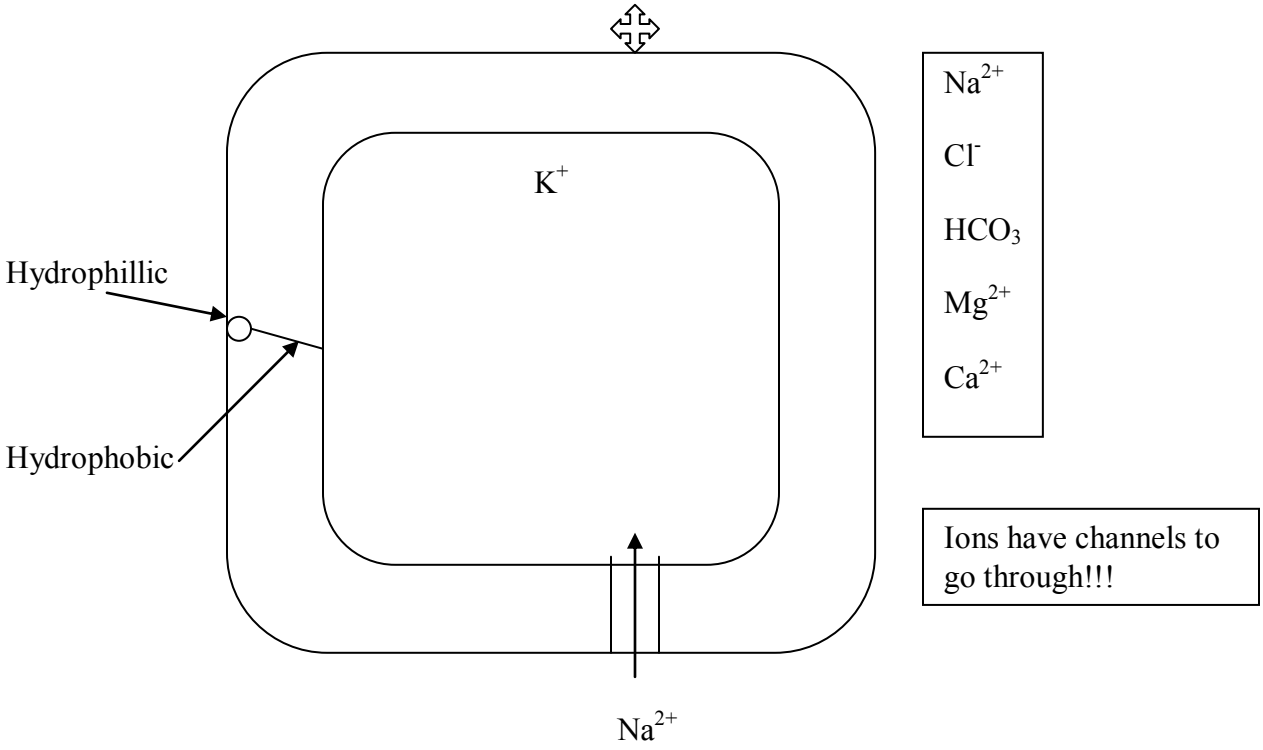
- Types of Anemia
  - MCV = size of RBC
  - MCH = tells how much Hb (done by absorption of light)
  - MCHC = MCH/MCV

<table>
<tr><th colspan="4">↓ MCV, MCH = Microcytic hypochromic → Defect in Hb synthesis</th></tr>
<tr>
<td>MCC = Fe^{2+} Deficiency
D/t poor intake
Baby does not need Fe^{2+} until 4 months → Check Fe levels at 6 mos.
> 40 y.o. MCC = GI Bleed, recall that 90% is absorbed in the duodenum
Diagnostic Tests:
Check Ferritin levels (Fe^{2+} Storage) → 10% in plasma, 90% in GI mucosa
TIBC – Transferrin – controlled after mRNA is made; Fe^{2+} binding protein suppresses translation = ↑ TIBC
Labs
↑ TIBC, ↓ Ferritin, ↓ Fe^{2+}
Treatment:
Iron Supplements
Ret Count ↑ at day 4
Peaks at Day 7
Check Hb in 1 wk → 1 mo.</td>
<td>Anemia of Chronic Disease
Chronic disease is defined as > 3 years with disease
RBC dying fast
Smear can appear normocytic for the 1st 60 days
The body conserves energy by using most of it to combat sickness → Slows down
Therefore, BM suppression and the BM will not replace RBC's right away, so some unknown protein comes and starts to destroy the RBCs quickly
Labs:
↑ Ferritin b/c nothing is going on → no reason to store iron
↓ TIBC because liver not making transferring or requiring iron</td>
<td>Lead Poisoning
Most common source – Lead based PAINT
Screening for Pb poisoning at age 2
Why? B/c it is the age where the child tends to get into everything!! Pb tastes sweet
Normal Pb levels < 10 µg/dl
If > 10 → notify Public Health officials → they will find the source
Treatment:
Succimer
If > 30 → Hospitalization
Treatment:
Ca EDTA Challenge → checks to see if free Pb still floating around
EDTA → chelator
Ca^{2+} → body has higher affinity to this than Pb
Penicillamine → bind Pb out of the PLASMA
Dimercaprol → works on BM to pull out lead
If > 50 → skip EDTA challenge treat immediately
CLUE: Lead line on abdomen and gingival line</td>
<td>Hemoglobinopathies:
Thalassemias
Sideroblastic anemia
MΦ eating all free/stored iron
1^0 → rare
2^0 → MCC is Blood transfusion
Labs:
↓ TIBC b/c nothing is being transferred since MΦ are eating all the iron
Serum Iron ↑
RBC ↓</td>
</tr>
</table>

↓ MCV, ↑ MCHC **Microcytic hyperchromic** **Very small cell**	**nl MCV, nl MCH** **Normocytic** **Not enough**	**↑ MCV** **Macrocytic – defect in nuclear division**
Heredietary Spherocytosis • AD → extravascular problem • Ret Count ↑ • **Tear Drop/Howell Jowel bodies** • Problem with defective spectrin → NO central pallor • Osmotic fragility → hypotonic fluid • Aniso/Poikliocytes • **(-) Coombs**	***Acute Hemorrhage*** • Area of trauma • Ex. Gall Bladder Surgery → Give fluids, if still bleeding STOP fluids b/c the patient will continue to bleed → Close the wound ***Early hypothyroidism*** • Recall that Thyroid hormone has a permissive effect → without it erythropoietin will not work!! ***Renal Failure*** • Kidney secretes erythropoietin!!!	General Characteristics: • Cytoplasm dividing to fast → **hypersegmented neutrophils** ***Vitamin B12 Deficiency*** • Megaloblastic anemia • Recall that it is requied for methyl malonyl-CoA mutase & homocysteine transferase • **(+) Neuropathy** ***Folate Deficiency*** • (+) Reticulocytosis • Can be due to ↑↑ Alcohol → suppresses nuclear division • Without Neuropathy ***Pharmacological:*** • Chemotherapy • **Anti-convulsants** - **Phenytoin** - **Carbamazipine** - **Valproate** - **Ethusuximide** ***Mylodysplasia*** • PRV → ↑↑ RBC • Essential Thrombocytopenia • Aplastic anemia • Myelofibrosis

Cellular Physiology

- Membrane Potential
  - Protects the INSIDE
  - Gives cell it's shape
  - MAINTAINS GRADIENTS



- Membrane Components:
  - Lipid bilayer
    - Amphipathic – like fat & water
    - Fat soluble fold is in the INSIDE
  - Unsaturated fats (C=C)
    - Cause kinks within the membrane to form the gradient
  - Saturated Fats (No C=C) → line up perfectly – cells can't "breath"
  - Polyunsaturated fats
    - Better at temperature regulation
    - Better fluidity within the membrane d/t lots of "holes"
  - Our body prefers unsaturated because has kinks, fluidity, flexibility, and better temperature control
    - Important b/c provides for lateral movement of proteins in order to find another site that will allow transport
  - Receptors = glycoprotein
    - Minimum of at least 7 or more domains inside the membrane to anchor it
- Transport – Transmembrane
  - Charged particle must go "in" with H_2O → lysine will point inward if it's part of a channel
- Temperature control
  - Radiation = moving heat down the concentration gradient.(Dance Floor Analogy)
  - Conduction = moving down a concentration gradient **requiring contact**
  - Convection = movement through a medium → environment moves past you (Air will suck out hot air from you = "feel cool" when you walk at night
- Concentration Gradient

- **Fat-soluble material**
  - Fat soluble will move right through membrane
  - **Steroid hormones**
  - **ALL have receptors in the nuclear membrane except Cortisol, it has its receptor in the cytoplasm, but still moves into nucleus**
  - All Steroid hormones stimulate the nucleus for DNA replication, transcription, translation, and out comes the protein that manifests its action.
    - The **only difference** in the function of steroid hormones **is the protein that comes out. Nothing to do with membrane receptors**.

- **Water soluble material-Still move according to:**
  - **Concentration gradient → will overcome forces**
  - Charge → ↑ charge = ↓ ease of diffusion
  - Size → if ↑ the size = ↑ the difficulty to enter cell
  - pH (acid/base) = ↑ pH acid gains more charge
  - Membrane thickness
  - Total surface area of the membrane
  - Flux = movement of particles over time, $\frac{dX}{dt}$. "Bum Rush" the door
  - Reflection coefficient= number of particles sent across the membrane, $\frac{\#\ particles\cdot.returned}{\#\ particles\cdot.sent}$
    - Coefficient < 0.5 ➔ neutral, uncharged
    - Coefficient > 0.5 ➔ water soluble, charged
    - Coefficient = 0 → all went through

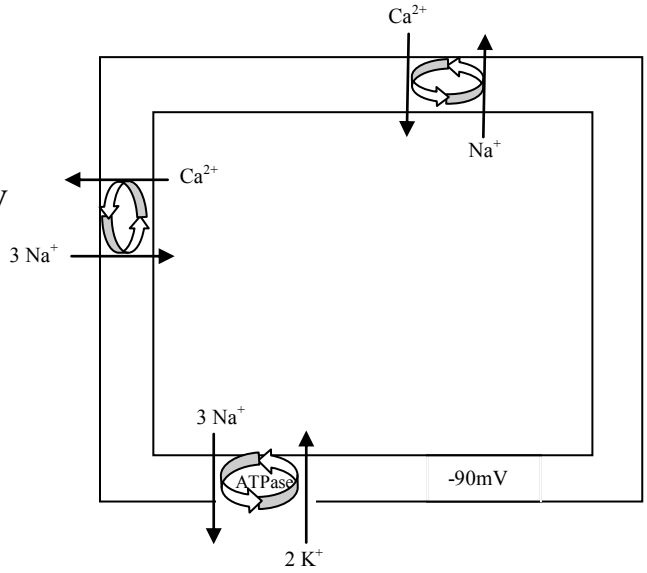
Promotes Diffusion = 1
Impairs diffusion

- **Fick's Principle**
  - Promotes Diffusion → numerator
  - Impairs Diffusion → denominator
    - ***Which Factors impairs/promotes diffusion?***
      - Think of components that are directly related to particle movement (as they increase, the movement into the cell will increase)➔ Numerator
        - **Ex. [conc.], pH, surface area, flux =↑ DIFFUSION**
      - Components that are indirectly related (as they increase, movement into the cell should decrease) ➔should be in denominator:
        - **Ex. charge, size, pH, thickness, and coefficient. = ↓ DIFFUSION**

- Transport
  - 3 ways to get through membrane:
    - Channel- used for ions.
    - Pore – sweat gets through pore, NaCl and H_2O
    - Transport – for any other large molecule (HCO_3^-, glucose…)
  - Primary active = moving against the gradient
    - Will cost ATP ➔ ATPase is Always involved
    - Look for key word **"concentrate"**
    - Ex. "how does your stomach concentrate acid?" – with ATPase by pushing acid against its concentration gradient.
  - Secondary active
    - **Governed by a Na^+ GRADIENT**
      - Symport, cotransport = movement in the same direction
      - Antiport = opposite direction

- Phagocytosis
  - Endocytosis – moving in
    - Nutrients
  - Exocytosis – moving out
    - Waste products ➔ **lipofuscin** = oxidized fat and protein, brown pigments ➔ become age spots as cells become older and can't exocytose as well.
  - Pinocytosis – moving ions/fluids
    - We don't do it a lot because it is unregulated movement of electrolytes.
    - Only skin can be forced to "drink" water → Excema treatment

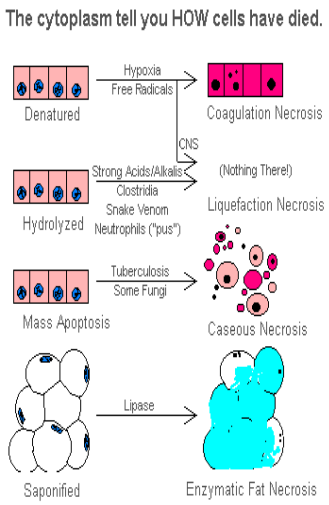
- Every Cell in the body has these channels:
  - Na/K pump → requires ATP
  - Na/Ca exhange → no ATP used
- Every cell membrane can depolerize
  - Depolarization = conduct electricity
    - All membranes are at –90mV
  - Except two at –70mV ➔ more likely to depolarize
    - Purkinje fibers
    - Neurons



- Ex. A child sticks his finger in the sockets, he is at risk for arrhythmias
  - Brain and heart will absorb most of electricity → HF, and seizures from neurons firing = causes of death.
  - He will need a monitored bed. But a complication of electrocution is hemorrhage due to destruction of endothelial membrane. → glycoprotein IIb/IIIa is fried

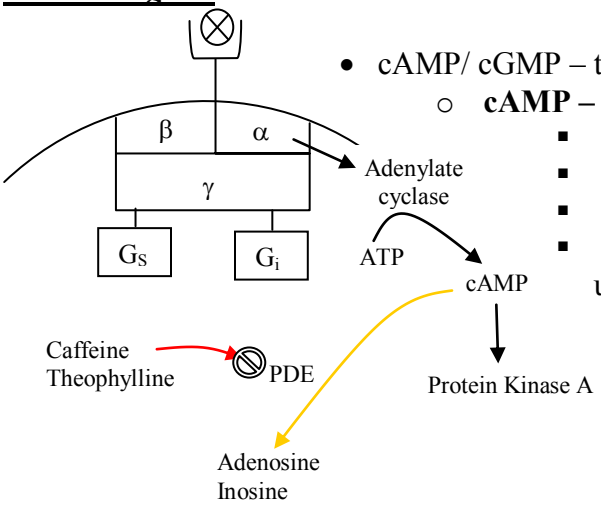
Signal Transduction: 2nd Messenger System

- Cell Death
  - Apoptosis
    - Programmed cell death → **cell membrane dies 1st**
  - Necrosis
    - Unprogrammed → nucleus dies 1st
      - Ischemia
      - Coagulative necrosis:
        - Due to ischemia
        - Accounts for 90% of necrotic cases.
        - Most common reason for cell death
        - Cell architecture is maintained
      - Purulent necrosis
        - Pus/bacterial
      - Granulomatous necrosis
        - T cells and macrophages
        - Non bacterial infections



- Fibrinous Necrosis
  - Fibrin deposition
  - Common causes:
    - Collagen vascular disease
    - Uremia (↑↑↑ BUN) → too much urea → stimulates fibrin deposition
    - TB → caseous necrosis
- Fat necrosis
  - Pancreas → d/t pancreatitis
  - Breast → d/t blunt trauma
    - Ex. battered woman
- Liquefactive necrosis
  - Abscess formation (day 7)
  - Brain most likely organ to form abscess
  - Architecture is not maintained
- Hemorrhagic necrosis
  - Bleeding into one area
  - Organs that have more than one blood supply or soft capsule
    - Lungs, GI, Kidney, Brain
  - Cell architecture is lost (brain turns to mush)

2nd Messengers:



- cAMP/ cGMP – they are opposites (90% of 2nd messengers)
  - **cAMP – sympathetic system → catabolic processes**
    - Ex. Tachycardia, diaphoresis,
    - Alpha subunit stimulates Adenylate cyclase
    - Causing ATP to convert to cAMP
    - cAMP activates protein kinase A = phosphorylates protein using ATP
      1. Catabolism = active when phosphorylated
      2. Anabolism = inactive when phosphorylated

- cAMP broken down by Phosphodiesterase, PDE to inosine, and adenosine
- PDE is inhibited by Caffeine and Theophylline (Asthma/Central Apnea in premature babies); both ↑ ADH (mild diuretics)

- **cGMP – parasympathetic system**
  - Exact opposite action of cAMP.
  - Sidenifil, Valdenafil
  - Don't mix with nitrate drugs
    - ↑↑↑ VD

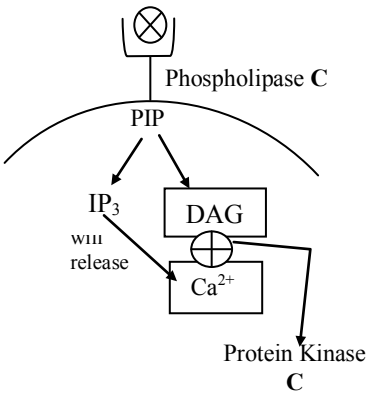
Microbiology Connection

- **ADP-ribosylates G_s = Turn the On, On**
  - Vibrio
  - ETEC
- **ADP-ribosylates G_i = Turns the Off, Off**
  - Bordetella pertussis
- **Ribosylation of EF_2**
  - Pseudomonas
  - Diptheria

ALL ↑ cAMP

All are Ca^{2+} dependent Reason why hypercalcaemia will trigger 3 2nd messenger systems causing ulcers, diarrhea, hypertension, bronchoconstriction, polyuria, polydipsia …

Hyperparathyroidism will cause hypercalcemia and all the above symptoms.



- **IP_3/DAG**
  - Used by
    - **Hypothalamic hormones**
    - Except CRH
  - All **smooth muscle contraction** by:
    - Hormone
    - Neurotransmitter
    - Example : GI
- **Ca^{2+}/Calmodulin (4:1 ratio)**
  - Used by:
    - Smooth muscle **contraction by <u>distention</u>**
    - Ex. Urine in the bladder, blood in blood vessels causing hypertension, fetus causing premature labor.
- **Direct Ca^{2+}**
  - used by Gastrin only

- Tyrosine Kinase
  - Used by insulin
  - Used by Growth Factor and stimulates growth
    - Ex. IL4, erythropoietin, thymosin, TSH, GH, somatomedian
- Nitric Oxide, NO ➔ activates guanylate cyclase (so look for cGMP if NO is not a choice)
  - ANP-anti-natriuretic peptide
  - Endotoxin
  - Nitrate drugs
  - Sildenafil (Viagra) → inhibits phosphodiesterase

<u>OPIATES</u>

- 3 actions:
  - Muscle Relaxation
  - Analgesia
  - CNS Depressant
- When deciding the Side Effects think about PHYSIO 1st !!!
  - Respiration depression
  - Weakness/SOB
  - Hypotension
  - Lightheadedness
- κ & mu receptors
  - κ → spinal cord = Analgesia
  - mu → MIND

Drugs:

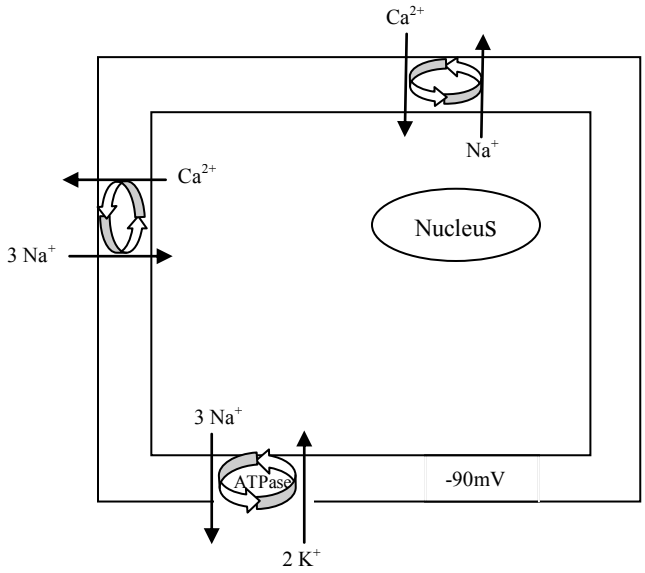
- Meperadine
  - GI pain
  - No sphincter of oddi spasms
  - Most commonly abused by physicians
- Morphine
  - Used of severe pain
  - Contraindicated use after head injury b/c of a possible ↑ ICP
- Heroine
  - Abused
  - Pinpoint pupils → overdose sign

- Methadone
    - ↑ t ½
    - Used instead for heroine withdrawal
    - Social intervention
- Fentanyl
    - Potent → used in anesthesia
    - If mixed with Respiradone = INOVAR
        - Neuroleptanesthesia
- Codiene
    - Anti-tussive
    - Dexomethorphan (DM) – OTC Tussive
- Loperamide
    - Diarrhea
- Diphenoxylide
    - Immodium
- Hydrocodiene
    - For moderate pain
- Pentazocin
    - Only opiate that antagonizes it's own receptor
    - Never use with an opiate addict
    - Use Ketorlac
- Antidote for opiate overdoses:
    - Naloxone (IV)
    - Naltrexone (oral)

Nitrates

- MOA
    - (+) cGMP → Vasodilation → relaxation of Smooth Muscle
    - Venodilation
    - SE:
        - N,V, Constipation (b/c not contracting and not moving)
- Nitroglycerin
    - Used for chest pain/angina
- Dinilatrate
    - BID → increased half-life
- Sodium nitroprusside
    - (+) HTN crisis → malignant HTN
    - Contains CN- → Do not use long term
- All of these can undergoe
    - TACHYPHYLAXIS → rapid tolerance
    - Down regulation of receptors
        - Take a night off (6-8 hr) in order to upregulate receptors again

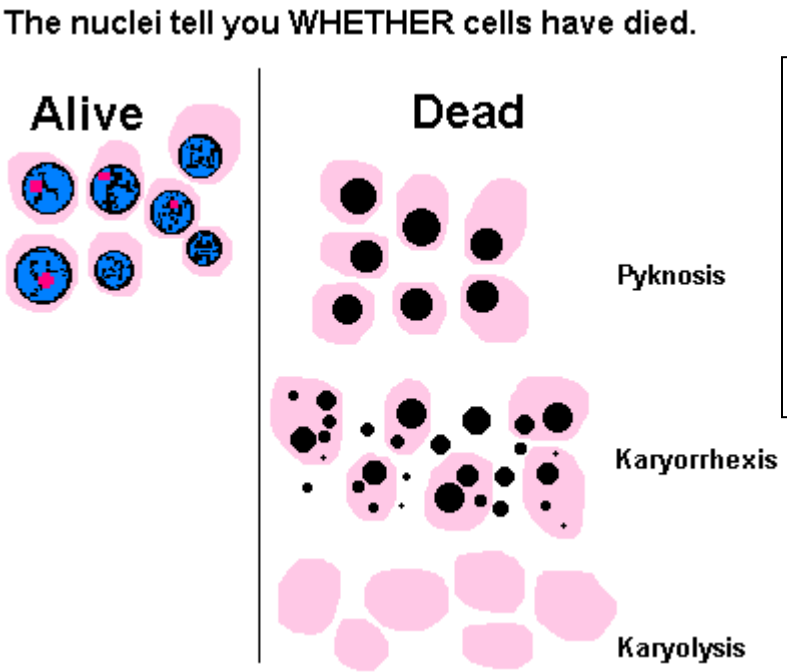
01-14-04



- RER
    - Protein Synthesis
    - Proteins that need to be packaged
        - Presequence → RER → Packaging (only collagen is fully packed here) → Golgi → add manose tag → Lysosome
        - What cell has a lot of plasma → Plasma Cells
        - What organ → Liver
- Modification
    - Post Translational
    - Where do you add…?
        - **Golgi** (Place of modification)
        - Damage = Modification is not performed all the time → Reversible Damage
- Smooth Endoplasmic Reticulum (SER)
    - Can undergo → Reversible Damage
        - Can die anyway due to exposure to TOXINS
    - Fxn:
        - Detoxify
        - Steroid Synthesis
    - 90% in Liver; 10% in Kidney
- Lysosome
    - IRREVERSIBLE DAMAGE
    - Contains acid hydrolases → acidic within lysosome
        - DNase
        - RNase
        - Both can destroy the nucleus!!!
- Mitochondria
    - IRREVERSIBLE DAMAGE
    - Produces all ATP
    - Na/K pumo will not work → cell death
    - Na/Ca gradient will also be lost
    - Mitochonrdria is inherited from the mother
        - Mitochondrial Disease
            - Leigh's
            - Leber → optic degeneration

- Nucleus
    - IRREVERSIBLE DEATH
    - Genetic material is stored here
    - If chromosome is messed with, so is the DNA = DEATH
        - Example: Monosomy 11 → DIE, DIE, DIE, DIE
- In cases of Monosomies, one must remember that "things are not growing at the proper rate"
    - **Chromosomal abnormalities will cause things to be "small"**

- **It takes 6 hours to save a cell before IRREVERSIBLE DAMAGE sets in**
    - Recall that CPK rises in…6 hours
- **In 20 minutes**
    - Will have irreversible death in the BRAIN
        - Once that is lost must resuscitate the BRAIN → not the heart
        - Therefore, the Brain is nost succeptible to ischemic damage
        - Posterior Frontal lobe → fartheset away from blood supply
        - Code Blue usually lasts 30 minutes
        - Always have a different pathological term when the brain is involved
            - Liver Failure → Hepatocellular Encephalopathy
    - If you fall into a freezing lake, the body freezes and the brain is no longer needed to "work"
        - Therefore, there is more time to save this patient

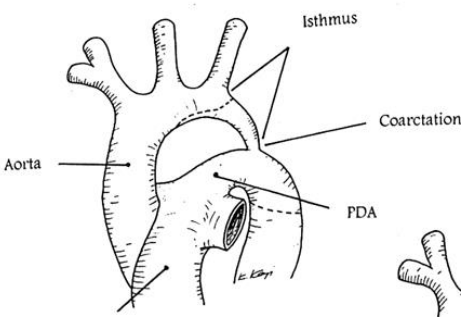


3 signs of Irreversible Cell Death

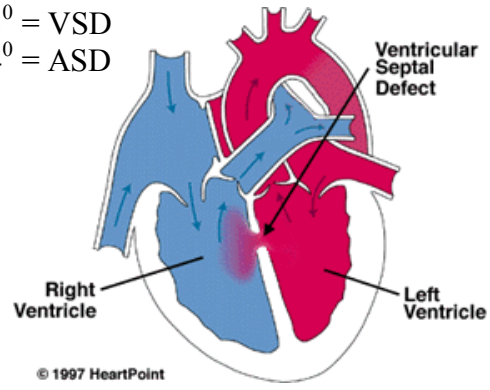
1. Pyknosis → cell turns into **BLEBS**
2. Karyorhexis → cell breaks into **chunks**
3. Karyolysis → cell **dissolves**

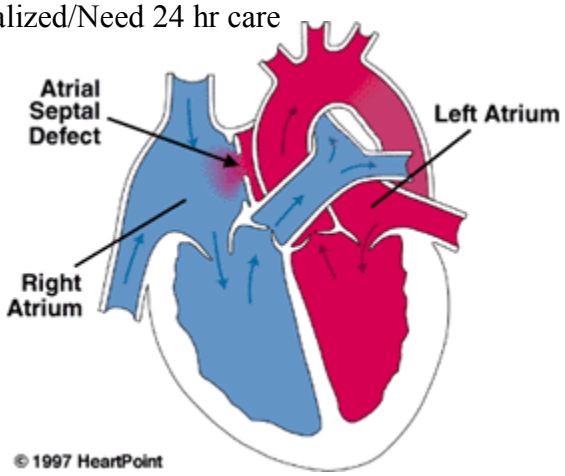
Damage to Mitochondria, Nucleus, and Lysosome

- Turner's Syndrome
  - XO
  - Short Stature
  - Shielded chest → waist did not grow
  - Webbed neck → it didn't grow
  - Cystic hygroma → no neck, brachial cysts did not grow
  - Gonadal Streaks
  - Coarctation of Aorta → aorta did not develop properly
    - Different pulses on PE
    - Rib notching d/t erosion of ribs



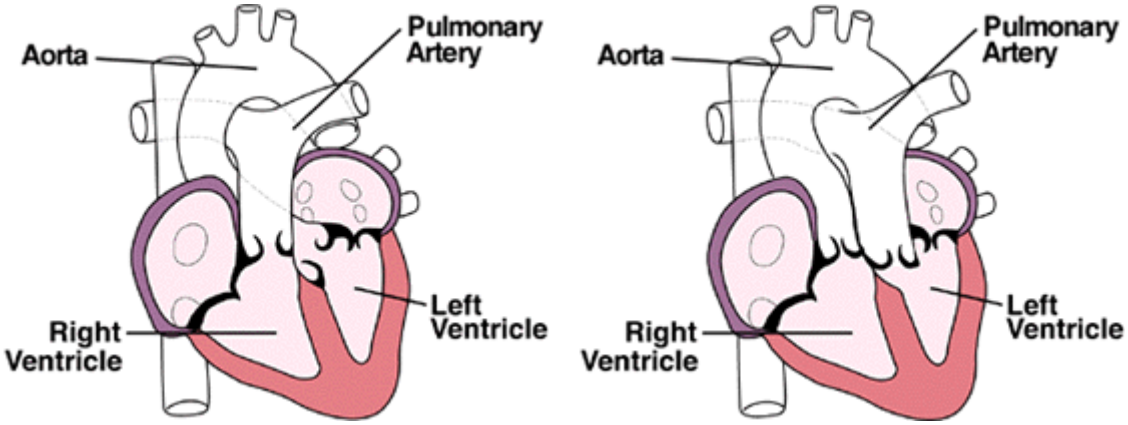
- Trisomy13
  - Patau's
    - 3 P's
      - Palate (high arched)
      - Polydactyly
      - "PEE" System (RENAL)
- Trisomy 18
  - Edward's
    - Rocker bottom feet/clenched fists
- Trisomy 21
  - Down's Syndrome
    - **MCC = Nondisjunction during Meiosis I (Anaphase = Apart)**
    - Mental Retardation
    - Robertsonian translocation
  - Mosaic = "Corky"
    - Not all cells are trisomy → only have some features of Down's
  - IQ Ranges
    - Average person = 85-100
    - Standard deviation of 15
      - Superior → 130 (2 standard deviations)
    - < 70 = Mild Retardation
    - < 50 = Moderate
    - < 40 = Severe → Able to do repetitive tasks
    - < 25 = Profound → have to be institutionalized/Need 24 hr care
  - 20-40% Have a congenital heart disease
    - Endocardial Cushion Defect
    - 1^0 = Common AV canal (no cushions!!!)
    - 2^0 = ASD + VSD
    - 3^0 = VSD
    - 4^0 = ASD



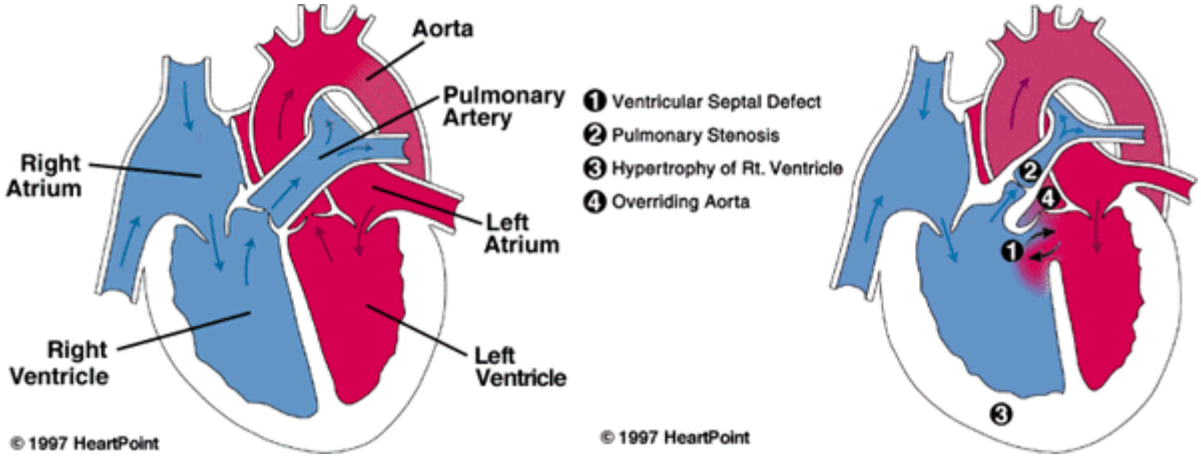


- Also can have Cyanotic Heart Diseases
  - Transposition of Great Vessels (Newborn)
  - Tetrology of Fallot

Transposition of Great Vessels



Tetrology of Fallot



- Down's cont.
  - Less incidence of Depression
  - Macroglossia
  - **↑ incidence of AML → Remember that the MC <u>in children is ALL</u>**
  - Simeain crease
  - Duodenal Atresia → double bubble sign/Hirschsprung's Disease
  - Mongolian eyes
  - **Widely spaced 1st and 2nd toes**
  - Wide sutures
  - Umbilical hernia
  - 40 % are hypothyroid
    - Check TSH levels
  - Early onset Alzheimers → 20 – 40's
    - MCC of dementia in America
      - Loss of cognitive skills, **Neurofibrillary tangles in hippocampus**
    - **AB Amyloid → tau pr- → Also found on Chr 21**
    - ↓ ACh in brain d/t lack of synthesizing enzyme

- ACh esterase inhibitors
  - Tacrine
  - Donezapil
    - Improves memory

Chemotherapy

- Kill CA to stop **rapidly dividing cells** → BEWARE
    - SKIN → MC Cancer in relation to cancer drugs
        - New cancer develops because of destruction of germ cells → Mutation
    - HAIR
    - CUTICLES
    - ENDOMETRIUM → no menses
    - GI → N,V,D
    - PCT
    - RESPIRATORY
    - BM
        - RBC → anemia
        - WBC → leukopenia
        - Platelets → thrombocytopenia
    - GERM CELLS → cells can't recover
    - SPERM
    - BLADDER
    - VASCULAR ENDOTHELIUM

- **Anti-metabolites → replaces a nucleotide with a … check the name!!!**
    - *ARA – **A***
    - *ARA – **C***
    - *5 – F**U***
        - **Inhibits thymidine synthase → can't make Thymidine**
        - Used for Colon CA (Duke Stage C = local invasion) in combinatinon with Levomisole (immune modulator) → 70 % 5 year survival
    - *6 – mercapto**purine*** → watch out for Gout (allopurinol)
    - *Thio**g**uanine*
    - *Azothio**prine***
        - Used for steroid resistance disease → 2nd line
            - Person may have had extensive treatment with Prednisone and experienced side effects → need to change treatment
    - ***Methotrexate***
        - Also, used for steroid resistance – 1st line
        - **Inhibits dihydrofolate reductase → Inhibition of THF synthesis**
            - S Phase specific
            - Recall that THF is a methyl donor → nucleotide synthesis
                - Can block all 5 nucleotide synthesis
            - **Leucovorin → Methotrexate rescue**
                - **Makes Folnic Acid**
- **Alkylating Agents → Binds dsDNA → can't replicate (used for Slow growing → won't present until > 40 years old)**
    - *Bleomycin*
        - **SE: Pulmonary Fibrosis**
    - *Busulfan*
        - SE: Pulmonary Fibrosis
    - *Adriamycin (doxyrubin)*
        - SE: Cardiac fibrosis
        - **Rescue → Desroxazine**
            - **Absorbs the free radicals that are produced**

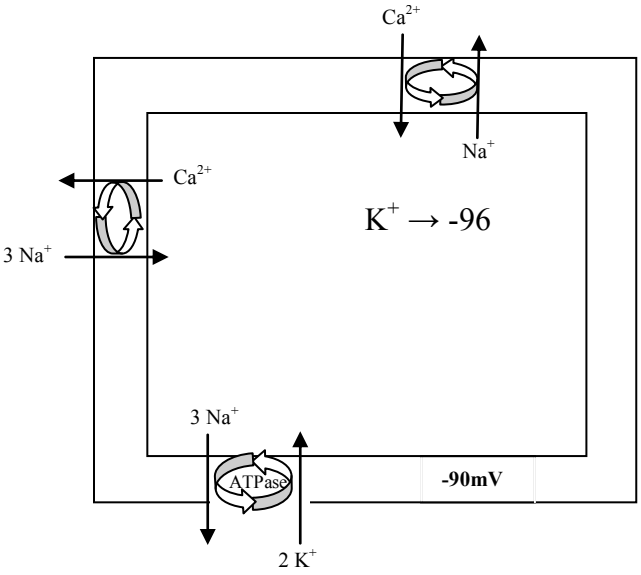
- *Cyclophosphamide*
  - SE: Hemorrhagic cystitis → can penetrate the Bladder and Skin
  - It is a pro-drug that is activated by the liver
  - Excreted by the kidney
  - **Rescue → Mesna (absorbs free radicals that are produced)**
- *Isophosphamide*
- *Cisplastin*
  - Causes RENAL FAILURE (PCT) → taken off the market
- *Mitocyin D*
  - Drugs for Lymphomas
    - Procarbazine
    - Dacarbazine
    - Mechlorethamine
- *Hydroxyurea*
  - **Inhibits ribonucleotide reductase** → dATP is the allosteric inhibitor
  - Stops DNA synthesis
  - **Can wipeout bone marrow and ↑ HbF**
    - Can be used in Sickle Cell Anemia
- *Chlorambucil*
  - MC used for Chronic Cancers (slow growing) → CLL, Multiple myeloma,

- **Microtubule Inhibitors (recall that microtubles can be found in MΦ, Sperm, Cilia, neurons)**
  - Vincristine
    - SE: Neuropathy
  - Vinblastine
    - SE: Blasts BM → aplastic anemia
  - Paclitaxel
    - M-Phase specific
    - **Will inhibit microtubles after they are made → METAPHASE ARREST**
    - Used in Intraductal Breast CA

- **Nutrient Depletors**
  - L – asparaginase
    - **Anaphylaxis** after chemotherapy

- **Immune Modulator**
  - Levamisole
    - Enhances natural killer cell's ability to kill cells

SEQUENCE OF EVENTS OF DYING CELL



Na^+ ➔ +65

Cl^- ➔ -90

HCO_3^-

Ca^{2+} ➔ +120

Mg^{2+} ➔ +120

- Nerst #
    - Membrane potential at where the concentration gradient and the electrical gradient balance each other out
    - NO NET MOVEMENT
- Driving Force
    - Electrical Membrane potential – Ion involved
    - Absolute number
    - Example
        - Na > K = ↑ driving force
        - (65) – (-90) =155
        - -96 – (-90) = - 6
- Conductance
    - Stimulates permeability
    - All channels are 100% regulated
    - At Rest
        - K^+ - most conductance b/c K+ channels are partially open
        - K sets the membrane potential
        - Na has the greatest driving force

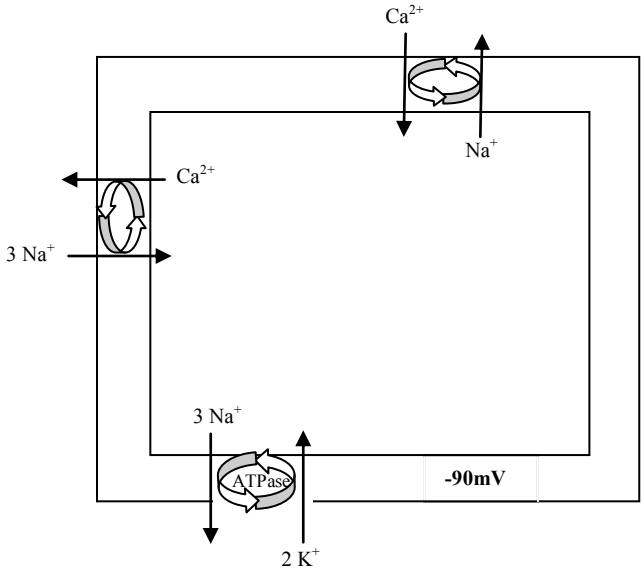
Ischemia:

- If the blood supply is cut off , no O_2 is being delivered to produce ATP (oxidative phosphorylation) → Shut down Na/K pump
  - K^+ will start to leak out and the cell becomes more and more negative
- Recall that all the ions have voltage regulated channels
  - Except K^+ ➔
    - 1/2 are voltage regulated
    - 1/2 are wide open – will allow ion movement outside the cell when at rest making the cell more negative
  - This in turn will cause → **ST depression on ECG, which indicates early ischemia and partial occlusion (70% occlusion)**
    - More specifically, sub-endocardial ischemia because this is the layer that is the farthest away from the blood supply → 1st to experience damage
- But Na will always enter the cell because of its concentration gradient
  - Will cause Na^+ to accumulate inside the cell, because the cell is trying compensate for the large negative charge it has inside and try to return Na/K pump activity
  - This leads to **ST wave elevation = total occlusion (90%) of the vessel**
- By Na rushing into the cell …
  - Cl^- will come in after it because opposite charges attract
  - H_2O will follow NaCl → Cellular swelling
    - Remember that the first change in every inflammatory response is swelling
  - Ventricular arrhythmias will occur first because Na is first stuck inside the cell depolarizing the cells. A cell that depolarize but can't contract → Vfib.
    - Venricle requires Extracellular calcium to flow across to trigger a contraction = Contractility
    - Depol but not contract → V fib.
  - Ca is flowing into the cell, SA node and AV node are more likely to fire → Afib and A flutter → conduction through atria will decrease, K is stuck inside cell → heart block
- After awhile Na^+ gradient will switch causing plasma Ca^{2+} to drop as it draws Ca^{2+} in 1:1 ratio back inside the cell
  - Smooth muscle is dependent on Ca (2nd messenger), so it will be more susceptible to
    - Ileus
    - Hypotension
  - That's why you don't worry about A fib after MI, there won't be any Ca^{2+} anyway to depolarize the Atrium → you worry about ventricular arrhythmias because there is nothing to regulate ventricle
- Ca^+ will get stuck inside the cell and decrease the threshold.
  - Ischemic cells are more likely to be depolarized and start firing
    - Arrhythmias after MI
    - Seizures after a stroke, along with cerebral edema
- Na^+ is necessary to depolarize every membrane in the body except the Atrium that uses Ca^{2+}.

- After initial inflammatory change, Na^+ still trapped in the cell and makes the cell more likely to depolarize → Arrythmias, Seizures, Diarrhea
- Angina – vasospasm will cut off blood supply completely causing ST wave elevation but by the time they come into the hospital their coronaries are not occluded anymore.
  - **Elevation ALWAYS comes AFTER depression.**
  - Rx: Give a vasodilator to open the radius of the vessel = ↑↑↑ Blood Flow
- **Ischemia is the most common reason for any spontaneous depolarization causing MI and such.**
- Calcifications occur normally with age and cancer as cells begin to die
  - Monckeberg = normal aging process, seen primarily in the aorta

- Why do we give oxygen right away in ER?
  - It relieves ischemia by ↑↑↑ Oxygen in the body to stimulate Na/K pumps again!!!

- INFLAMMATORY RESPONSE
  - **1st 24 hours = Swelling**
  - **In 24 hours → neutrophils → peak at Day 3**
  - **Day 4 → T-cells/MΦ → peakat Day 7**
  - **Day 7 → Fibroblasts → peak at Day 30**
    - **Takes 6 mos. to finish scarring**
  - **If Acute = look for neutrophils**
  - **If Chronic = look for fibrosis/sclerosis**



Na^+ ➔ +65

Cl^- ➔ -90

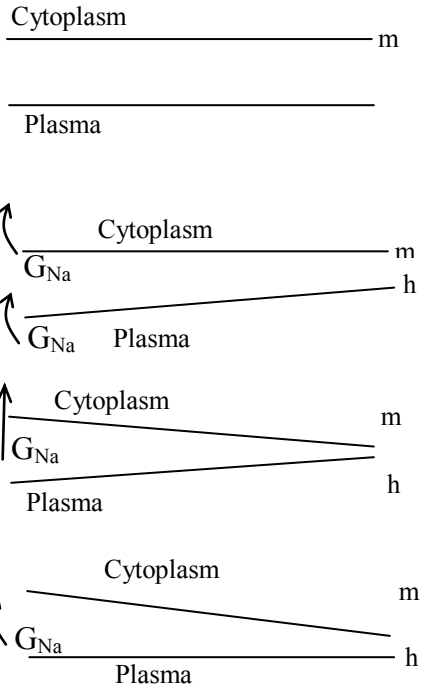
HCO_3^-

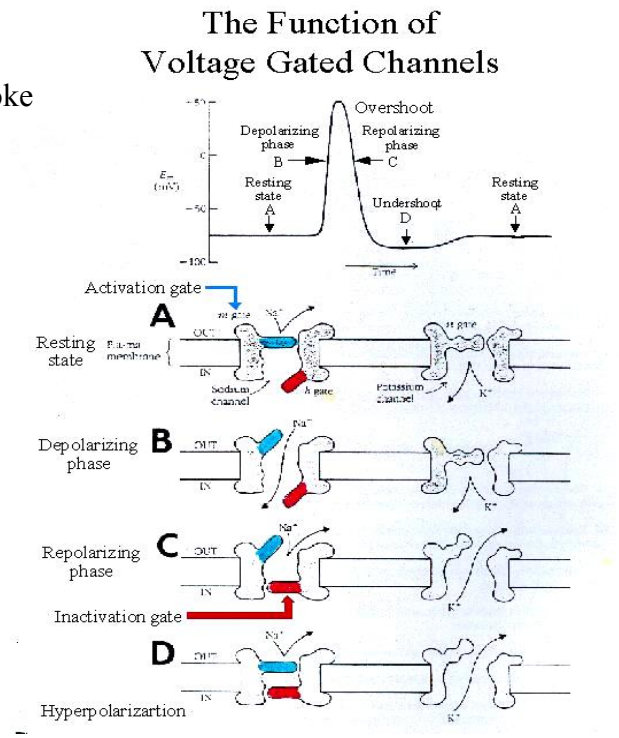
Ca^{2+} ➔ +120

Mg^{2+} ➔ +120

- Remember the E of any ion is the membrane potential at which the concentration and the electrical gradient are equal and opposite → No net movement
- Membrane potential is = –90mV
  - Na is always moving in (except Na/K pump)
  - K is always moving out to reach threshold
- I = current, movement of ions
  - Determines charge across membrane when electrolytes cross
- G = conductance, movement of ions across the membrane
  - G of K^+ occurs more than any other ion at rest. → only K moves at rest freely.
    - Ex. maintain resting potential
- Depolarization → Get Positive
- Repoleration → Get Negative
- Hyperpolarization → Below resting membrane potential

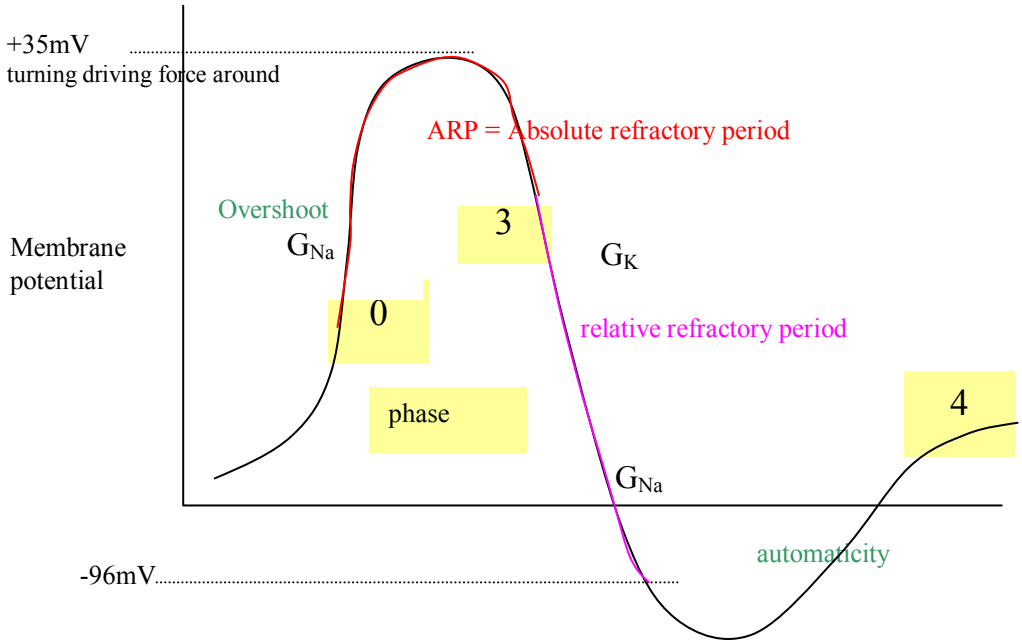
- Only h gate is open during slow upstroke





- Re-polarization = coming back from depolarization

- 2 Reasons why G_{Na} cannot reach E_{Na}
  - Na channels are timed so h gate will close (= inactivated gate), and m gate will remain open to allow whatever Na there is to drift in and another depolarization cannot take place ➔ Absolute refractory period
  - During the depolarization, when the membrane potential reaches +35 the driving force of G_K overcomes the driving force of Na → G_K drives repolatization
- Relative refractory period ➔ could get another action potential but it will be of lower amplitude, need a bigger stimulus
- Why can G_K reach E_k but Na can't → because K channels are "unregulated"
- Na/K pump is the most active when G_K reaches –96, gradients are reset, Na moved outside and K moved inside.
- But Na/K makes a membrane more negative
- So G_{Na} will make potential more positive by moving through Na/Ca exchange.
  - Net positive ➔ Na/Ca
  - Net negative ➔ Na/K pump
- Ca and Mg have the biggest driving force of all.



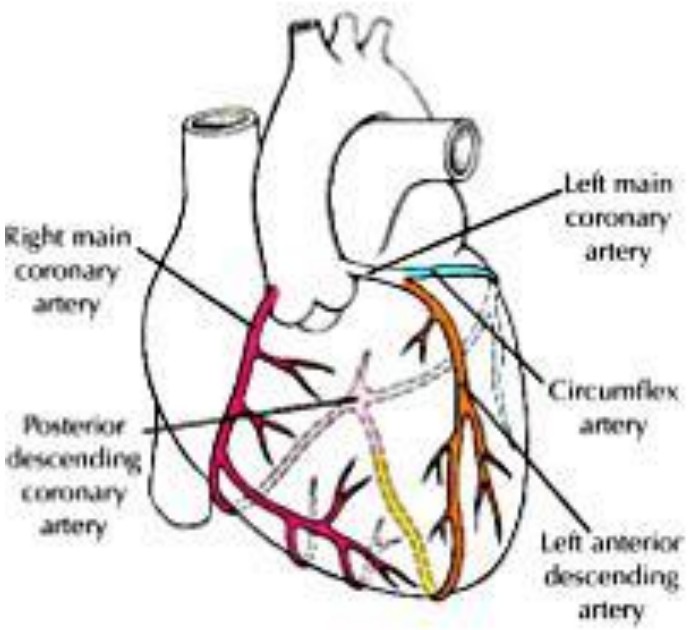
- The RRP needs a very strong stimulus to set off another AP
- Na/Ca exchange is most active during phase 4
- Na/K pump is most active at the end of phase 3 → Hyperpolarization → it is responsible for resetting the membrane potential at -90 mV

<u>Every membrane has phase 0, 3, and 4</u>

- Every membrane uses Na to depolarize except the atrium (uses Ca)
    - Depolarization → Phase 0
    - Resetting → Phase 4
    - Rate → Phase 4

BLOOD SUPPLY TO HEART

- Right coronary
    - Supplies the SA node
    - That is why the Right coronary artery is considered the Dominant Artery in 90% of people
    - Patient with Heart block with acute HF
        - Can be interpreted as 40% of the myocardium is lost and the ejection fraction is < 45%
        - HR WILL BE NORMAL!!!
- Left main coronary
    - Supplies the AV node
    - Breaks off into the Circumflex Artery
    - Also, the LAD comes off this artery to supply the majority of the Left Ventricle
    - Left Coronary Infarct
        - Causes HF, sudden death and Massive ventricular arrhythmia



HEART

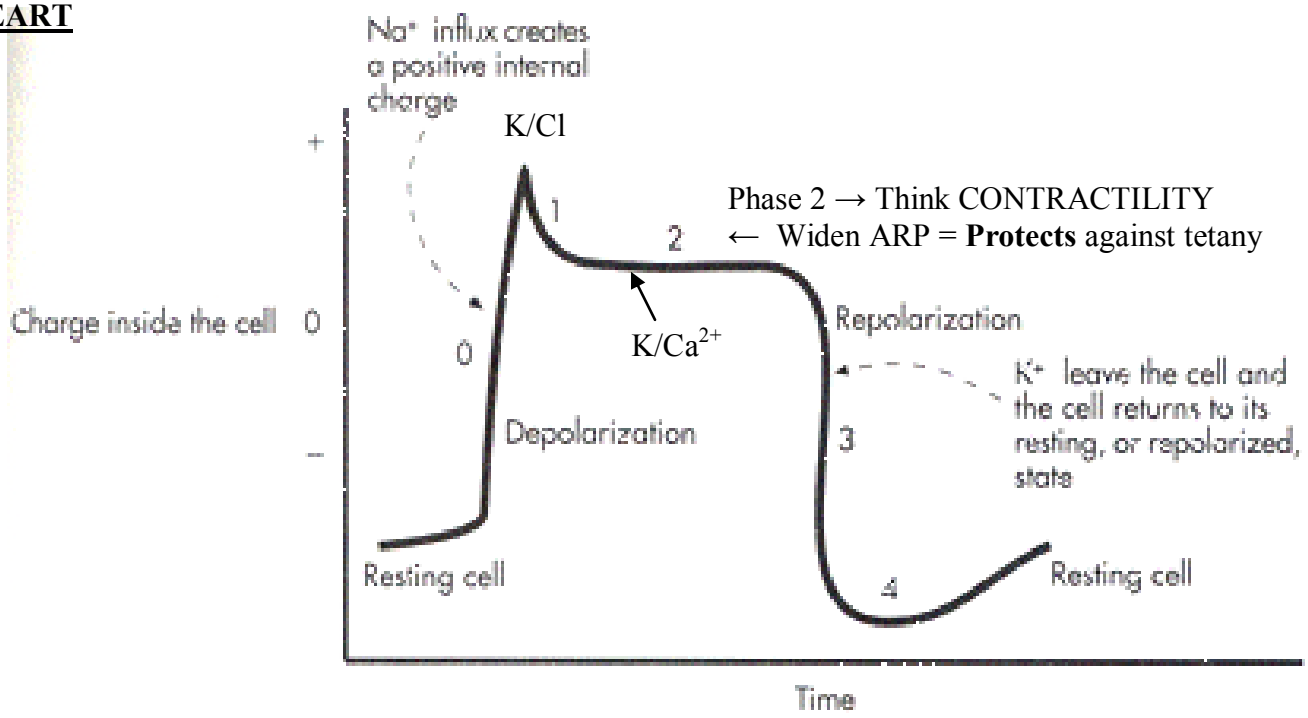
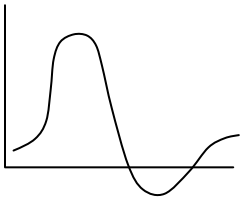


Fig. 5-4 Relative changes in electrical charge within a cardiac muscle cell during depolarization and repolarization.

- Ventricle
  - Fires faster, holds on to allow all the cells to **depolarize at the same time**.
  - Fastest depolarization because it has Purkinje fibers.
  - Phase 2 depends on how long to the heart needs to sustain a contraction.
  - Anterior wall has to hold on to the contraction the longest.
  - Wave of Depolarization

- SA node → Contains a β_1 receptor
  - Fastest Phase 4
  - has the most automaticity
  - resetting quickly → Able to control HR
  - no phase 2
  - High slope on phase 4
  - Slurred curve

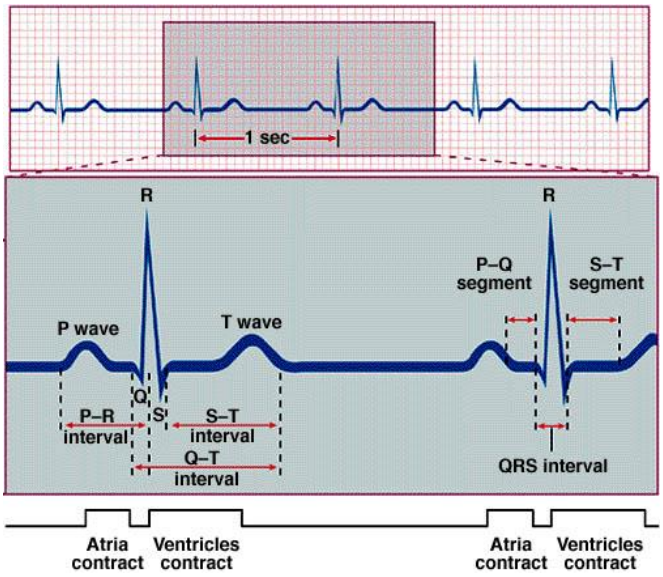


- AV node
  - holds on to signal➔ phase 2
    - Heart needs to "pause" to let the ventricle fill
  - less steep automaticity (phase 4),
  - Slowest conduction site of the heart because there are no Purkinje Fibers
    - Anterior wall to Posterior wall

In ACLS → Lidocaine attacks ischemic tissue only so it will shut up an ectopic focus

- SA Node Loss
  - AV node takes over
- AV Node Loss
  - Purkinje fibers in the ventricle are the next in line to take over
  - Ectopic site wants to take over so begins to beat wildly!!!
    - Need it to SHUT UP!!! → SHOCK IT
- Shocking will cause heart to **pause** so that SA node (without phase 2) will take over for rhythm
  - It is necessary that all the Na Channels be reset = Pause → short FLATLINE on EKG
- If persistent → Give Na^+ Channel Blocker

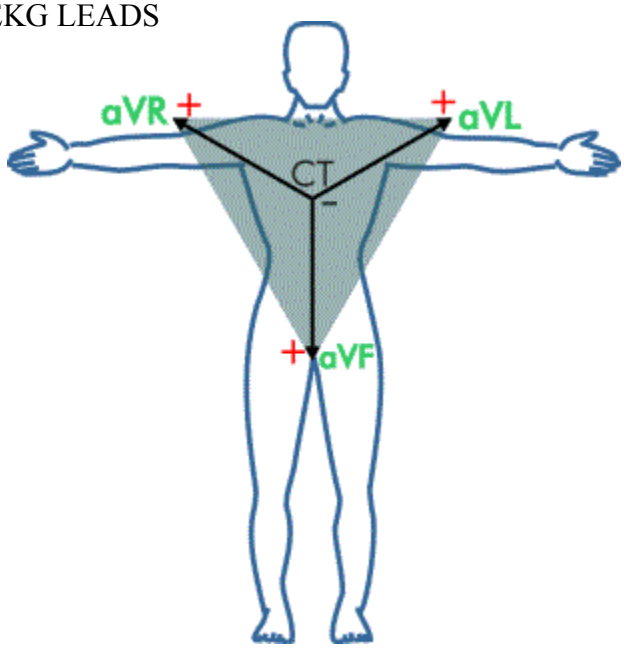
EKG

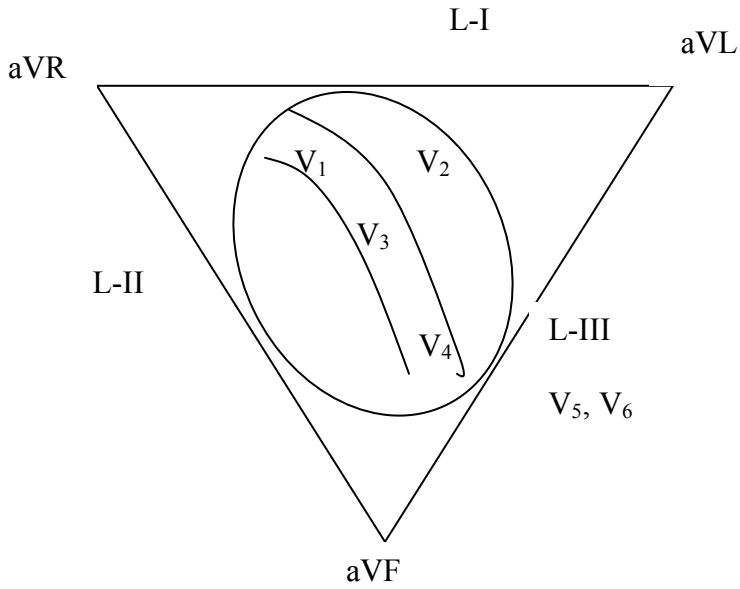


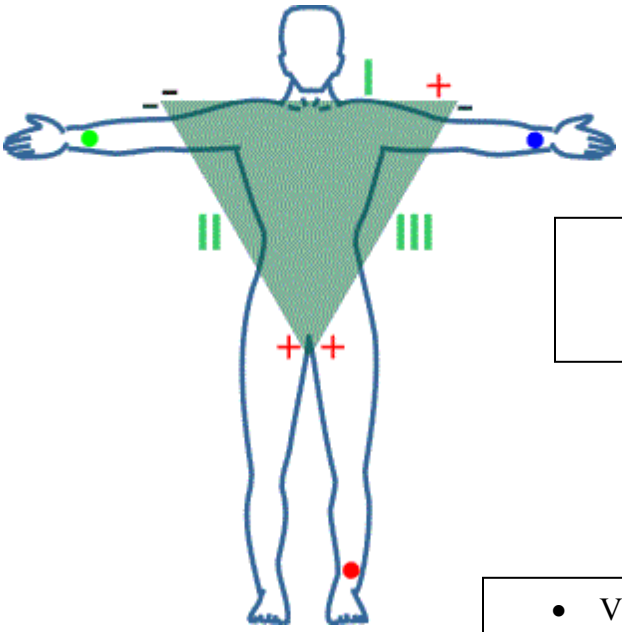
EKG Component	*Ion Going Into Cell*	*Phase*	*Represents*	*Misc.*
P Wave	**Ca^{2+}**	**Phase 0**	**Atrial Depolarization**	**↑ P wave d/t hypertrophy**
PR Segment	**Ca^{2+}**	**Phase 2**	**AV Node Plateau phase**	
PR Interval	**Ca^{2+}**	**Phase 2**	**Total SA-AV nodal conduction time (.2 s) Phase of contractility**	**If prolonged → Heart Block 1⁰ Block = ↑ Fixed PR interval If PR Interval > .2 sec = Having trouble at SA node or b/w SA and AV nodes 2⁰ Block = Mobitz Type I → *Wenckebach* – Progressive prolongation of PR Interval = there is mild ischemia in the AV node, therefore less likely to depolarize → QRS drops Mobitz Type II → PR Interval normal but drop QRS randomly → moderate ischemia at the AV node 3⁰ Block = AV Dissociation Atrium and vent. Not "communicating" → infracted AV node**
QRS Q → Septa R → Anterior Wall S → Posterior Wall	**Na^{+}**	**Phase 0**	**Ventricular Depolarization (.12 s) Height → Voltage Width → Duration**	
ST Segment	Ca^{2+}	Phase 2	Phase of contractility	
T wave	K^{+} going OUT	Phase 3	Ventricle Repolarization	Inverted T wave = still reversible
u wave	Na/Ca exchange	Phase 4		
QT Interval			Mechanical contraction of ventricles	QT interval ↑ d/t Ca^{2+} Channel Blkr → Exposure to arrhythmia b/c waiting to long in RRP

EKG LEADS

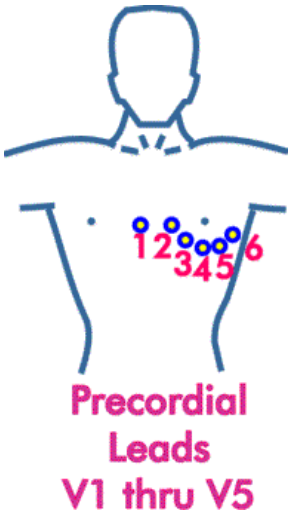
aVL → sees the Left side of the heart
aVR → sees the right side of the heart
aVF → sees inferior wall (apex)







- Lead I = Left heart
- Lead II = Right heart
- Lead III = Left inferior heart/Left Ventricle



- V1 → Right atrium = Septum
- V2 → Left atrium = Septum
- V3 → ½ way b/w V2 & V4
- V4 → Left lower sternal border
- V5 → mid clavicular line = Left Vent
- V6 → mid axillary line = Left Vent

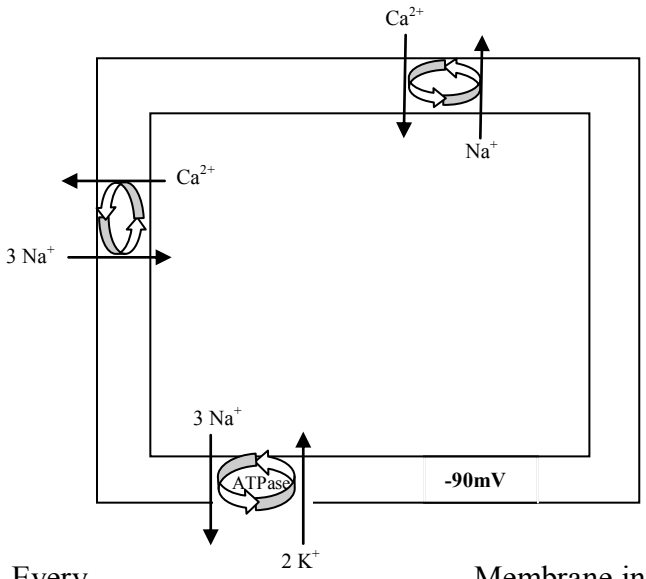
V1,V2, V3 ST Elevation
- 90% Stenosis
- LAD must be infracted because these leads see the anterior wall the best

ANTI - ARRHYTHMICS

Class I	**Na^+ Channel Blocker**
MOA	**↑ QRS Duration = ↑ AP Duration**
Class Ia	
Quinidine	**Strongest anti-cholinergic effects → "Hot, Dry Skin"** **Cinchonism =** tinnitus, hearing loss, autoimmune hemolytic anemia Quinidine will act as a hapten on RBC Related to Quinine (anti-malarial) → (+) hemolytic anemia with G6PD def. patients
Procainamide	**Ester anesthetic** **It's an AMIDE** → can produe SLE like rash Breakdown product is NAPA (in Class III)
Dyseppyramide	Weak anti-cholinergic effects
Class Ib	
Lidocaine	Affects ischemic tissue only → **DOC for Vent. Tachycardia**
Tocainide	Ester Breakdown product of Lidocaine Can cause **Pulmonary Fibrosis** Fat soluble → can redistribute quickly
Mixeletine	Can cause **Bad upset stomach**
Phenytoin	**Gingival hyperplasia** **Hirsutism** **Also blocks Folate**
Class Ic	
Flecanide	**Las resort** **It will block 90% of Na Channels**
Encainide	
Propofenone	

- **Procainamide, Phenytoin, and Quinidine can block both Na and Ca^{2+} = Good for Wolf Parkinson White**

CLASS II	β - Blockers
Facts	**↓ mortality after MI** **Prophylaxis against migraine headache, HTN, and angina**
<u>If 1st letter is…</u> **A – M (not L) = β_1 Blocker** **N – Z (including L) = Non-selective β blocker**	
Propranolol	**Longest acting**
Esmolol	**Shortest Acting**
Labetalol **Carvedilol**	**Also blocks α receptors**
Timolol	**β_2 Blocker in the IRIS = MIOSIS**
Sotalol	**Also blocks K^+ Channels**
Acebutalol **Atenolol** **Pindalol**	**Intrinsic sympathomemetic activity** **Good for asthmatics**
CLASS III	**K^+ Channel Blocker**
MOA:	**↑ QT interval**
NAPA	
Sotalol	
Bretylium	
Amiodarone	**Turns skin blue** **Made from Iodine → Initial hyperthyroid but long term hypothyroid** **↑ Phase 3** **Inhibits p450** **Pulmonary fibrosis** **Fat soluble**
CLASS IV	**Ca^{2+} Channerl Blocker**
MOA	**↑ ST segement, ↑ QT interval, affecrts AV nodal cells**
Verapamil **Diltiazem**	**Verapamil can induce Constipation** **Both are CARDIOselective**
Nefidipine, Nimopdipine, Amlodipine. **Fenlodipine**	**These are Vasoselective** **Nimodipine stops vasospasm after subarachnoid bleed**



Na^+

Cl^-

HCO_3^-

Ca^{2+}

Mg^{2+}

- Ca and Mg have a bigger driving force and will get to the channels first thereby delaying Na and delaying depolarization, everywhere but atria
- If there is too much Mg^{2+} & Ca^{2+} = Too much competition for Na^+ and thus, ↓ the chances for Na to enter the cell and allow the cell to depolarize!!!
- Getting into the night club

- Every Membrane in the body uses Na^+ to depolarize except the Atrium
  - The atrium uses Ca^{2+} to depolarize

<u>There are 4 specialized membranes</u>

1. **Brain and neurons:**
   - Uses Na to depolarize
   - Less likely to depolarize will cause
     - Lethargy, mental status changes, depression,
   - More likely to depolarize will cause
     - Psychosis, seizures, jitteriness
2. **Skeletal muscle**
   - Uses Na to depolarize
   - When less likely to depolarize will cause:
     - Weakness, SOB
   - When more likely to depolarize will cause:
     - Muscle spasms, tetany,
3. **Smooth muscle**
   - Uses Na to depolarize, but then uses Ca^{2+} as a 2^{nd} messenger.
   - When less likely to depolarize will cause:
     - Initial constipation
     - Later diarrhea because Ca will use 2^{nd} messenger system
4. **Cardiac**
   - Ventricle
     - Less likely to depolarize will cause:
       - Hypotension, ventricular bradycardia
     - More likely to depolarize will cause:
       - Tachycardia, HTN
   - Atrium
     - Uses Ca^{2+} to depolarize
     - When less likely to depolarize will cause:
       - Hypotension, CHF
     - When more likely to depolarize will cause:
       - Tachycardia, PVC, PSVT, **A-fib, A-flutter**

CALCIUM

- **↑ Ca^{2+} = You are LESS LIKELY to depolarize (except for the ATRIUM)**
  - GI has 2 phases
    - 1st block nerve conduction to GI = Constipation
    - 2nd it takes awhile but calcium will leak through the cell → IP_3/DAG = Diarrhea
- **↓ Ca^{2+} = You are MORE LIKELY to depolarize → b/c Na can now pass through!!!**
  - Tetany, Cramps, seizure, Ventricle Tachycardia
  - Remember that the atrium needs Calcium to depolarize therefore if ↓ Ca = Atrium slows down

Mg^{2+}

- **↑ Mg^{2+} = You are LESS LIKELY to depolarize b/c ↑↑↑ competition to Na^+**
- **↓ Mg^{2+} = You are MORE LIKELY to depolarize b/c ↓↓↓ competition to Na^+**
  - Atrium remains unaffected, but the Ventricle will be affected
    - V. Tach

Na^+

- **Hypernatremia → 2 Phases**
  - 1st – Na rushes in = More likely to depolarize
    - Seizures, HTN
  - 2nd - Na/K pump kicks in and ATPase will pump Na out making the cell **more negative, making it less likely to depolarize**
    - HEART FAILURE
- **Hyponatremia - Low Na → Na will flow out of the cell through Ca/Na channel, as Ca goes in, the inside** of the cell will become **MORE POSITIVE = making cell more likely to depolarize**
  - Na^+/Ca^{2+} pump is concentration driven and when it is switched it is in a 1:1 ratio.
  - Ex. exercise will cause excretion of NaCl and H_2O to be excreted, serum Na is low making muscles more likely to depolarize and cause muscle cramps, flatus, ↑BM.

K^+

- **Hypokalemia will make cells more negative making them less likely to depolarize slowing everything down**
  - K is more likely to leave the cardiac cell making phase 3 and T wave more likely
  - EKG
    - Narrow T-wave
    - T wave inversion
  - Stuck in repolarization → heart slows down
- **Hyperkalemia – more likely to depolarize**
  - **Cells are more positive during depolarization and are slow in coming out because the concentration gradient will oppose it → Forming a Peak T wave.**
  - Longer time to repolarize – widened T wave (cell is more positive)
  - Stuck in repolarization so less likely to depolarize again

- **Both hyper and hypo predispose to arrhythmias because while depo/repo take longer, an ectopic site will fire.**

- **Treatment for Hyperkalemia:**
  - Ca^{2+} gluconate → protect SA node from losing control
    - Insulin & glucose because Insulin will push excess K into surrounding cells & Glucose will prevent from hypoglycemia → Recall BRI**C**KLE
    - Encourage Kidney to excrete K with HCO_3
    - K-exolate will pull K out of GI tract → poop it out

- Digitalis, digitoxin, and ouabain work by blocking the Na/K pump
    - Ex. Any kind of rapid spontaneous depolarization (eye twitching, restless leg…) first need to rule out ischemia.
- Drugs:
    - Intracellular Ca controls contractility and that's what accumulates with these drugs.
    - Increased Na inside the ventricular cells will also improve contractility of the AV SA node.
    - ADR: cerebral edema, arrhythmias, Seizures, cramps, orthostatic hypotension, Afib and Aflutter
    - Ventricular arrhythmias will occur first because Na is first stuck inside the cell depolarizing the cells. A cell that depolarize but can't contract → Vfib.
    - Ca is flowing into the cell, SA node and AV node are more likely to fire → Afib and A flutter → conduction through atria will decrease, K is stuck inside cell → heart block
    - Dig toxicity
        - Low K
            - Dig binds to K arm of the Na/K pump
            - In a low K state, there are more pumps open for Dig to inhibit. → Competitive inhibition process
            - Patient on diuretics and digitoxin with arrhythmias need to give potassium
            - Digitalis antibodies are given IV when there is Digitoxin toxicity
            - Ouabain is experimental

Digitoxin	Digitalis
Oral only	Oral and IV
hepatically excreted	renally excreted
Inhibits Na/K pump → ↓ extracellular Na→ ↑intracellular Ca→ ↑ contractility	Stimulates vagus nerve centrally- will slow down AV to SA node conduction during Afib .

MUSCLE PHYSIOLOGY

- Any action is a depolarization
    - Preeclampsia
        - Placenta experiences ischemia → begins to act like the kidney by excreting RENIN → Vasoconstriction = ↓ Blood flow and ischemia to the rest of the body
    - Give Mg^{2+} sulfate
        - This will block Na^{+} entering the cell = No Depolarization
            - Bronchoconstriction = Depol.
            - Arrhythmia = Depol.
            - Seizure = Depol.

- All muscles use Na to depolarize
    - All muscles use INTRA-cellular Ca for contraction
    - Ventricle needs extra-cellular Ca to trigger off intracellular Ca release
    - Atrium requires extra cellular Ca for depolarization
    - Smooth muscle needs extra cellular Ca for 2nd messenger system

3 Types of Muscle:

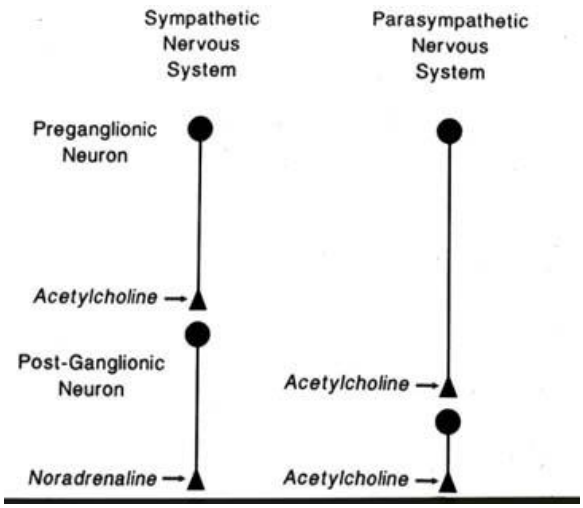
- Skeletal Muscle
    - Stirated
    - **No syncitial activity → One fiber can contract at anytime**
    - Electrochemical coupling → nerve fires = Muscle contraction (vice-versa)
- Cardiac muscles are related
    - Striated
    - **Complete syncitial action → Every muscle fiber contracts at the SAME TIME**
    - **Depends on extracellular Ca^{2+} to trigger intracellular Ca^{2+} release**
        - Ventricle can depolarize but not contract = Fibrillation
- **Both Cardiac and Skeletal muscle have sarcomeres.**
- Smooth muscle
    - Has no sarcomere → that's why it is smooth
    - **Depends on extracellular Ca^{2+} for it's 2nd messenger**
    - **Partial syncital activity → peristalsis**
- **ALL MUSCLES CONTRACT BECAUSE OF *INTRACELLULAR Ca^{2+}***

AUTONOMICS

- Cardiac and Smooth muscle have AUTONOMICS (action on their own)
    - Think about the ability to do transplantation
    - Bowel sounds

Neuron

- All Preganglionic fibers use ACh as a NT
- All Postganglionic Parasympathetic Fibers use ACh
- All Poseganglionic Sympathetic fibers use Norepinepherine >> DA >> 5HT



Receptor

- Parasympathetic → Muscarinic
    - Except skeletal muscle & ganglia → Nicotinic
- Sympathetic → Nicotinic
    - Except hair

Alpha$_2$ Adrenoceptor Activation

Receptor	Response
$\alpha_2 \rightarrow G_i \rightarrow$ ↑ adenylyl cyclase → ↓ cAMP	
prejunctional nerve terminals	↓ **transmitter release & NE synthesis AUTOREGULATION**
platelets	Aggregation
pancreas	↓ **insulin secretion (dominant) – inhibit β – cell release**

Examples:

- Clonidine = α_2 agonist
    - Has rebound HTN
    - Must ween off slowly d/t ↑ stored Norepinepherine
- α-methlydopa
    - DOC for Pregnancy b/c methyl group will not allow the drug to cross the Blood Brain Barrier

Alpha$_1$ Adrenoceptor Activation

Receptor	Response
$\alpha_1 \rightarrow G_q \rightarrow$ ↑ DAG & $IP_3 \rightarrow$ ↑ intracellular Ca^{2+}	
Eye **radial** (dilator) muscle	Contraction – mydriasis w/o cycloplegia
Arterioles (skin, viscera)	Contraction - ↑ PVR - ↑ afterload
Veins	Contraction - ↑ venous return - ↑ preload
Bladder trigone & sphincter	Contraction - urinary retention
Male sex organs	**Vas deferens contraction**
Liver	↑ glycogenolysis → ↑ sugar production!!!

- All sphincters have α_1 receptors
    - Therefore, inhibition of these receptors are good for BPH

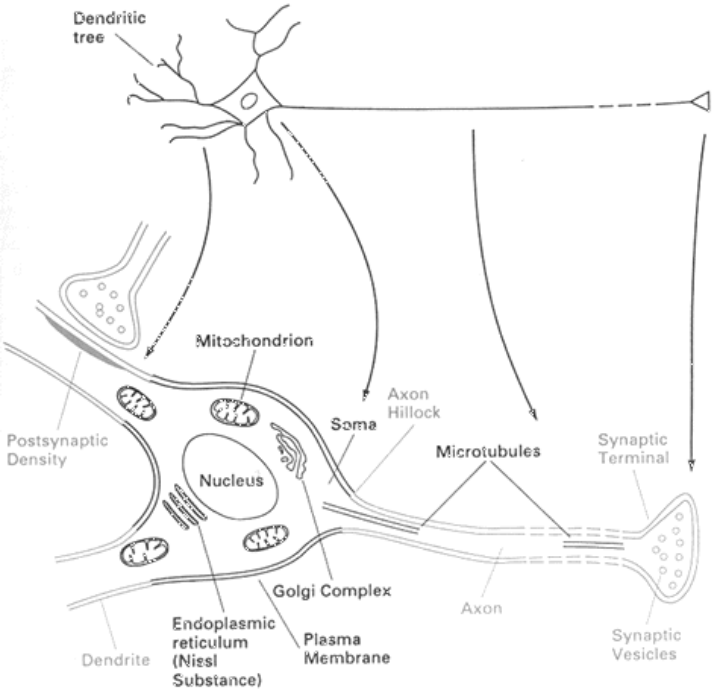
Beta$_1$ Adrenoceptor Activation

Receptor	Response
β_1(HEART) → G_s → ↑ adenylyl cyclase → ↑ cAMP	
SA node	↑ **HR (+ve chronotropy)**
AV node	↑ conduction velocity (+ve dromotropy)
Muscle	↑ force of contraction (+ve inotropy), ↑ conduction velocity ↑ CO & oxygen consumption d/t ↑ of oxygen demand
His-Purkinje	↑ **automaticity & conduction velocity = ↑ activity**
kidney (JGA)	↑ **renin release**
Pancreas	**α cells of pancease → ↑ Glucagon**

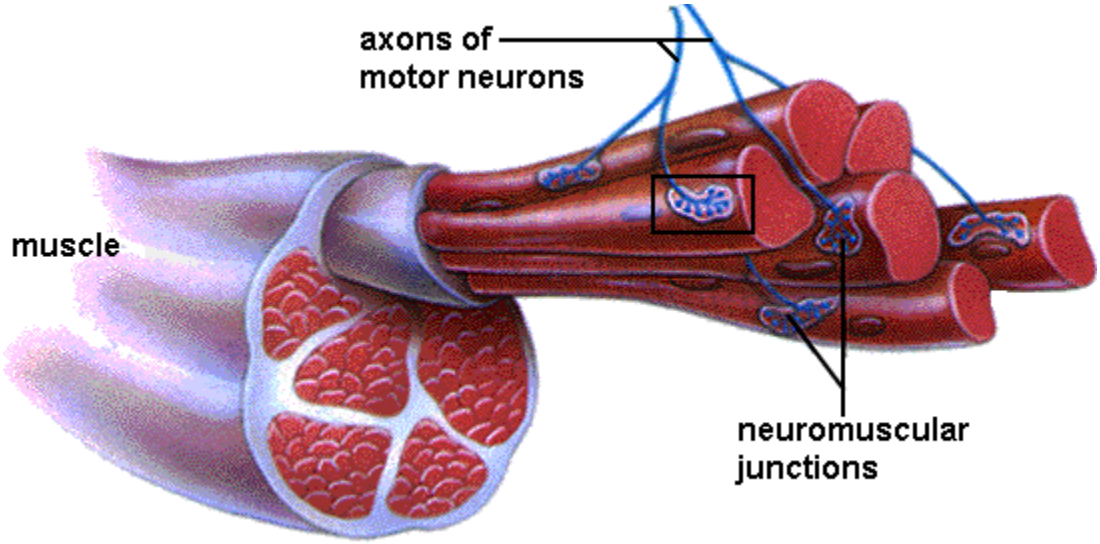
Beta$_2$ Adrenoceptor Activation

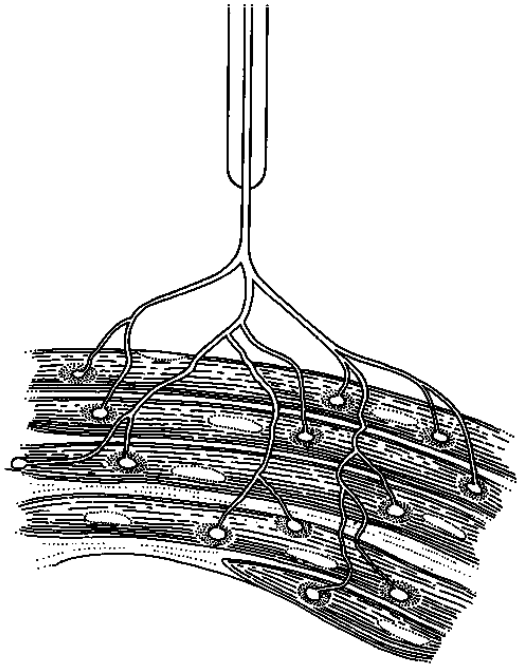
Receptor	Response
β_2 (not innervated)	
blood vessels	vasodilation - ↓ PVR - ↓ diastolic pressure, ↓ afterload
uterus	Relaxation → NO CONTRACTIONS want to SLOW ↓
bronchioles	dilation
skeletal muscle	↑ glycogenolysis – contractility (tremor)
liver	↑ glycogenolysis
Pancreas	↑ insulin secretion (islet cells)

- Choline
  - Choline acetyl transferase
  - Tyrosine hydroxylase
  - Tryptophan hydroxylase
    - These enzymes make NT
    - **They are made in the soma**
- Transport
  - **Anterograde**
    - **Use kinesin**
  - **Retrograde**
    - **Use Actin**

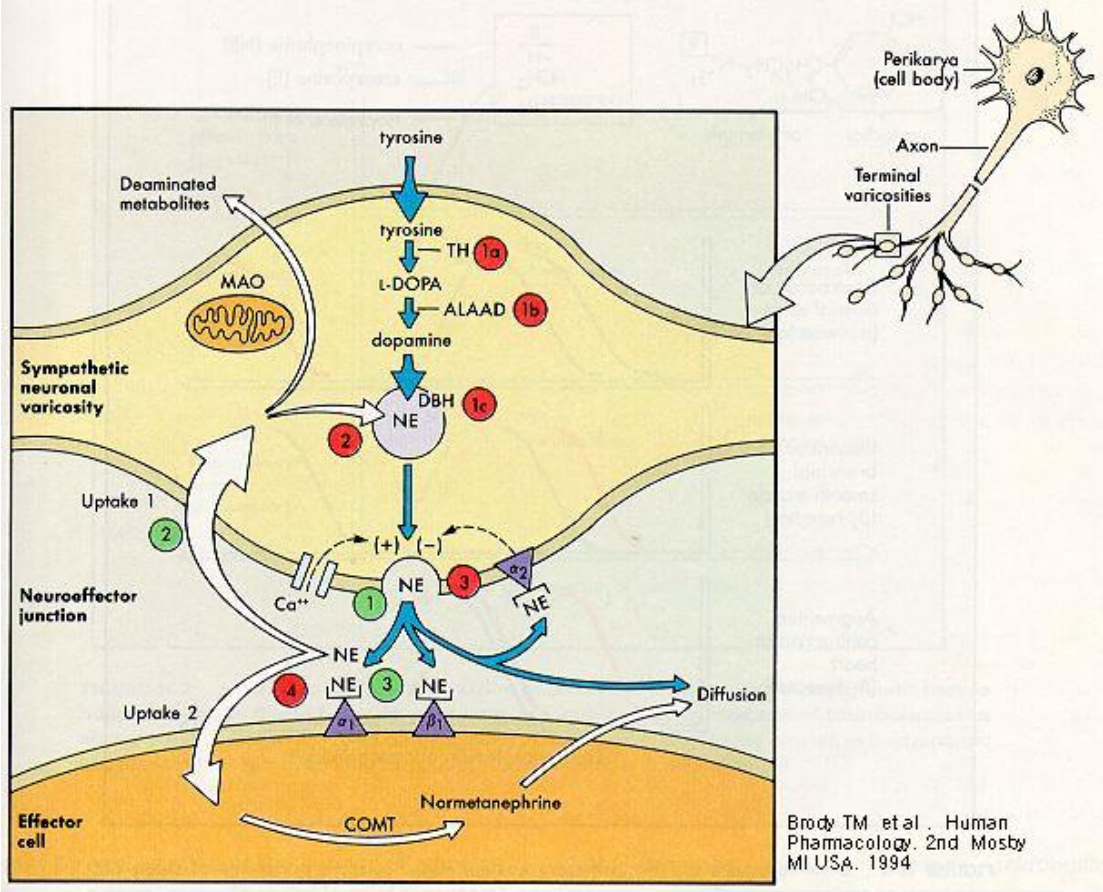


NEUROMUSCULAR JUNCTION

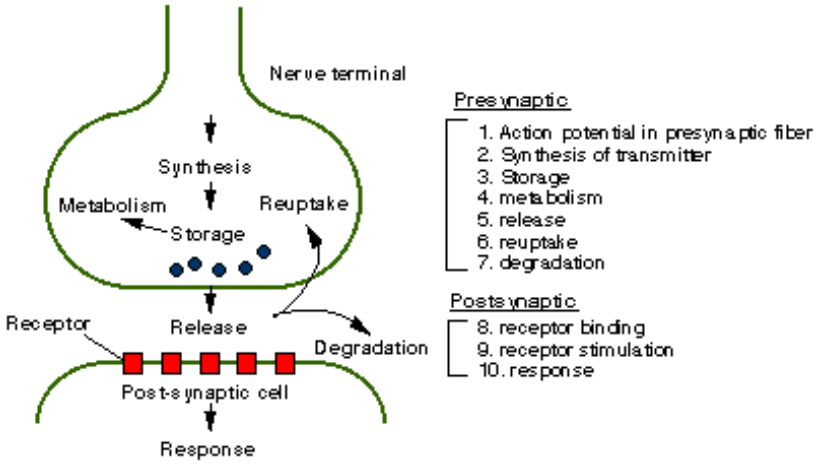


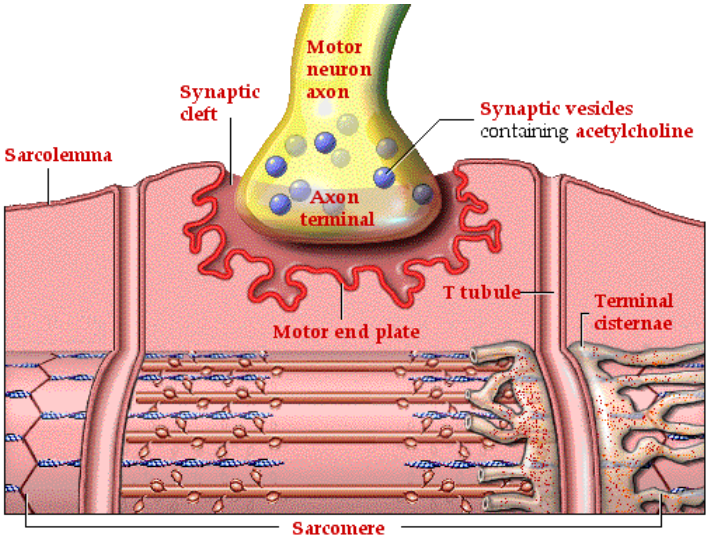


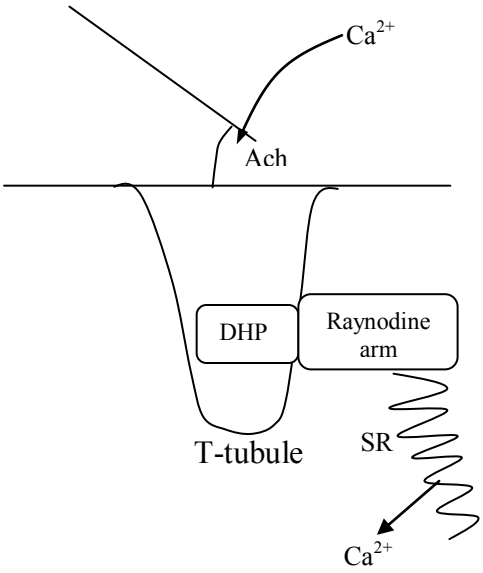
- At the synaptic terminal needs Ca influx for NT to be released.into cleft
- **If blocked = Neuropathy**
    - **Ca channel blockers**
        - **Verapamil**
            - **Most potent; constipation**
        - **Diltiazam**
            - **Good for atrial arrhythmia**
        - **Nimodipine**
            - **Stops vasospasm after subarachnoid hemorrhage**
        - Nifedipine
        - Nicaradapine
        - Amalodopine
        - Fenlodipine
    - EDTA
    - Penicillamine
    - Gentamycin and aminoglycosides
    - Botulinum toxin inhibits presynaptic release of ACH.
        - All block Ca presynaptically and cause neuropathy.
    - Black widow spider venom causes increased release of ACH leading to tetany and death.



- **AChesterase**
  - **Breaksdown ACh**
- **MAO**
  - **Presynaptic**
  - **Breaksdown Catecholamines**
- **COMT**
  - **Postsynaptic**
  - **Breaksdown Catecholamines**
- **Reserpine**
  - **Impairs vesicles**
  - **Can't store Norepi**
- **Guanethidine**
  - **Displaces Norepi out of the vesicle**
  - **MAO will break this down**
  - **SE: Retrograde Ejaculation**

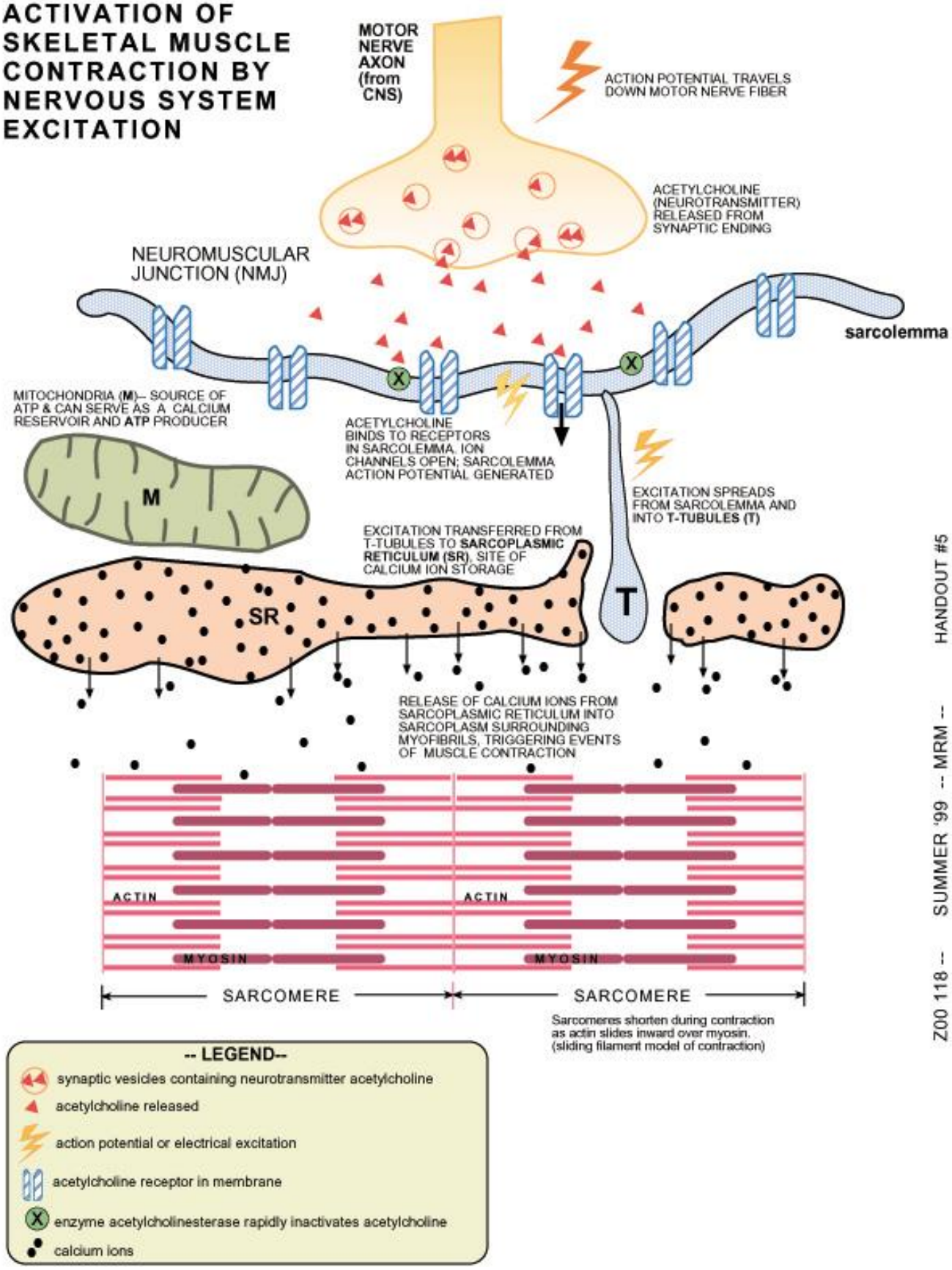






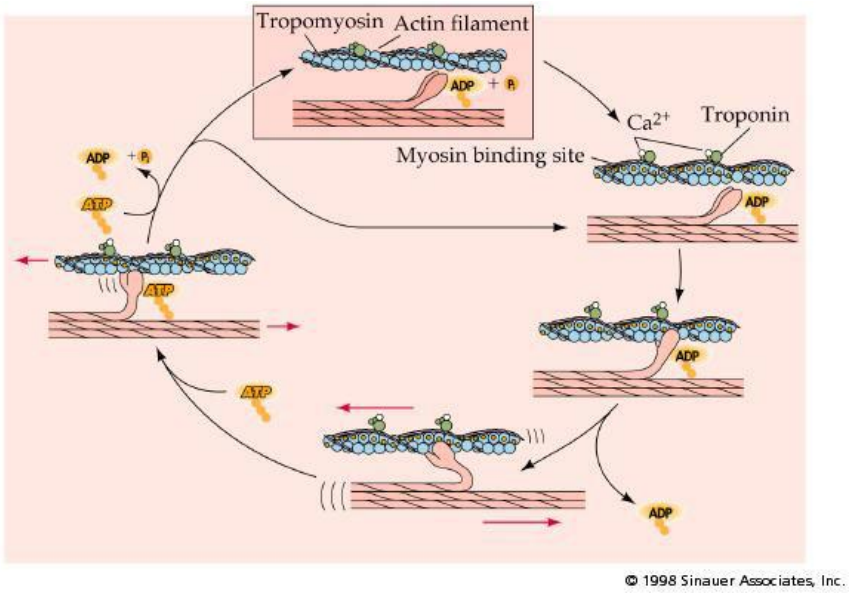
- ACh gets released and causes depolarization over entire membrane of the muscle.
- Wave of Depolarization travels down t-tubule
- Stimulates DHP = DiHydro Pterydine → moves the Raynodine arm
- Raynodine arm gets stimulated → Open SR and release intracellular Ca^{2+}
- In skeletal muscle electrochemically coupled → tied to the nerve
    - If you lose the nerve the muscle that goes with it will atrophy.
- Cardiac muscle has electrochemical coupling
    - But also has autonomy → will beat automatically
    - Also has extracellular Ca^{2+} running down T-tubule in addition to the wave of depolarization
        - Nerve disease will cause skeletal muscle atrophy but Heart won't be affected
- **All neuromuscular disease patients will die of respiratory failure because diaphragm will stop working**

ACTIVATION OF SKELETAL MUSCLE CONTRACTION BY NERVOUS SYSTEM EXCITATION



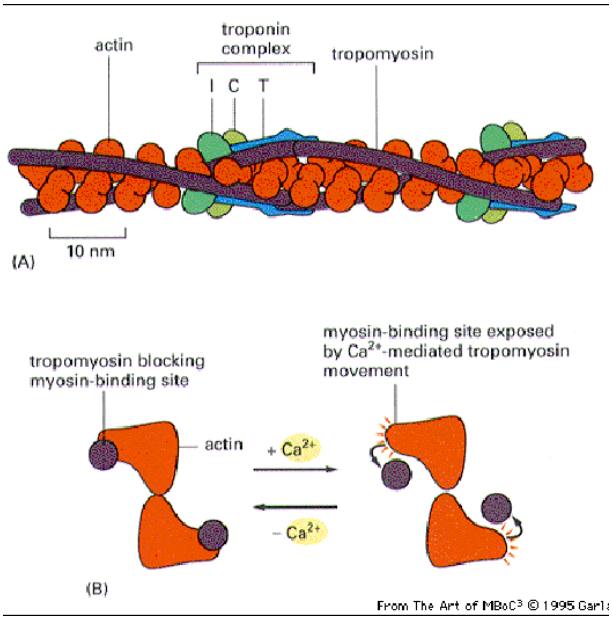
Z00 118 -- SUMMER '99 -- MRM -- HANDOUT #5

Muscle Contraction



Sequence of Events for Muscle contraction:

1. Ca binds Troponin-C
2. Troponin C releases Troponin-I (arrives 2 hrs. peaks 2 days, gone by 7 days)
3. Troponin I releases Tropomyosin
4. Tropomyosin uncovers Actin binding sites
5. Myosin heads bind Actin
6. **Contraction – No energy required**
7. Myosin heads release ADP (from previous cycle)
8. Myosin heads bind new ATP
9. Myosin heads hydrolyze ATP → ADP +Pi (releasing 7300 cal)
10. **Release occurs → Requires ATP**
11. Myosin returns to start position
12. Tropomyosin covers actin
13. Troponin I covers tropomyosin
14. Troponin C covers Troponin I
15. Ca^{2+} -ATPase pumps Ca^{2+} into the SR
16. Protein called phospholambin inhibits Ca-ATPase when its done

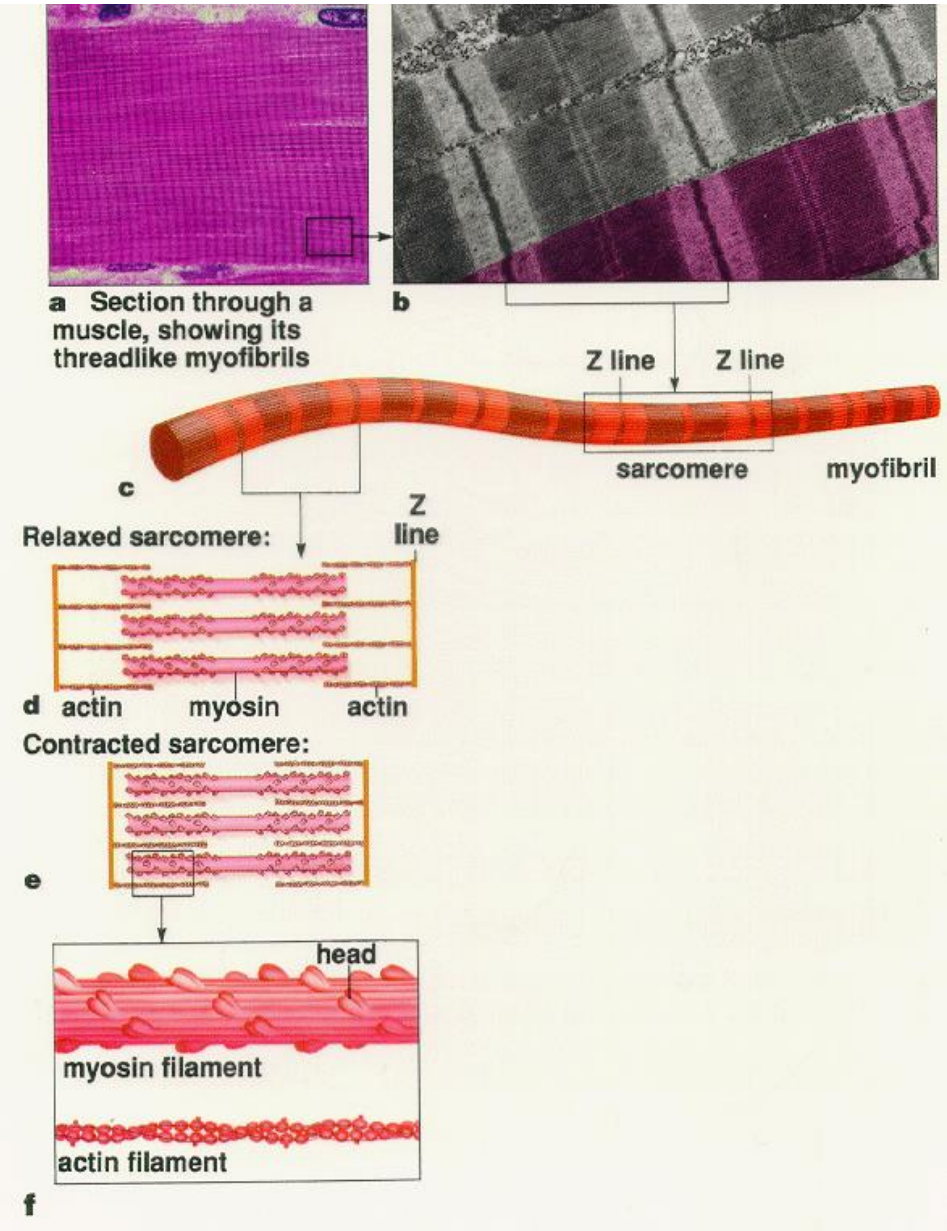


- Get tight muscle contraction without ATP → Cramp = "Rub it out" → inflaming the skin will bring more blood = ↑ O_2 = ↑ ATP → Relaxation
- If don't have ATP, muscle is stuck unreleased, in full contraction.
  - Swimming after a meal → drown b/c most of the energy is digesting food
    - Can't scream either!!!
  - Death → rigor mortis
- Any Ca^{2+} left over in the cytoplasm (by Ca^{2+}-ATPase) will be excreted by Na^{+}/Ca^{2+} exchange.
  - Without Phospholambin, Ca^{2+}-ATPase activity will increase and pump intracellular Ca^{2+} back into SR
  - Cytoplasmic Ca^{2+} will decrease → Muscle weakness
  - There won't be enough Ca^{2+} to cause contraction → Will die of respiratory failure

Smooth Muscle

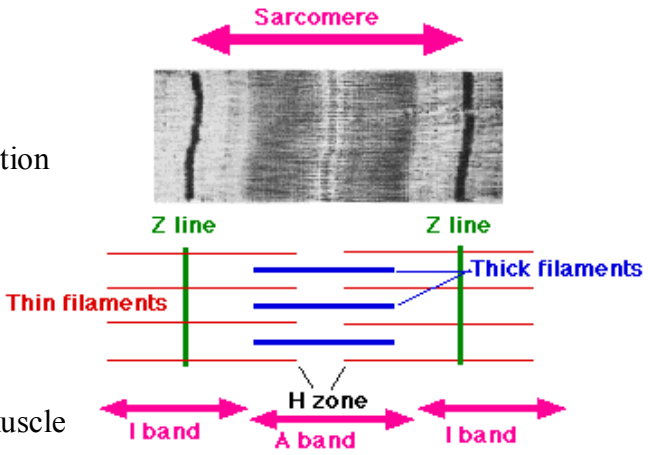
- **Has No troponin**
  - Actin and Myosin are always bound ➔ Latching
    - After you eat → release Muscles and burn more ATP in the GI
  - Sounds created by latching called Boborygmi (gut sounds)
- **Has no ATPase activity**
  - uses MLCK = myosin light chain kinase
  - And MLCP = myosin light chain phosphatase
- Employs Basal bodies
  - They are more mobile
  - Moves Glucose from one place to another

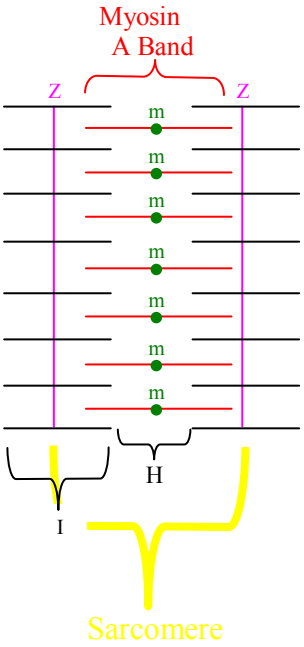
Skeletal Muscle



Functions of the Sarcomere:

- Sarcomere = from 1 Z line to the other Z line.
  - **Distance will decrease during contraction**
- Light chain = actin
- Heavy chain = myosin
- A band = length of myosin
  - Contains both Myosin and actin
  - No change in length during contraction
- I band =
  - Has only actin in it
  - No overlap → will shrink during muscle contraction
- H band =
  - Has only myosin
  - No overlap → will shrink during muscle contraction
- T-tubules of:
  - **Cardiac muscle – is found in the z –line**
  - **Skeletal muscle – is found in AI junction**
- m-line:
  - Where you will find CK-MB

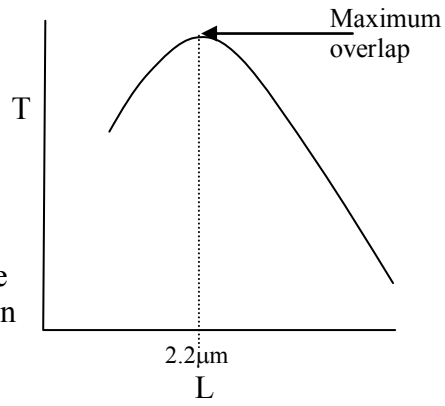




Actions of Sarcomere during contraction

- **Sarcomeres get smaller**
- **H & I bands get smaller (HI)**
- **Distance b/w Z lines gets smaller**
- **A band no change**
- **Force and Tension ↑ as length ↓**

- Pre load = tension on a muscle before work is done
  - As increase preload, you increase the time it takes for cross bridging.
  - Too much stress on a muscle will cause the tension to release

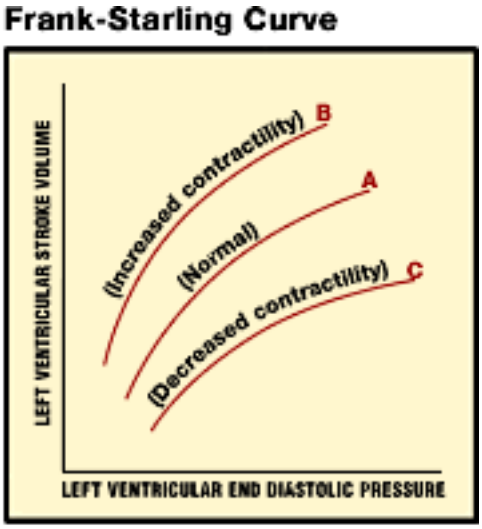


- Golgi Tendon Organ
  - Senses maximum overlap → max tension in muscle
  - It holds for 1 sec and GTO fires and releases tension
  - Protects from destruction
    - Think about a weight lifter

- Recruitment of more motor units
  - 1 motor unit = 1 nerve and all the muscle fibers it innervates
    - 1 nerve innervates several muscle fibers
    - 1 muscle fiber is stimulated by only one nerve
  - Muscle cells hypertrophy by increasing the size of the cell to create more cross bridges to handle increased pre-load.
    - Preload = tension put on a muscle before any distance moved
  - ↑ Stress = ↑ Hypertrophy = ↑ Cross bridges
    - **Muscles will anticipate stress = Hypertrophy**
    - That's why weight lifting gets easier with time as muscles hypertrophy due to increased pre-load.

Frank - Sterling Curve

- As EDV rises (heart dilates) get more CO up to a certain point until Heart stops completely ➔ sudden death
  - ↑ Amt. of Bloof flow = ↓ contractility = ↑ ability to hold more blood
  - It's the same principle as preload and muscle tension
    - Once you reach a certain point the tension releases and lose contractility
- Treatment for CHF
  - Diuretic → ↑ contractility
  - ACE inhibitors
    - Vasodilatation and vasodilatation = balanced dilatation and ↓ preload and afterload
  - Digitalis



Frank-Starling Curve
Hurst et. al., Hurst's The Heart, 1998

MYOPATHY

- Myositis = **one muscle hurts**, caused by
  - Drugs: **"RIPS" Muscle**
    - **R**ifampin
    - **I**NH
    - **P**rednisone
    - **S**tatins

Disease/Infection that can cause MYOSITIS:
- **Hypothyroidism**
- **Cushing's**
- **Trichinella spirallis**

- **Poly**myositis = **more than one muscle hurting**
  - Elevated enzymes:
    - CK
    - LDH
  - Inflammatory cells found:
    - T-cell
    - macrophages
- **Dermatomyositis = myositis + rash**
  - **Heliotropic rash**
    - violatious rash on eye lids
    - Look for Colon CA in the patient → must rule out INTERNAL MALIGNANCY

- **Fibrositis = inflammation in tendon <u>insertions</u>**
  - **pain only with movement**

- **Fibromyalgia = tendon insertions and muscles hurt all the time**
  - multiple tender trigger points
  - Amytriptyline is the treatment → because of ↑↑↑ incidence of depression

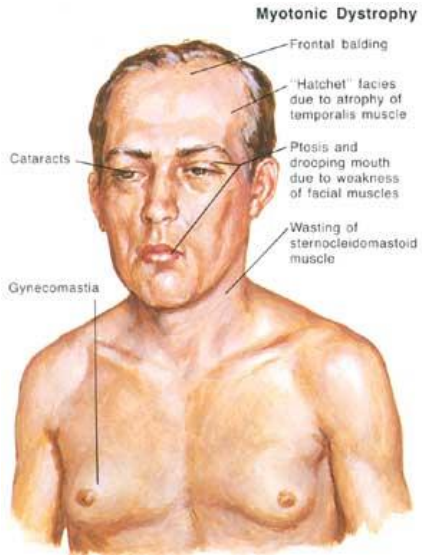
- **Polymyalgia rheumatica = when the shoulder girdle is the weakest**
  - **Pain in the shoulder girdle (actions of waving, combing hair)**
  - Tender trigger points
  - very high incidence of **Temporal Arteritis (Giant cell)**
    - temporal headache
    - very high ESR
    - **Rule of 60's**
      - age>**60 years old**
      - ESR >**60 sed rate**
      - Need more than **60mg of Prednisone** to treat it.
    - Diagnose with temporal artery biopsy (MUST DO)
    - **Complications – blindness due to involvement of ophthalmic artery.**

Duchene/Becker MD

- **X-linked recessive → Nonsense/frameshift mutation (trinucleotide repeat)**
  - **Dystrophin gene**
  - ***Recall inheritance is that the maternal father and grandfather also had disease***
- **Dystrophin protein**
- **Gower sign – patient uses hands to walk up their own legs**
- **They have pseudohypertrophy of the calf due to fat deposition = Cankle's**
  - **Also seen in Gaucher's**
- **Waddling gait- due to transferring torso on the hips**
- Onset of Duchene before age 5.
  - Ex. 6 year old with Sx for 3 yrs.
  - Frame shift, nonsense mutation
- **Becker's has symptoms. after age 5.**
  - **missense mutation → late onset**

Myotonic Dystrophy

- **Face looks like a birds beak**
  - Facial muscles are worn
- Increased muscle tone
  - Can't let go of hand when shaking it.



Guilliam Barre

- **Ascending paralysis (starts in feet)**
- 2 wks after a URI → Viral prodrome
- Inflammation around peripheral nerves
- polyrediculoneuropathy – **many dermatomes involved**

Syphilis

- Many ripping, stabbing, lancenating neuropathy

DM

- glove and stocking distribution
  - Always symmetrical and bilateral

Myasthenia Gravis	Myasthenic Syndrome (Eaton Lambert)

• **Middle age female with ptosis**
• Gets weaker as the day goes by, strongest in the morning
• **Anti ACH Antibodies is the problem**
• Associated with **Thymoma (40%)**
  o Do a CT scan of the neck
  o Removal of the thymoma will be curative
	• Associated with small cell CA (malignant)
	• Gets stronger as the day goes by
	• Ca^{2+} is slow in returning into the SR
	  o **muscle contractions become stronger**

DIAGNOSIS

- To differentiate the two:
  - Do an EMG (electro myogram)
    - increased contraction will cause stronger amplitude of contraction
  - Medication
    - **MG is diagnosed using Endrophonium (ACH breakdown inhibitor, short acting)**
      - **MG patients stronger**
      - **Myasthenic Syndrome will get weaker.**
  - Treatment:
    - MG:
      - Neostigmine, (#1 choice)
      - Pyridostigmine
      - Don't like Physostigmine – because can cross BBB = CNS side effects.
      - **SE = parasympathetic side effects.**
- To differentiate between worsening MG and cholinergic crisis need to do an Edrophonium test again:
  - if get stronger → MG got worse
    - need to increase neostigmine dose
  - if get weaker → **cholinergic crisis**
    - **need to treat with atropine**
    - Need to decrease neostigmine dose

Pharmacology Aside:

Organophosphates

- **MOA:**
  - **IRREVERSIBLE AChesterase inhibitors (non-competitive)**
- Examples:
  - Pesticides
    - **"… phates"**
    - **"…thions"**
- Antidote:
  - Atropine
  - Scopolamine

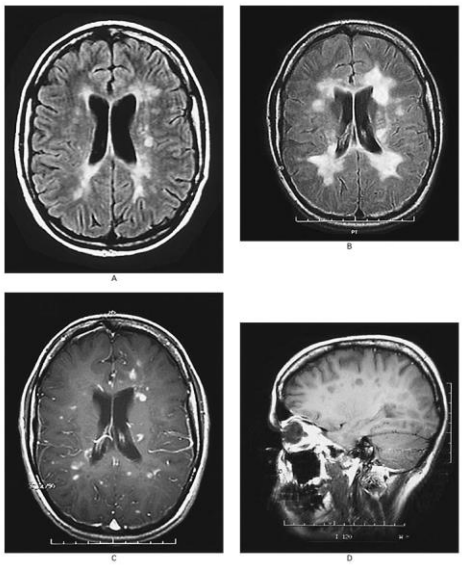
Other notable anti – cholinergic drugs

- Glyropyrolate and Atropine
  - Dries up secretions before surgery
- Benztropine
  - Stimulates 2PAM → inhibits toxins
  - Used for dystonia
- Scopolamine
  - Motion sickness

Myopathies Cont.

Multiple Sclerosis

- **Middle age woman with vision problem**
  - Optic neuritis
    - inflammation of the optic nerve
  - halo vision
    - can see things off to the periphery
    - can't see things if looking right at them
- Internuclear opthalmoplegia
  - MLF = medial Longitudinal fasciculus is taken out
    - connect CN III and CN VI
  - the connection between the two CNs is destroyed but each CN is functional
- **Associated with Anti-myelin Antibody**
  - Presents **2 wks after infection**
- Diagnosis
  - MRI can see **demyelinated plaques → bilateral asymmetric distribution**
  - **LP will show myelin baic protein in CSF**



Metachromatic Leukodystrophy

- MS equivalent in a child
- **Arylsulfatase deficiency**

Cerebellar problems can present as three diseases:

- Ataxia – telangiectasia
  - Telangiectasia all over skin
  - lady with spider veins
  - **Have IgA deficiencies**
    - diarrhea, respiratory illness
- Fredriechs Ataxia
  - Retinitis pigmentosa (pigments on the retina)
  - Scoliosis (5-10%)

- Adrenoleukodystropy
  - adrenal gland is knocked out
    - electrolyte problems
  - Long chain fatty acids accumulation in the mitochondria (transferred by carnitine)
    - Involvement of Cortex early on
      - spasticity
      - babinsky

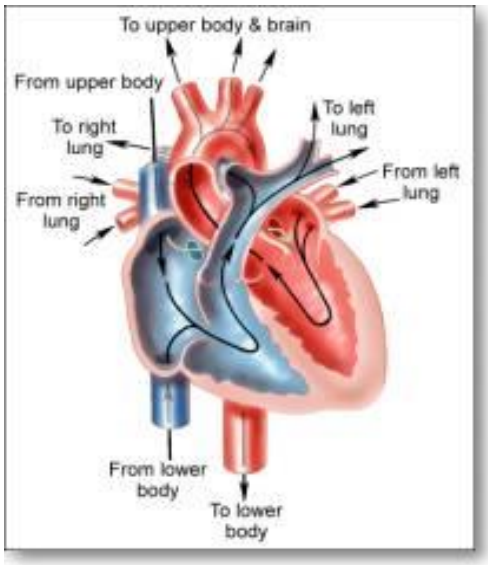
Lower Motor Neurons

- Fasciculations = LMN deficit
  - ALS
    - Fasciculations in middle age male
    - **Descending paralysis**
    - No sensory involvement, all motor nerves
  - Werdnig Hoffman
    - **Fasciculations in a newborn**
    - **born with no anterior horns = no motor neurons**
    - will die of respiratory failure
  - Polio
    - Occurs in children < 2 years old
    - anterovirus
    - **Will present 2 weeks after diarrhea first**
    - Develop into **asymmetrical** fasciculations and paralysis

Cerebral Palsy

- Permanent neurological damage suffered before age 21.
  - Not just at birth
  - Ex. 18yr old breaking back and get paralyzed
- Spastic diplegia
  - UMN
    - Cortex is involved
    - **Legs are worse than arms**
    - Midline cortical problem because legs are medial in the brain
      - Hydrocephalus can cause this
- Spastic Hemiplegia
  - Cortex involved → lesion on one side
  - One side of the body is affected more than the other → Contralateral symptoms
    - Ex. herpes likes temporal lobe, toxoplasmosis loves parietal lobe
- Choreoathetosis
  - dance-like movements
  - ringing of the hands and **quivering** voice
  - Problem in the basal ganglia
  - **MCC = kernicturus (bilirubin)**
- Atonic cerebral palsy
  - no muscle tone
  - **Frontal lobe tumor/stroke/AVM**
- Pancreatic CA
  - Trousseau Syndrome

Cardiac Physiology:



- Left side of the heart is higher pressure and higher resistance
  - Will always close first
  - Always open second
    - Mitral Valve/AorticValve
- Right side of the heat is under lower pressure
  - Will always close 2nd
  - Open 1st
    - Tricuspid valve/Pulmonary valve

Heart sounds are never made by valve OPENING → Sounds are primarily made by valves CLOSING

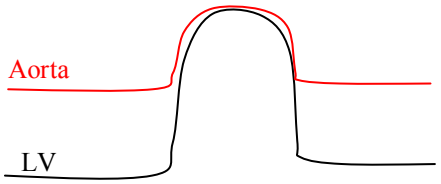
- **Ejection Click** is a sound made by the "tight valve" at systole → High Pressure
  - Aortic Stenosis
  - Pulmonary Stenosis
- **Opening snap** – when the valve is forced open during DIASTOLE
  - Mitral stenosis
  - Tricuspis stenosis
- **Mid-systolic click ➔** Mital valve regurgitation (prolapse)

S_1 --------- Systole --------- S_2 --------- Diastole --------- S_1

Soft S_1, Holosystolic	• M = C = MR • T = C = TR	• M = O = MS • T = O = TS	Loud S_1, Diastolic rumbling, opening snap
Loud S_2, Ejection Click	• A = O = AS • P = O = PS	• A = C = AR • P = C = PR	Soft S_2, Diastolic Blowing

- **Left Side has higher pressure → always close first and open second (Mitral valve 1st)**
- **Right side has lower pressure → close 2nd and open 1st (valves are Easier to open)**
- *Soft S_1 ➔ regurgitation → valves not closing when they should be* → swaying back and forth
  - Mitral regurgitation
  - Tricuspic regurgitation
- *Loud S_1 → Valve is stenotic doesn't want to stay open or Presence of High Pressure in the ventricles*
  - MS
  - TS
  - RVH, Sarcoidosis, Digitalis → think about what makes the ventricel contract harder!!!
  -
- *Soft S_2*
  - Valve not closing
  - AR & PR
- *Loud S_2*
  - Stenotic valve
  - Slamming shut because of high pressure behind it
  - AS & PS

Pulse Pressure:



- during isovolumetric contraction
  - need to overcome aortic diastoic pressure of 80
  - At 81 blood will overcome pressure in the aorta and valve will open
  - Between 81-120 blood will <u>enter</u> the aorta
  - At 121 blood will begin to <u>flow through</u> the aorta. Will be done by the L ventricle and the recoil of the aorta
  - Afterload = the max resistance the L ventricle has to overcome to flow through the aorta
  - Mean arterial pulse pressure = $\frac{systolic + diastolic}{2} = \frac{120+80}{2} = 100$
- **S_2 splitting**
  - Occurs during **inspiration**
  - When you breathe in (inspire), oxygen dilates pulmonary vessels = (Intrathoracic)Resistence in the lungs ↓ = ↑ BF to the right side of the heart → Pulmonary valve stays open longer
    - **Inspiration = ↑ blood volume on the R side of the heart.**
    - **↑ volume of R side of the heart**
  - **Auscultation with inspiration**
    - **isolates the R side of the heart**
    - **Tricuspid & Pulmonic valves**

Inspire → blood goes to the lungs
Expire → blood goes to the body

  - **Auscultation with expiration**
    - **isolated the L side of the heart → Mitral and aorta**
      - **Example: pulmonary stenosis, ASD, VSD, hyperventilation**
  - **Physiology behind S2 splitting**
    - Widens because …
      - **↑ O_2 in the lung**
      - **There will be a delay in the opening/closing of the pulmonic valve due to the ↑ volume → Ex. AVM**
      - **↑↑↑ Blood volume in the right ventricle (L→R shunts)**
    - What can widen S_2 splitting
      - Dilated heart
      - PS/PR
      - Deep breath
      - ASD (L→R shunt)
      - Early in Exercise
      - ↑ Fluid intake
      - SIADH
      - Right Bundle Branch Block

- Fixed wide splitting of S_2
  - Can only be caused by **ASD**
  - Most commonly missed congential heart disease →the most likely congenital heart disease to present as an adult
- **S_3 = Sound made when blood hits the ventricle wall**
  - **Volume Overload**
  - **Decompensation → muscle is stretched too far out**
  - **Dilated ventricle (cardiomyopathy)**

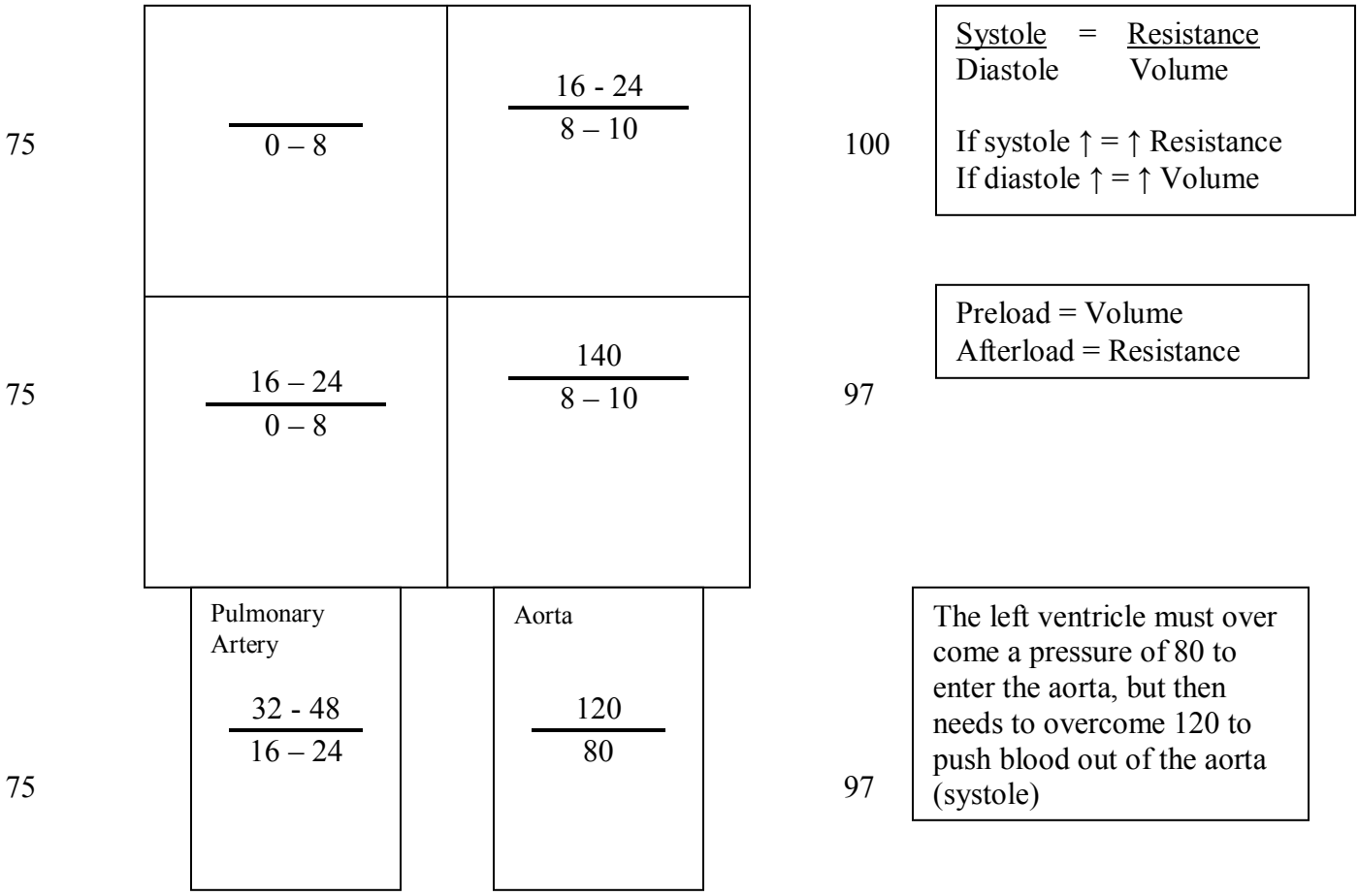
- ***Why does a adolescent female have a dilated heart?***
  - She is an a period in her life that has ↑↑↑ Estrogen = (+) S_3
    - It is greater than males = Don't have an S_3
  - Therefore, Estrogen must be a MUSCLE RELAXANT!!!

• Estrogen Connection

- Estrogen is a muscle relaxant and will cause:
  - S_3
  - Constipation in pregnancy
  - urinary retention
  - DVT
  - hemrroids
  - reflux
  - Relaxed gall bladder → ↑ gall stones
  - Hips expand
  - Muscles are "weaker"
  - "GLOW" → d/t vasodilation
- Example: The most common presentation of pregnancy is weakness and SOB, most common cause of death is HF... → **neuromuscular weakness**
- Estrogen will protect the heart in women by causing vasodialtion and ↓ BP
- Estrogen is broken down by the liver (p450) →
  - Anyone with liver failure will have a high estrogen state and will present with the above symptoms
    - Cirrhosis → ↑ estrogen levels
      - Gynecomastia
      - Spider telangectsia
      - Testicular atrophy
      - COMA
      - Seizure

- **S_4 → ATRIAL CLICK**
  - **Pressure overload**
  - **Hypertrophy**
  - **Compensatation**
- Diastolic Heart failure
  - Heart not filling properly at diastole = too much hypertrophy (weight lifters)
- High QRS complex = Dilated → muscle is being stretched
  - Hypertrophy → building more cross bridges → only a slight increase in QRS
- Pulmonary hypertension
  - Any extra blood to lungs will eventually lead to pulmonay hypertension
  - when distended will increase pressure activating the Ca-Calmoduling system
    - will increase resistance 2° to distension
    - arteriols will eventually hypertrophy
  - Follow clinically by S2 → pulm htn = S2 narrowing
  - QP/QS = 2/1 thats what the pediatrician follows

Values of Different Chambers



- Pulmonary Capillary Wedge Pressure
  - It is the indirect measurement of Mean Left Atrial Pressure
  - Think of it as the Volume of Blood in the PULMONARY CAP. BED
  - Ex.
    - Mitral regurgitation → PCWP ↑ because of blood returning to the lungs
- CVP
  - Filling pressure in the Right Atrium
  - 3 – 5 cc

- Oxygenation
  - Oxygen saturation is at 75 when entering the right atrium → 75 in right ventricle → 100 in the capillary bed
  - That 100 then goes through the lungs and back to the left side of the heart into the left atrium → but then drops to 97 in the left ventricle
  - Why does the Oxygen saturation in the left ventricel drop from 100 to 97?
    - It is because of the Thesbian veins that drain the myocardium and into the left ventricle
    - Therefore, be aware of where the oxygen saturation first is disrupted and ask your self why?
      - Maybe atresia or a left to right shunt occuring

Murmurs:

Reynolds # **> 2500-3000** indicates turbulence ➔ a murmur

If there is turbulance in the blood vessel = Bruit

S_1 --------- Systole --------- S_2 --------- Diastole --------- S_1

Soft S_1, Holosystolic	• M = C = MR • T = C = TR	• M = O = MS • T = O = TS	Loud S_1, Diastolic rumbling, opening snap
Loud S_2, Ejection Click	• A = O = AS • P = O = PS	• A = C = AR • P = C = PR	Soft S_2, Diastolic Blowing

- Closed valves will have **regurgitation murmurs**
  - Only 3 murmurs described as holosystolic or pansystolic
    - Mitral –
      - pansystolic ↑ expiration and radiates to the axilla (left lateral decubitus)
    - Tricuspid
      - holosystolic ↑ inspiration
    - VSD – radiates to midline
      - pansystolic ↑ expiration

- Systole Ejection murmurs = occurs to Opening valves
  - Pulmonary Stenosis
    - Able to hear it on the back on auscultation
  - Aortic Stenosis
    - Radiates to the neck
    - Will have **Pulsus Tardus** (delayed carotid upstroke) due to **crescendo-decrescendo murmur**
    - Diagnosis
      - Make a fist → ↑ BP, then sit down = ↑ sound amplification
      - Louder with valsalva
    - **Valvular area < 1.5 cm^3 → need to replace valve = moderate stenosis occurring → want to prevent progression to severe**
    - Chest pain + AS = 5 yr. life expectancy
    - Heat failure + AS = < 2 yrs.

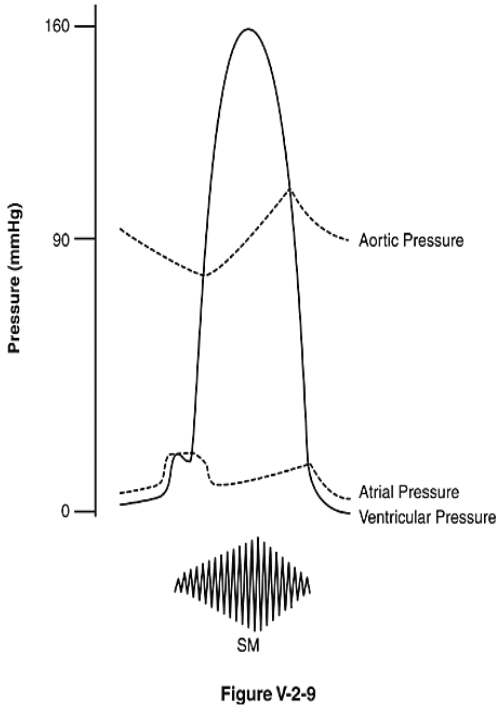
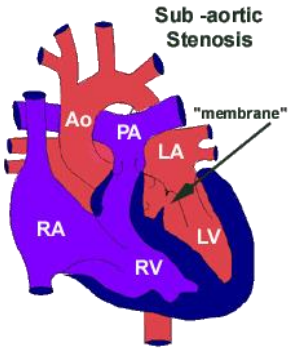


Figure V-2-9

- **Idiopathic Hypertrophic Subaortic Stenosis (AD)**
  - Biopsy = see disorganized muscle fibers
  - Hypertrophy of the septum → top heavy
    - The heavy part will fall downs and hang's into the left ventricle
    - The volume in the ventricle holds it up
  - 60% present with sudden death
  - Most common cause of sudden death in athletes
  - Sometimes present with Syncope



    - Valsalva (bear down) will ↓ venous return by ↑ abdominal pressure
      - If murmur gets louder its IHSS
      - If murmur gets softer its Aortic stenosis
    - Maximum sinus rate is (220-age)
      - at max rate you are mostly in systole
      - ↓ diastole, ↓ EDV, septum will fall and there will be no blood flow to aorta→ drop dead.
  - All these patients will have an S_4
    - Cardiac hypertrophy causes ↑ contraction in heart muscle.
    - Constant contraction will cause constant blocking of coronaries. At peak exercise there is ↓ Blood flow as well.
  - Treatment:
    - **β_1 blocker → ↓ HR, <u>↓ contractility</u> = ↑ EDV = Therefore, the heart doesn't reach MAX**
    - Needs to drink 8 glasses of water/day
  - **Pulsus Bisferiens**
    - 2 peaks to the pulse
    - 1st strong contraction, then the septum falls and the heart contracts again

- **Diastolic: valves are closed**
  - Diastolic Blowing (decrescendo)
    - **AorticRegurgitation:** look for **wide pulse pressure** → most common reason is sepsis due to Gram – , endotoxins.
      - Look for "head bobbing" due to ↑systolic P vs. ↓ Diastolic P
      - Bounding pulse ("water hammer" pulses)
      - Quincke's pulses in the nail bed due to pressure difference
    - Graham-Steele – Occurs on right side → TR – 2^0 to PR
    - Austin Flint murmur – Occurs on the left side → MR – 2^0 to AR
      - These murmurs are created by the vacuum created by the blood going back into the LV and the leaflets get caught

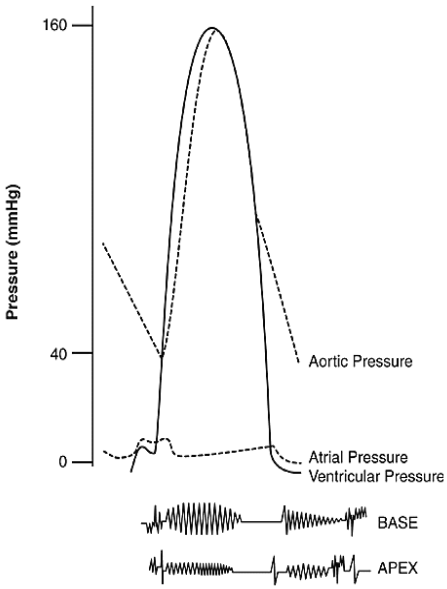


Figure V-2-10

- Diastolic rumble
  - Caused by **"whirlpool"** effect due to stenosis of valve
    - Tricuspid Stenosis
    - Mitral Stenosis

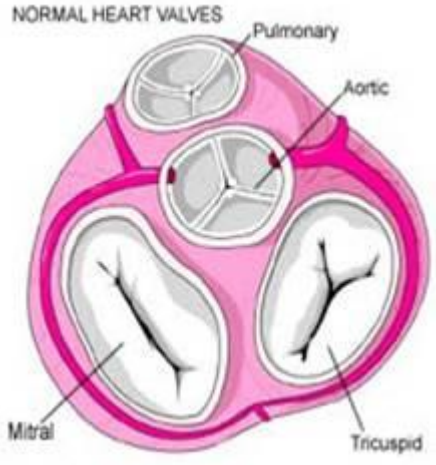
Continous Machinery

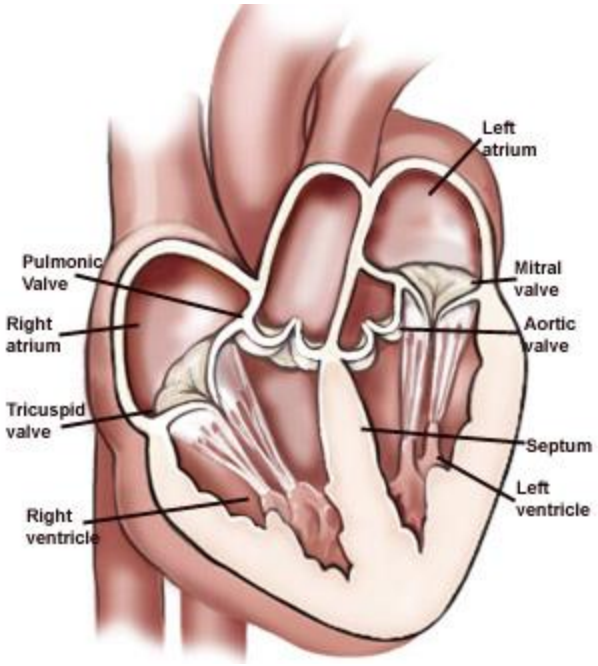
- There is a connection between an artery and a vein.
- The murmur never disappears.
  - Ex. continous murmur in **newborn baby indicates PDA**
  - **Continous murmur in the brain of a newborn baby indicates an AVM**
    - Osler-Weber-Rendu syndrome-
      - multiple AVMs in **lung**
      - Continous murmur in the lung
    - Von Hippel Landau
      - Multiple AVM in **brain and abdomen**
      - Short arm of chromosome 3 is responsible
      - High incidence of renal cell carcinoma (Like tubular sclerosis)
    - Diabetic fistula for dialysis will also create a continous murmur
- AVM Kills by…
  - Burst and Bleed
  - Sequester Blood → High output HF
  - Sequeter Platelets and bleed out

<u>Most common cause of every valvular disease:</u>

- Aortic stenosis
  - aging (calcification)
    - Under 30 year old its bicuspid aortic valve → congenital
- Aortic regurge
  a. aging (Ca)
  b. collagen diseases
- Mitral stenosis
  a. rheumatic fever
     i. common causes of carditis is rheumatic fever
        1. mitral stenosis
        2. mitral and aortic stenosis
        3. aortic stenosis
        4. Tricuspid stenosis
- Mitral regurge
  - mitral valve prolapse
    - 7% of women (estrogen connection)
  - Collagen disease
  - Endocarditis
    - Staph aureus
    - Strep viridans
- Tricuspid stenosis
  - Rheumatic fever
  - Carcinoid syndrome
    - flushing
    - wheezing
    - diarrhea & itching

- Tricuspid Regurge
    - IVDA
    - Endocarditis
        - Staph aureus
        - Strep viridans
- Pulmonary Stenosis and congenital
    - Congenital





Cardiac equations

- EDV ➔ preload
- ESV ➔ volume after contraction (End Systolic Volume)
  - Dobutamine → ↓ contractility and ↓ ESV
- SV➔ how much you actually pumped out = Stroke Volume
- **EDV-ESV = SV**
  - Average SV = 100cc/beat
- Ejection Fraction
  - $EF = \frac{SV}{EDV}$
    - Normal EF 50-80%
  - If trying to increase SV
    - Need to increase EDV =
      - IV fluids
      - Deep breath
      - venoconstriciton when walking
      - blood transfusion
  - The heart does not like to ↑ EDV to maintain SV
    - Decrease ESV =
      - ↑ contractility
      - digoxin, dobutamine

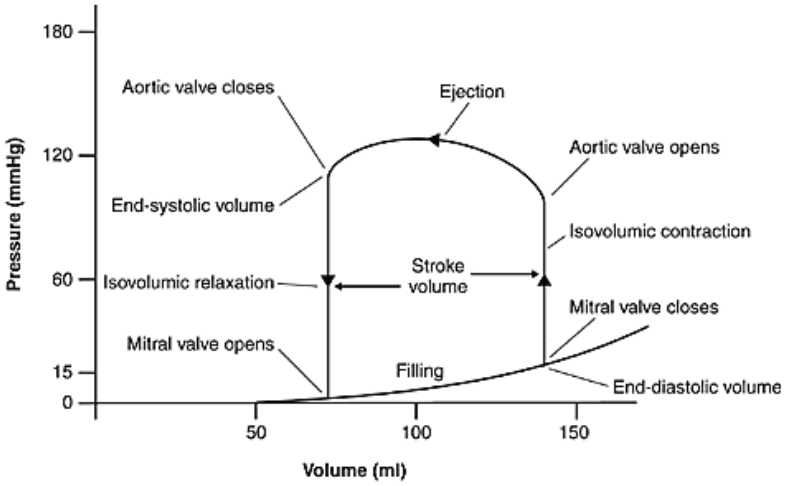


Figure V-2-13

  - If there is any loss of volume check the HR 1st
    - If HR ↑ = low volume d/t maintance → compensated shock vs. a problem due to hypertrophy
  - Ex. Patient with CHF
    - Has already lost 40% of heart volume
    - So EF is below 45% (that's the minimum needed to survive)
- **CO= SV x HR**
  - Ex. Athletes' heart have more contractility due to hypertrophy and ↓ TPR from the formatino of new capillaries
    - Therefore, Athletes will have ↑ contractility, ↑ ejection fraction, ↑ SV = ↓ HR, to keep CO the same
    - The athlete with the best endurance has the lowest HR
  - When SV goes down (dehydrated) need to ↑HR
- **Normal CO = 5L/min**
  - 20% goes to brain
    - Ex. Cerebral profusion rate = **1L/min**
  - 20% goes to heart = **1L/min**
  - 20% goes to kidney
  - Ex. Renal blood flow = **1L/min** ➔ GF= 20% of renal blood flow
- How to classify people with heart failure:
  - using NYHA
    - Asymptomatic
    - Symptoms with moderate exercise
    - Symptoms with minimal exercise
    - Symptoms at rest

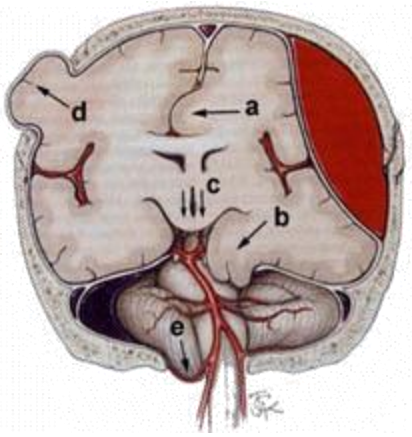
CO = SV x HR

- **BP = CO x TPR = SV x HR x TPR**
  - Raise BP by ↑SV, ↑HR, ↑ TPR and viceversa
    - Ex. HTN in blacks and hispanics is SV probelm
      - treat with diuretics
    - HTN in white male is caused by ↑HR (stressed)
      - Treatment ➔ β-blocker
    - HTN in white female is caused by ↑TPR
      - stress, smokes and drinks to vasocontric
      - Treatment ➔ vasodialation
- Average life expectancy for
  - white female ➔74-77
  - white male ➔ 71-74
  - Black female ➔ 67-70
  - Black male ➔ 61-64
- Anti-hypertensives
  - SV ➔ use diuretics
  - HR➔ use β blocker, Ca channel blocker
  - TPR ➔ ACE Inhibitor, Ca channel blocker, nitrates and non specific vasodialtors: hydralazine, diazoxide, minoxidil
  - **Pregnant women ➔ α-methyl dopa first and hydralazine second = least teratogenic**
  - Be careful mixing drugs:
    - Marathon runner on β-blocker will sweat → ↓ SV but the HR doesn't go up because of the β blocker, therefore must ↑TPR → the body will not let heat out and he will die of heat stroke
    - Can't give β-blockers and Ca-channel blocker together
      - β blocker → knocks out HR, SV and Renin
      - Ca-blockers → ↓SV and TPR

- **Mean Arterial Pressure – Intracranial pressure = cerebral perfusion pressure**
  - **MAP – ICP = CPP**
    - ↑ ICP = ↓ CPP
    - Ex. hypertension causes a headache because ↑MAP will cause ↑ of ICP by the same amount to keep CPP the same.
    - Cushings reflex = ↑ICP (after MVA) will cause ↑MAP in order to ↑BP and maintain CPP
      - The brain tells the body to do this!!!
      - When in a hypertensive crisis → prsent with a headache
    - Anything that ↑ ICP will present with a headache
      - Think about cerebral disease
  - Patient presents to the ER with ↑ ICP
    - MC presenting sign is papilledema
      - Do a CT scan to check for it
    - IF the MAP drops then the CPP will decrease → LOSE THE BRAIN → swelling →herniation!!!
    - Put them on a ventilator

- Treatment for ↑ICP
  - Ventilator: 100% O_2, to ↓CO_2
  - IV Mannitol: osmotic agent to pull fluid out of the brain
  - IV Acetazolamide: carbonic anhydrase inhibitor → cuts off CSF production
  - Burr Hole in the brain → when all else fails
    - Drill the hole in thetop of the head then the brain will get sucked back up

- **Papilledema → indicates pressure on the brain → (+) CN VI (lateral rectus) → eye deviates inwards (estropia) → CN III (loss of pupillary eye reflex) = BRAIN HERNIATION**
  - **Decorticate posture** → upper extremities flexed, lower extremities extended
  - **Decerebrate posture** → full extention of ALL extremities

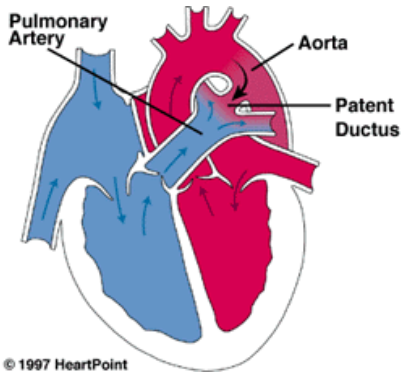


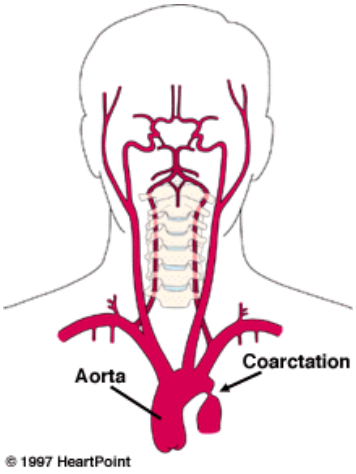
Congenital heart disease

(be careful not to confuse with cyanotic disease).

These are the most common congenital heart disease

- VSD
  - pansystolic murmur
- ASD
  - adult presentation
  - fixed wide splitting
- PDA
  - continuous murmur
  - Pulse pressure will decrease
  - Mixed venous O_2 will ↑
- Coarctation
  - Common in Turnur's syndrom
  - Differential pulses
  - Differential cyanosis- always associated with PDA
    - between up/down and R/L
  - Adult type will not have a PDA

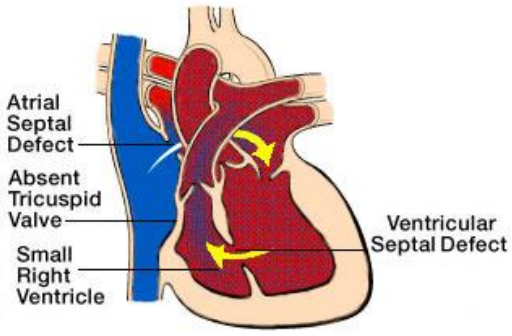




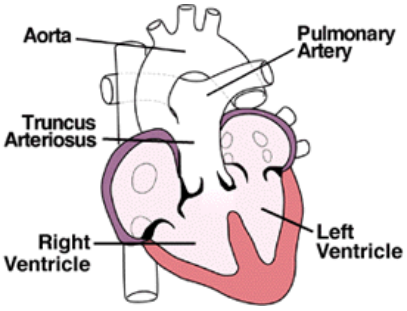
Cyanotic Heart Disease

Know the 5 T's

- Transposition of the Great Arteries
  - Most common cyanotic heart disease at birth
  - Need to create a L→ R shunt and
  - Keep PDA open with PG-E
    - DOES NOT require O_2
- Tetrology of Fallot
  - Most common cyanotic heart disease AFTER 1 month of age.
    - look for Infant or Child
  - Remember Cause and Affect
    - Overriding Aorta
    - Pulmonary stenosis
    - Right ventricular hypertophy
    - VSD (to shunt blood to the left side)
  - Prognosis will be determined by pulmonary stenosis
  - In children with mild pulmonary stenosis will need to diagnose tetrology by TET SPELL
    - cry and turn blue
    - stop crying and pink up
    - during crying they will shunt blood away from left side
    - Squat to ↑left to right shunt to ↑O_2 by compressing the poplateals and ↑ pressure in aorta
- Total Anomalous Pulmonary Venous return
  - all pulmonary veins go to the Right atrium
  - didn't make it to left side
- Tricuspid Atresia
  - soft S_1
  - Right atrium will contract harder→ Get S_4 that will increase on inspiration.

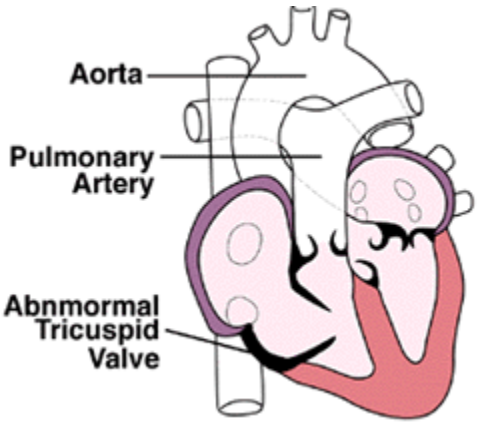


- Truncus Arteriosus
  - spiral membrane didn't develope in embryo
  - No aortic/pulmonary septum
  - One large trunk without difference in aortic pulmonary valves
  - venous and arteria blood mixing

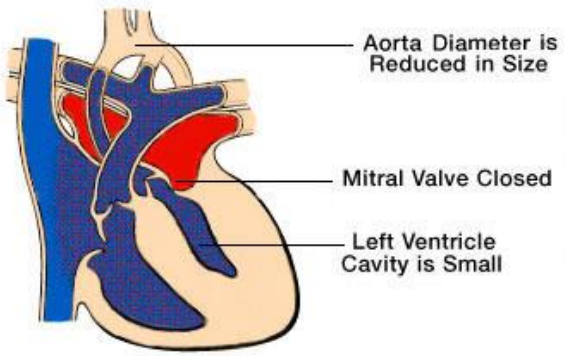


*ductul dependant lesions because need a PDA

- Pulmonary Atresia
  - No blood to lungs
  - Soft S_2
  - Louder S_1
  - Will get an S_4
  - Will increase on inspiration
- Aortic atresia
  - Blood can't get out of the heart
  - soft S_2, louder S_1
  - Get an S_4
  - Will increase on expiration
- Ebstein's Anomaly
  - tricuspid valve is displaced into the R ventricle
    - hanging too low, insufficient, swinging back and forth
  - Soft S_1
  - Pansystolic murmur will increase on inspiration
  - With R Ventricle dialation → S_3 that ↑ with inspiration
  - Lithium taken by mom will create a higher incidence



- Hypoplastic left heart
  - Baby's pulse is very weak
  - Left ventricle is very small, BP is low
  - S_2 is soft because valve won't open.



Pressure-volume curve:

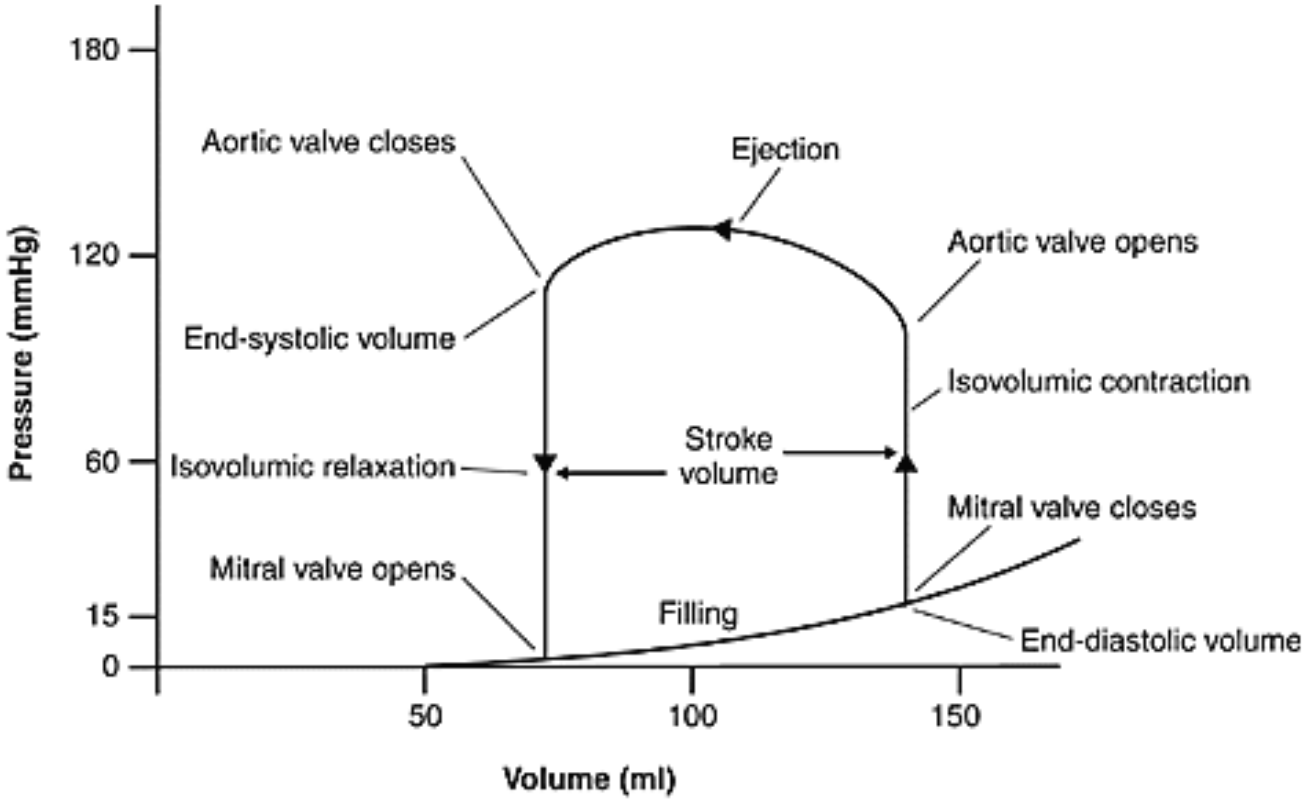


Figure V-2-13

- Diastolic = Volume
- Systolic = Resistance

To figure out reason for high blood pressure:

- First look at diastolic P
  - If high ➔ volume problem
    - Would expect systolic to be high as well because there is an increase in resistance volume is increased.
  - If low ➔ resistence problem
    - Ex. Caffeine, NE

In the lung:
Ex. (nl P = 40/24), 50/15 indicates a hypoxic lung disease causing pulmonary hypertension and .
50/30 ➔ L sided heart failure causing volume overload in the lungs.

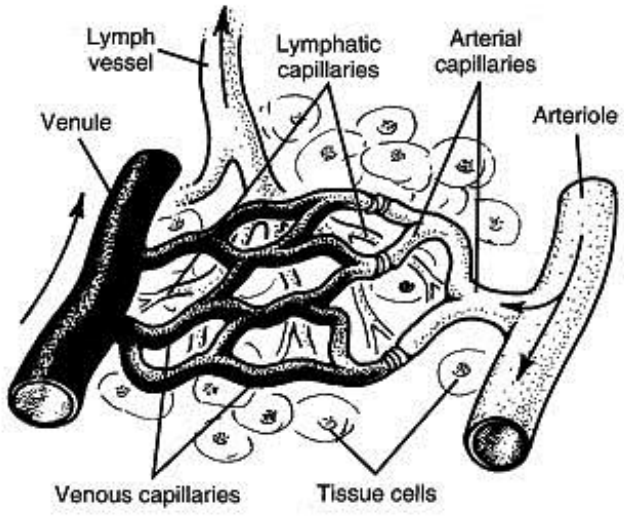
BP:
Ex. 120/110 → heart isn't pumping so the fluid overload isn't getting to the vessels.
120/40 ➔ compensating hypovolemic shock, needs fluids

Vascular Physiology

Aorta

- Largest vessel in the body
- Has the thickest layer of smooth muscle = stratified squamous cell epithelium on the interior → Because blood comes out of the Ventricle at high speeds and makes a sharp right
  - Therefore, the basement membrane is made for abrasion (like skin)
  - Remember that any collagen disease can affect the aorta

- The Aorta has the most compliance
  - Compliance= $\frac{\Delta Volume}{\Delta Pressure}$
    - Will allow to accept a lot of volume without change in Pressure
    - Recall that Elastin contains demosin
  - Atherosclerosis → artery will lose compliance → systolic HTN → Widened Pulse Pressure
- Arterioles have the most smooth muscle by cross sectional area
    - Therefore, can have the most significant influence on BP
    - Arterioles have β_2 receptors
    - Act as stop-cocks b/c they protect the capillaries
    - They try to maintain perfusion



- Capillaries have the thinnest wall → this allows diffusion fxn (renal capillaries)
  - Recall Fick's Principle
  - ↑↑↑ Surface Area
- Veins and Venules
  - Have the most capacitance = ↑ ability to hold on to blood
    - Hold > 60% of blood at one time.
  - Function:
    - When a patient is HYPOVOLEMIC the body will squeeze blood from the veins back into circulation
- Arteries and Veins have α_1 receptors
  - When someone veno/vasoconstrict → shunt blood away from the SKIN & GI = Skin turgor and ↓ bowel sounds
  - Vessels are usually under Sympathetic control → Vasoconstriction
  - Reactive Hyperemia
    - Vasodilation of an arteries will occur in the area where there has been damage to a sympathetic nerve
    - If you cut a Parasympathetic nerve the vessel will constrict
  - Veins are regulated by the parasympathetic system
  - Arteries are regulated by the sympathetic system

- Vessel Pathology
  - Hyperplastic arteriosclerosis
    - Scarring and bad HTN for at least 6 months → Malignant HTN
    - The vessels are trying to hold on
    - Onion skinning

- Hyaline atherosclerosis
  - Much milder → no scarring involved
  - Hyaline deposition

Resistance:

- **Series**
  - As blood vessels shrink you get resistance in series (traffic jam)
  - **$R_{total} = R_1+R_2+R_3$**
    - ↑ resistance = velocity ↑ (squeeze garden hose)
    - That would mean that the velocity at capillary level would be very high
  - That's why there is an increase number of vessels as the vessels get smaller
- **Resistance in Parallel**
  - $\frac{1}{R_{total}} = \frac{1}{R_1} + \frac{1}{R_2} + \frac{1}{R_3}$
  - Velocity is slowest at the capillaries, and there least resistance when arranged in parallel
    - One RBC at a time goes through a capillary
    - Going slowly, in order to extract nutrition
    - Think of it as a toll booth on a freeway
  - **Any loss of capillaries will increase resistance fast and lead to hypertension**
    - Every cause of vasculitis
    - Old age
- Every organ has RESISTANCE in PARALLEL except…
  - Liver- to allow detoxification
  - Kidney – to allow filtration
    - Pressure in these organs is higher
    - Blood is sitting in "traffic jam"
- In the capillaries the v (velocity) is low so most of the pressure is in the form of transmural Pressure.
  - Maximum filtration ➔ pushing nutrients out
- **$P_{Total} = P_{Transmural} + P_{linear}$**
  - $P_{linear} = \frac{1}{2} pv^2$
- **High velocity** will cause blood **to flow straight out (when young most of the blood is in linear pressure), so there is less pressure on the wall**
- In the aorta velocity is high so the blood is moving linear down the middle to prevent tearing

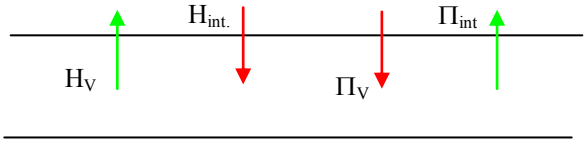
During Systole why is there little blood flow to the coronary?

- Aortic valves open
  - **The coronary ostia is occluded by aortic valves**
  - **Resistance increases in coronary vessels during systole**
- **Transmural pressure is very low during systole**
- Ventricle contracts (ST segment) = ↑ Coronary resistance
- The reverse occurs during Diastole
- ↑ arrhythmia time = ↑ compression of coronaries

- Vacuum within the vessel
  - Speed "sucks" the blood from the periphery and blood no longer touches the sides
  - That is how an airplane gets airborne
  - Hula Hoop example
- Heart needs the most extracted Oxygen when it contracts
  - Heart has the greatest AVO_2 Difference
  - Oxygen delivery to the heart is completely flow dependent because it extracts 90% at rest
    - Anytime there is a loss of blood flow → Angina

Filtration forces: Π

- For Filtration
  - Hydrostatic pressure (in the vessel)
  - Oncotic pressure (protein in the interstitium)
- Against filtration
  - Hydrostatic pressure (in the interstitium)
  - oncotic pressure (protein inside the vessel)
    - ➔ FF= $(H_v+\Pi_{int.})-(H_{int}+\Pi_v)$



- H_V and π_V have the most influence on FF
  - Example:
    - Explain edema in HF: ↑ hydrostatic pressure in vessel (pooling)
    - Explain edema in cirrhosis: liver is not making protein ➔ ↓oncotic pressure in vessel.
- Venules suck waste product in.
  - As blood goes through arteries, oncotic pressure sucks water out of arteries leaving RBC in the vessels
  - That increases osmolarity in the vessel until the blood reaches the venules
  - In the Venule the osmolarity will cause water (and waste) to go into the vessel

Flow:

- Flow, $Q = \frac{\Delta P_1 - P_0}{R}$
- ↑ R (Resistance) will ↓ flow (Q)
  - Pressure will have to ↑ by the same amount to keep flow (Q) constant
    - Any vasculitis will lead to increase BP b/c you ↑ R = ↓ Q
- Resistance, $R = \frac{1}{r^4}$
  - As the ↑ radius ➔ ↓ Resistance ➔ ↑ Flow
    - **Radius has the largest impact on flow**
      - Vasoconstrict vs. Vasodilate
    - That's why we have so many mechanisms to control radius
- *Q = 1/nL*
  - n = Viscosity, L = length of tubing
    - So as Viscosity ↑ ➔ flow will ↓ ➔ ↑ BP to maintain flow
  - Example: DIABETES
    - diabetes = ↑ glucose in blood = ↑ viscosity = ↓ Q
    - In order to return flow → resistance must ↑ to compensate → this will offset atherosclerosis
    - If the heart isn't enough to compensate pressure will ↑↑
    - Therefore, important to keep Glucose under control in order control BP
      - Need to keep blood glucose at 126 in the kidneys.

        - Diabetics get foot ulcers because they are further away (↑ L), and therefore get the least amount of flow = "Glove and Stocking" loss of sensation
        - Always checks the diabetic's feet
    - Polycythemia will ↑ blood viscosity → ↑ BP
        - Need to ↓ viscosity by phlebotomy

    - A "larger" person will have more tubing → ↑ L → ↓ Flow → ↑BP to compensate because the body's response to vasodilate has been exhausted
        - Therefore, Obesity will lead to hypertension
- Poissielle Law
    - $Q = \frac{(\Delta P_1 - P_0) r^4}{nL8\prod}$

The most important way to regulate flow is through changing the radius

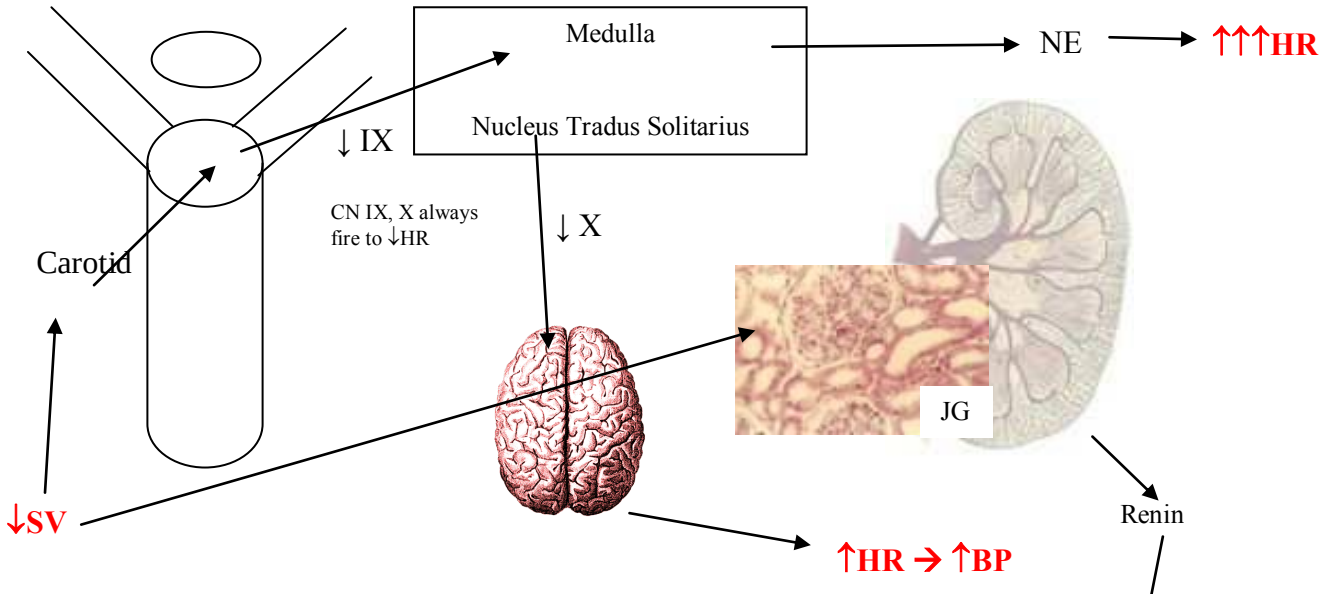
Organs and their Vaso-regulators

Brain	↑pCO_2, ↓pO_2 Ex. HA at high altitudes when pO_2 decreases
CV	Adenosine Ex. used in arrhythmia because ischemia is the most common cause, so adenosine will stop ischemia, increase flow to SA node making take over and block ectopic site.
Lungs	↑pO_2 Ex. If you don't breath in there will be no blood flow through the lungs → Vasoconstriction in hypoxia
GI	Food Ex. Blood rushes to stomach after meal
Skin	Temperature, ↑pCO_2 Ex. In cold temperatures, blood goes away from toes and fingers. In summer the face flushes
Muscle	↓pH, ↑pCO_2
Arterioles	β_2 receptors
Kidney	PGI, PGE_5, ANP, D_2 Ex. dopamine given to people in cardiogenic shock to increase blood flow to the kidneys, NSAIDs are dangerous to the elderly because will decrease blood flow to kidney.

- Dopamine
    - Give to ↓ TPR
- Dobutamine
    - β_1 – Selective
    - Works on HR

ROLE OF THE BRAIN

- The brain is sensitive to changes in pCO_2
- The periphery is sensitive to HYPOXIA (pO_2 ↓)



Carotid Bodies

- Control **immediate changes in BP**

Carotid sinus

- Baroreceptor that **regulates BP**
- **SENSES stroke volume (SV) → via response to <u>stretch</u>**
- **CN IX & X are always firing**
  - Anything that drops SV (standing for a long time)
  - Will decrease firing by CN IX and X
  - Will increase HR (reflex tachycardia) and increase BP
  - **Reflex Tachycardia occurs because sympathetic innervation is no longer opposed and DOMINATES → ↑ BP**
    - **β_1 Blocker will ↓ HR by inhibiting Reflex Tachy.**
- Anything that will increase stroke volume
- Will increase firing by CN IX and X
- Therefore, decrease BP and decrease HR =
  - **Reflex Bradycardia**
  - When stand up
    - BP drops 5-10mm Hg
    - Pulse ↑ 5-10 bpm

Angiotensinogen → Angiotensin I

ACE

Angiotensin II

↑TPR→↑BP

CO=SV x HR
BP=CO x TPR

- Autonomic neuropathy:
  - When standing up the HR ↑ by 5-10 bpm and BP ↑ by 5 – 10 mmHg
  - But Pulse didn't ↑ by AT LEAST 4 bpm = Autonomic Dysfunction
    - Most common cause = DM
    - **Riley-Day syndrome** = Newborn
      - Familial dysautonomia
      - No autonomic reflex
    - **Shy-Drager**
      - **Parkinsonian patients** that develop autonomic neuropathy

        - **Sick Sinus Syndrome → Elderly**
            - Calcification of the carotid sinus due to aging
            - Old lady will pass out when standing up

- If the BP decreased by > 10 mmHg there is more going on than a reflex problem
    - Orthostatic Hypotension
        - HR ↑ by > 20 or if the BP ↓ below 10 mmHg when the patient stands up
- Carotid massage works by increasing stroke volume to increase firing by CN IX and X and cause reflex bradycardia.
- Vaso-Vagal Syncope → pass out because one induces ↑ reflex bradycardia
    - Hickee
- Malignant Htn. caused by cutting CN IX
    - CN IX runs behind the tonsils, so if accidentally cut will create malignant hypertension. Will cause reflex tachycardia.

Intermediate Control of BP

- If reflex tachycardia is not enough **NE** will come out as 2nd messenger
    - High affinity for α receptor
    - Then affinity for β receptor
        - Increasing HR by a lot (NE & HR ↑ together)
    - TPR goes up every time Stroke volume is low.
        - Normal BP and High HR means going into early shock, still compensating.
            - Need to hydrate them
                - Will reverse by ↑ firing of CN IX & X
            - Check HR to monitor for adequate hydration

Long term Control of BP

- **Stimulate JG apparatus- by low flow to the kidneys.**
    - Renin comes out
    - Cuts Angiotensinogen (formed in liver) to Angiotensin I
    - Angiotensin I is converted by ACE (in lungs) to Angiotensin II
    - Angiotensin II
        - **Very potent vasoconstrictor**
        - ↑ TPR
        - **↑BP**
    - Ag II will also stimulates Aldosterone
        - To decrease loss of volume
        - Aldosterone goes to kidney and reabsorbs Na from DCT
        - Excretes K in the process.
            - **Serum Na will be diluted and decreased. Because Na brings in 3x the Water!!!**
            - Serum Cl will also decrease due to dilution
            - Serum K will decrease because of secretion
            - Also excretes H+
                - Serum pH will go up

LOW VOLUME STATE (after chronic period of time)
Will always present with:

- **Hypertension**
- **↑TPR → Renin/Angio System**
- **↑BP**
- **↓Na → Aldosterone**
- **↓K → Aldosterone**
- **↑pH (metabolic alkalosis)**
    - Examples:
        - CHF
        - Pregnant woman with emesis
        - Child with projectile vomiting
        - Patient with renal artery stenosis
        - Exercise
        - ANY TIME ↓ Blood flow to the kidneys!!!

3 Exceptions: Low volume states that present with METABOLIC ACIDOSIS
1. Diarrhea → loss of HCO_3-
2. DKA → ↑ ketones
3. RTA II – loss of HCO_3-

- **GOES ON TO THE LOW ENERGY STATE**

<u>Cardiomyopathies</u>

- Dilated = Volume Problem
    - S_3, ↑ EDV, ↓ contractility, ↓ CO, ↑ ESV
    - Causes:
        - Infections (coxakie B)
        - Drugs
        - Low E State
- Hypertrophic = Pressure problem
    - ↑EF, ↑ contractility
        - HTN
- Restrctive
    - fibrosis
        - Collagen vascular disease
        - Cancer
    - Amyloidosis
        - Protein that stains CONGO RED and appears with a APPLE GREEN BIFERINGENCE = Speckled pattern
        - 1^0 → AD
            - Large organs → spontaneos intracerebral hemorrhage ina young child
        - 2^0 → due to any chonic inflammatory disease
            - More common
    - Types of Amyloid
        - AA → Autoimmune Chronic Inflammatory Disease
        - AB → Alzheimer's
        - AB2 → Chronic Renal Failure
        - AL → Multiple Myeloma

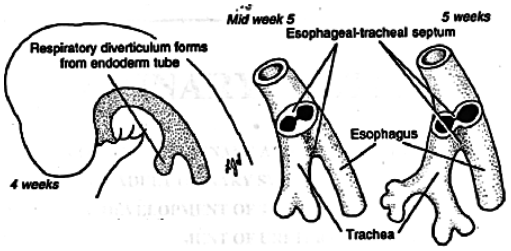
- Constrictive
    - something around the heart
        - MCC = Tamponade
            - most common cause is after trauma, followed by CA
            - Pressure will equalize in all 4 chambers (look for swan-gantz reads)
                - Ex. Stabbing in the left side of the chest will cause death by:
                    - tamponade
                    - pneumothorax
                    - hemothorax
                - Stabbing on the Right side of the chest will cause death by:
                    - pneumothorax
                    - hemothorax
            - Without blood movement → cyanosis
            - Massive JVD = kussmul sign
                - ↑JVD with inspiration
                - caused by
                    - tamponade
                    - pneumothorax
            - Pulses paradoxicus
                - Exaggerated drop in pulse or BP with pulse or inspiration
                - Indicates that something is causing a blockage and cannot fill the right side of the heart
                - positive intrathoracic pressure
                - Pulse and blood pressure will disappear. (small quiet heart) upon inspiration

- Restrictive
    - MCC = Hemochromatosis
        - 1^0 → autosomal recessive HLA-A3 and 6 → overwhelm duodenum with Fe
        - Secondary → d/t blood transfusion
    - Don't get confused with Hemosiderosis, which is Iron in the BM

Effusions:

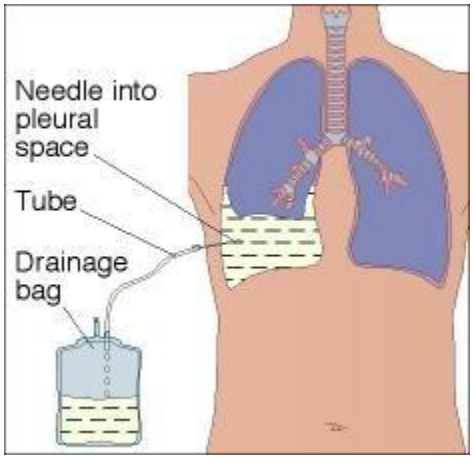
Transudate	**Exudate**
Mostly water	Mostly protein:
< 2g protein specific gravity < 1.012	>2g protein spg> 1.012
Too much water: 1. CHF 2. Renal failure Not enough protein: 1. Cirrhosis 2. Nephrosis	1. Purulent (bacteria) 2. Fibrinous (collagen vascular disease:lupus, RA, uremia, TB) 3. Granulomatous (non-bacterial) 4. Hemorrhagic (trauma and cancer)

Pulmonary Physiology



Embryology:

- Notochord develops in the 3rd week of gestation
- Brain develops in the 8th week of gestation
- 12th week of gestation the other organ systems begin to form
- Lung develops in 1st trimester
  - It is derived from the Foregut
    - From the lip → 2nd part of the duodenum, including the respiratory tract = FOREGUT
- Surfactant is not completely made **until 32-34 wks**.
  - **Lecithin : Sphigomyelin** ratio is **2:1** to indicate maturity
    - < 2/1 = ↓ in surfactant → immature
      - Beclamethasone → (+) surfactant production
      - If respiratory distress → give synthetic surfactant via endotracheal tube → ↓ mortality
    - > 2/1 = ↑ in surfactant → enough for labor = mature lungs
      - Check for Phosphatidylglycerol →breakdown product fo surfactant
  - Function
    - Surfactant acts as an oil
    - Main job is to decrease surface tension of alveoli → prevents collapse by keeping the alveoli open
    - **If no sufactant → Atelectasis = collapse of the alveoli**
- **Atelectasis**
  - Diffusion problem
  - Collapsed alveoli → no oxygen exchange → **Respiratory Distress Syndrome** = Pulmonary distress in a Premature Baby:
    - When a premature baby is born he goes into respiratory distress until his alveoli pop open.
      - Need to give baby Oxygen to create a concetnration gradient that will allow Oxygen to get into the lungs.
      - More O_2= more free radical formation ➔ lungs undergo metaplasia and will form a **hyalin membrane**
- **Hyalin membrane disease:**
  - Induced by giving O_2 to a baby who is hypoxic due to atelectasis.
  - Try to figure blood gasses:
    - **↓pO_2 will cause**
    - **↑ respiration → ↓ pCO_2**
    - **↑ pH**
  - ➔ **Restrictive lung disease**
    - Need to put baby on a ventilator, PEEP/CPAP
      - This provides a positive airway pressure to keep the alveoli open → gives some RV
    - Complicaton: bilateral pneumothorax because of the increased pressure required to infuse the oxygen
      - Will need chest tube.



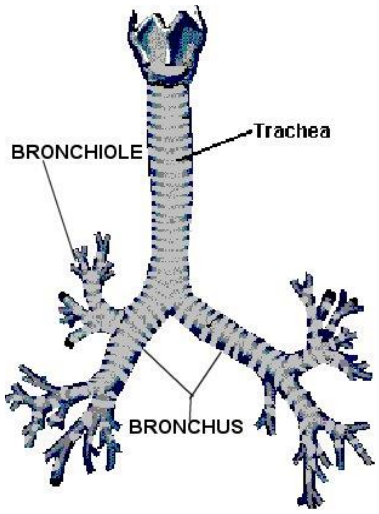
    - The free radical smade by oxygen will irritate the airway and stimulates mucous production

- Goblet cell hyperplasia and hypertrophy
- **Narrow airway lumen = Obstructive lung disease ➔ Bronchopulmonary dysplasia**

- Bronchopulmonary Dysplasia
  - common complication of Hyalin membrane disease
  - obstructive lung disease
  - Acts like asthma
    - Treated the same
  - Majority of children will outgrow O_2 by age 2 (when their lungs are almost adult size)
    - Will continue to have obstructive airway disease for the rest of their lives.
  - Artifical surfactant is used to ↓ need for O_2 and hospitalization
    - 1st give mother beclamethasone to ↑ baby's own surgactant production

- Adult disease
  - ARDS –
    - Most common cause
      - Sepsis
        - Will need intubation and ICU
        - Will have same disease course and complications as child
        - 60% mortality rate

- Aspiration Pneumonia
  - Most commonly involves the Right main stem bronchus & straight down into the right lower lobe
  - If the kid is **standing/sitting upright** and aspirates, it will go straight down to the **superior segment of the R lower lobe**
  - If the kid is **laying down** it will enter the **posterior segment of the right lower lobe**
  - Only way to aspirate into the **upper lobes** is to aspirate the foreign body while **lying down on their side**
    - Usually a seizure patient
  - Always look for foreign body in recurrent R upper lobe pneumonia
  - Diagnosis
    - Need to get Inspiratory/expiratory films
      - On inspiration everything inflates
      - On expiration one bronchus remains inflated
  - Removal
    - For a child the best way is to lay them on their stomach and performa back thrust
    - For an adult → Heimliech Manuver



- **3 Narrowings of the Trachea where objects get lodged**
  - Glottis
  - Middle of the trachea (landmark → aortic arch)
  - Bifuraction of the Trachea at T4

<u>Concept</u> ➔ Restrictive and Obstructive pattern.
Restrictive Disease = problem in the interstitium

- O_2 diffusion will be affected the most
  - diffusion and perfusion limited
- CO_2 diffuses fast so it is airway limited
  - airway problems, ventilation problems

Obstructive Disease = caused by Bacteria producing mucus

	Problem in the…	pO_2	pCO_2	pH	Cause
Restrictive lung disease • signs of :dyspnea, and tachypnea • presenting as SOB & weakness	Interstitial Can't breath in	↓	↓	↑	Everything else Virus, fungus, etc…
Obstructive lung disease • increased respiratory rate→ dyspnea and tachypnea • presenting as SOB & weakness	Airway Can't breath out	Normal	↑	↓	Bacterial Infections → Mucus Plugs

- CONNECT TO LOW ENERGY STATE & LOW VOLUME STATE
- **MCC of Death → Bronchiectasis**

- In order for the lungs to inflate in the baby you need negative pressure within the amnionic sac. Amnionic fluid is there to keep pressure off of the baby while the negative pressure inflate the lungs
  - Baby will be affected by atmospheric pressure if fluid wasn't there

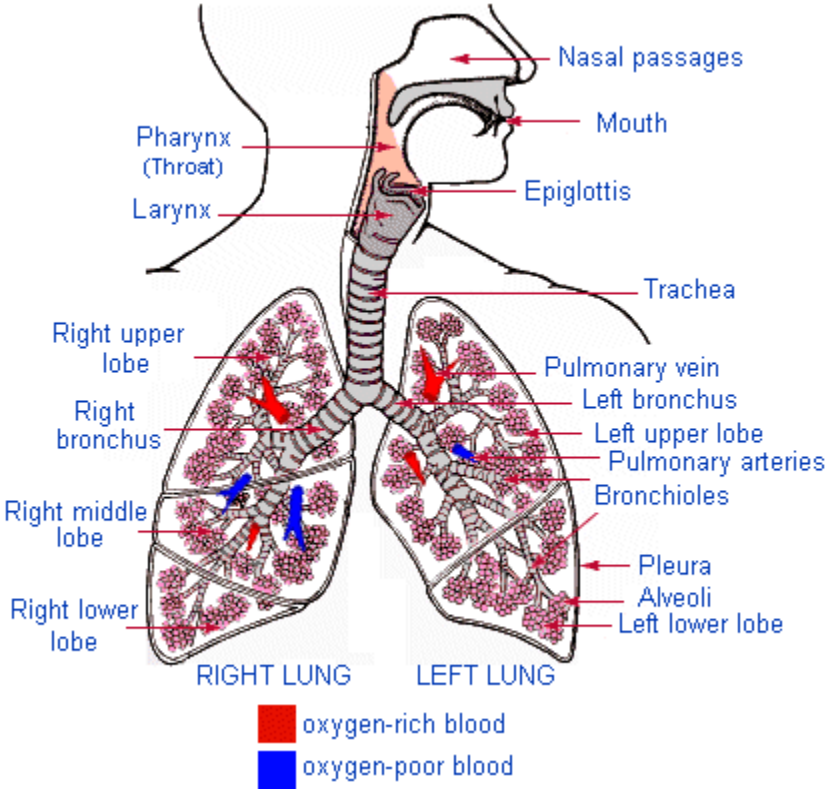
- **Amnionic Fluid**
  - Function:
    - Create negative pressure around the fetus and absorbs external trauma to the mother's abdomen
  - Composition
    - 80% is filtrate of mom's plasma
    - Baby must be able to
      - Swallow & digest → then process → adds 20% to it then urinates in the amniotic sac
- **Polyhydramnios**= baby can't swallow or absorb fluid (neurological, muscular problem, GI obstruction)
  - Mom continues to make 80% of the amniotic fluid but the baby isn't swallowing it = the baby has a Neuromuscular disease (swallowing is a reflex) or GI obstruction
    - Think of Werdnig – Hoffman Syndrome
  - Duodenal or esophageal Atresias can present this way.

- **Oligohyramnios** = Low amnionic fluid
  - Baby has **renal defect (agenesis/obstruction)** and can't pee → can't add 20%
    - Will cause increased pressure on the baby because there is no Amnionic fluid to protect the baby from any trauma
  - ***Potter's syndrome***
    - See the physical manifestation of oligohydramnios
    - ↑ atmospheric pressure will cause **facial deformity** and baby's facial features to be flattened (due to pressure) = smashed face

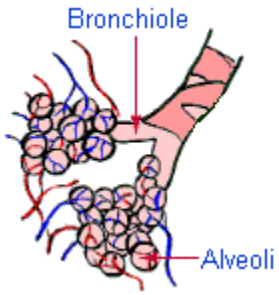
- ***Prune Belly***
  - No Abdominal wall muscles, therefore can't bear down to pee, so there is no muscle to push fluid out creating ↑ pressure and a prune like appearance in baby
  - This baby will dies of infections (UTI) because always has a catheter

Anatomy of the Lungs

- Extrathoracic (outside chest cavity) and intrathoracic (inside chest cavity) are separated by glottis.
- Breath in → Extrathoracic collapses and intrathoracic expands
- Breath Out → Extrathoracic expands and intrathoracic narrows



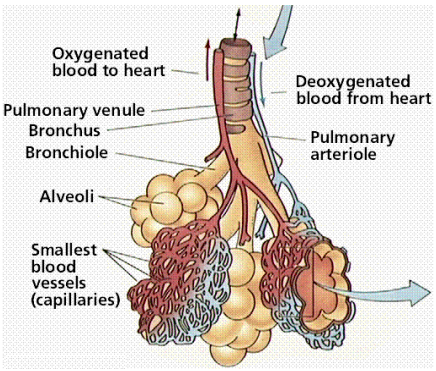
- Main stem Bronchus
  - Breaks into parenchyma ½ way and gets smaller
- After Main stain bronchi will divide into
  - large
  - medium
  - small bronchioles
- Terminal Bronchiole
  - Most dependent part of airway → therefore, most Lung Cancers like to form here
- Will deposit in the terminal Respiratory bronchiole
  - **Respiratory unit = the only 3 units where O_2 Exchange occurs**
    - **Resp bronchiole**
    - **Alveolus**
    - **Alveolar duct**
      - **made of 1 layer of epithelium**
      - **Can have O_2 exchange.**



- Physiologic Dead Space
  - Composed of all CO_2
  - Taking a deep breath can clean out the dead space

Ventilation

- Total ventilation = dead space ventilation + alveolar ventilation
  - $V_T = V_{Dead\ Space} + V_{Alveolar}$
  - $V_{Minimum}$ = TV x RR
    - Tidal Volume = 10 – 15 cc/kg
  - Example:
    - TV = 600 cc
    - RR = 12
    - V_{DS} = 40%
    - What is the ventilation in the alveoli?



- The true measure of ventilation is in the pCO_2 changes
  - If truly ventilating the pCO_2 will drop
  - Patients presenting with SOB/tachypnea are not ventilating properly
- 500 cc is not universal!!!
- One can be breathing fast (tachypnic) but not ventilating properly!!!

Management of a Ventilator

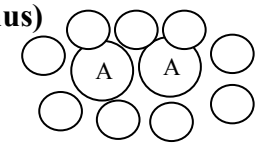
1. **How much O_2 do you want**
   a. Restrictive needs more
   b. Obstructive needs less
2. **Put in the Rate**
   a. Normal 12-16
   b. Faster → lung disease are all tachypnic (need to be higher than they already are)
3. **Tidal Volume**
   a. calculate by 10-15cc/Kg
4. **Plug in IE**
   a. No lung disease I:E = 1:1
   b. Restrictive needs more I
   c. Obstructive needs more E
   d. always in increments of 0.1
5. **Do you want to do all the breathing for them**
   a. assist control = will breath for them and monitor everything they do and compensate and assist with every breath
   b. SIMV – standard inspiratory … volume
      i. Machine will breath only when they don't
      ii. Won't assist every breath
      iii. Used for weaning off a ventilator.
   c. Pressure Support
      i. Used for restrictive lung disease (have trouble lifting chest, problem with surfactant)
   d. Measure blood gas to monitor progress.

Chest Cavity

- Diaphragm normally develops Ventral (midline) → Dorsal (back)
- **Diaphragmatic hernia=**
  - Intestines are in thoracic cavity
  - Present with bowel sounds in the chest cavity
    - See a feeding tube curled into his chest on x-ray
  - Common types:
    - **B**ochtalek (90%)
      - Herniation is in the **b**ack
    - Morgagni (10%)
      - Herniation is in the front/mid-line
  - Complication
    - **The lung won't develop because the GI/Intestines are pushing down on the lungs and can't inflate → pulmonary hypoplasia**
    - Next step is to try and close the hole
      - Need at least 90% of the lung to develop in order to live.

Lung Histology

- Trachea :
  - Top 1/3 = Squamous cells (protect against abrasion)
  - Middle 1/3 = Transition cells
  - Lower 1/3 = short colunmnar epitherlium
    - Beat upward → to swallow foreign debris and let stomach acid digest it
- **Respiratory Epithelium**
  - **Tall columnar ciliated epithelium (bottom 1/3 and into bronchus)**
- Cilia
  - **9+2 (actin microtubules) configuration =**
    - With a **Dynein Arm**



- Dynein arm
  - Allow cilia to dissengage from mucus and push it forward to move it always is only one direction → toward the mouth → orad movement
  - When cough, mucus moves 1"/ cough
  - Sinus drainage → short cough
  - Bronchitis → deeper cough...
  - Also needed in sperm
    - **Kartagner's Syndrome:**
      - **Defect of the Dynein Arm →not working = Can't clear mucus**
      - **Triad**
        - Obstruction → Bronchiectasis
        - Infertility → because sperm are immotile
        - Situs inversus (liver/ kidney on other side= **midgut rotation**)
- Common bacteria in the back of the throat
  - Strep. Pyogenes
  - S. pneumonia - encapsulated
  - H. influenza - encapsulated
  - Neisseria Cataralis - encapsulated
    - These bacteria can live in the back of throat because **they contain IgA Protease** to protect against IgA activity
    - **Therefore, they are the MCC of sinusitis, otitis, bronchitis, and pneumonia**

- Cilia prevents these bacteria from entering the lung but if the cilia is paralyzed they can enter
  - Viral infections can paralyze cilia and allow for the encapsulated organisms to come into the lung = SUPER – INFECTION

- Cell type:
  - Goblet cells:
    - Most numerous
    - serve to produce mucus
  - Type I pneumocytes (95%) –
    - mostly macrophages
    - Found mostly in terminal bronchus where all the dust will settle
  - Type II (5%) pneumocytes
    - produce surfactant
    - Found in alveoli, surrounding alveolar membrane
    - Can become type I, but can't go the other way round. (Type I can not become Type II
  - Dust/ Clara Cells
    - macrophages that ingest dust particles
    - found in terminal bronchus

  - Smooth Muscle
    - found throughout airway down to terminal bronchiole
      - Can't have anything in the way of O_2 diffusion – so will stop in terminal bronchiole
    - **Most abundant in medium size bronchioles**
      - Therefore, the most constriction and dilitation occurs here
      - analogous to blood vessels (contain the most β_2 receptors)
      - **Asthma is a small airway disease but the whezing is coming from the Medium bronchioles**
  - Cartilage
    - Tracheal and Laryngeal cartilage is of **neural crest origin** (septum)
    - Trachea has 16-20 C shaped cartilage rings
      - Why C-Shape: Opening always faces backwards so esophagus, when full can compress trachea so you are less likely to aspirate.
    - Mid main stem bronchus – start fully circling cartilage
      - Because of the lung tissue all around it, if it where not fully encircled it would collapse
    - Stops at the Respiratory unit to **allow for diffusion**
      - Terminal Bronchiole – end of cartilage (because has to be only one layer of cells)

Respiratory Infections

- Epiglotitis = closure of trachea
  - Presentation
    - Child will be drooling, stridor, muffled voice and fever
  - MCC → H. influenza B
  - Treatment
    - Must make an airway → Intubate in the ER
      - Look for thumb sign on CXR
- Croup
  - Subglottic edema similar to bronchilitis.
  - Presentation
    - Barking cough and Stridor
    - Steeple sign on neck X-ray
  - Caused by:
    - Parainfluenze
    - RSV (send to ER immediately)
    - Adenovirus
    - Influenza
  - Treatment
    - Dexamethasone
- Bronchiolitis
  - Infectious asthma
  - Includes all symptoms of asthma with acute infection
  - MC in children < 2 years old → can be able to grow out of it
  - Caused by:
    - Parainfluenze
    - RSV (send to ER immediately)
    - Adenovirus
    - Influenza
- Asthma

Intrinsic	Extrinsic
Congenital	Environmental
Cold air/Colds set this off	Offending agents Dust mites >> Roach droppings >> Pet Dander

- Emphysema
  - Digestion of interstitium by elastase
  - Treat as an OBSTRUCTIVE disease but really is a restrictive disease

- Bronchitis (URI)
  - Acute = ↑ sputem production
  - Chonic = ↑ mucous production for at least 3 consecutive months for 2 consecutive years
  - MCC:
    - S. pneumo.
    - H. influenza
    - Catarallis

- Pneumonia
  - Inflammation in the alveolus
  - MCC
    - Strep. pneumonia
    - H. flu
    - Neisseria
    - Klebsiella → currant jelly sputem, homeless alcoholic; likes fissures of lung
    - Common after flu → S. aureus
    - Actinomyces → sulfur granules
    - S. aureus and pseudomonas → bullae production d/t elastase activity (pneumatocelle)
    - Anaerobic infection – foul smelling; (+) air/fluid levels

- Tracheitis
  - MCC → Diptheria → EF-2 ribosylation = gray pseudomembrane
- Tracheomalacia
  - Stridor since birth

Lung Cancers: See Cancer lecture
- MC intrathoracic = Sq. cell → PTH secretion
- MC Primary Lung CA → Bronchogenic Adenocarcinoma
- Most common lung mass in children is:
  - Hamartoma
- Most common lung mass in adults is:
  - Granuloma

Pulmonary Sounds
- Stridor:
  - Narrowing in the **extrathoracic area (above the glottis)**
  - Inspiratory sound only
  - Moving gas through small opening
  - Problem is from Lip to the glottis
    - need a lateral neck film
    - **Macroglossia** = big tongue seen in ➔ storage disease, hypothyroidism, Down's
  - **2nd Brachial Arch problem ➔ microagnathia (small jaw)**
    - Pierre-Robin
    - Treacher Collins
- Wheeze
  - Narrowing in the **intrathoracic airway**
  - Need CXR
  - Normally intrathoracic area narrows in expiration
    - You should hear it on expiration
    - If you hear wheezing on inspiration➔ is very bad
      - Ex. CA narrowing the pathway on inspiration
    - "Musical Wheezing" – wheezing on expiration and inspiration
- Ronchi
  - Air moving through mucous

- Crackles (rales)
  - Alveoli had to be popped open → Collapsed alveoli
    - Surfactant gone
      - Pneumonia, HF, ARDS, → any fluid that will wash away
    - Scarred down (fibrosis)
- ↓ Breath Sounds
  - **Something b/w alveoli and chest wall**
  - Non-specific
- Dullness to percussion
  - **There is something between the lung and chest wall**
    - **Fluid, puss, tumor, blood… Its absorbing the sound**
- Hyperresonance
  - There is air under the chest wall
    - pneumothorax
- Fremitus
  - There is consolidation → specific for pneumonia
    - 99% gives the most vibration
    - Area of greatest vibration is where the consolidation is
- Ergophony/Bronchophony
  - Consolidation
  - "ee" → "aa"
- Tracheal Deviation
  - **Deviates <u>towards</u> atelectasis (collapsed alveoli)**
  - **Deviates <u>away from</u> pneumothorax**

<u>Lung Volumes</u>

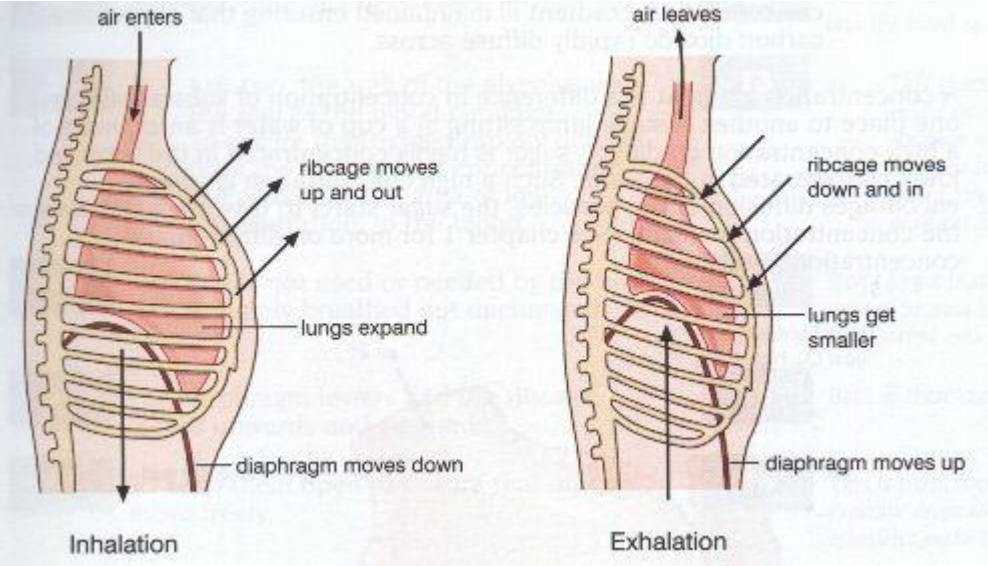
- FRC = functional residual capacity
  - FRC = RV + ERV
- IRV = Amount of air forced in
- RV = amount left in the lungs after forced expiration (cannot measure by pulmonary function test)
  - can only be calculated
  - **Keeps alveoli from collapsing**
- ERV = expiratory reserve volume
  - Volume that can be forced out (primarily from dead space)
  - **fills the dead space at rest.**
  - Sigh cleans out the air in the dead space and brings in a fresh column of air
- TV = regular breathing (10 – 15 cc/kg)

<table>
<tr><td></td><td>LITER</td><td></td><td rowspan="4">TLC</td></tr>
<tr><td rowspan="3">VC</td><td>IRV</td><td rowspan="2">IC</td></tr>
<tr><td>TV</td></tr>
<tr><td>ERV</td><td rowspan="2">FRC</td></tr>
<tr><td></td><td>RV</td></tr>
</table>

- Obstructive Disease
  - RV changes 1st = ↓
- Restrictive Disease
  - VC drops 1st; TLC drops next
  - In both TV changes last

Muscles for Breathing

- ***Breathing in (normal inspiratory effort):***
  - Innermost intercostals (contralateral chest wall)
  - External Intercostals (ipsilateral chest wall)
  - Diaphragm
- ***Breathing out***
  - Recoil
- ***Forcing air in (IRV)***
  - Scalenes
  - SCM -sternocladomastoid
  - Trapezius
  - Pectoralis Major/minor
    - All the shoulder muscles.
- ***Forcing air out, FEV_1 (only 1st 25% is effort dependant)***
  - Rectus abdominus
  - Internal/external oblique
  - transverse abdominus
  - Quadratus lumborum

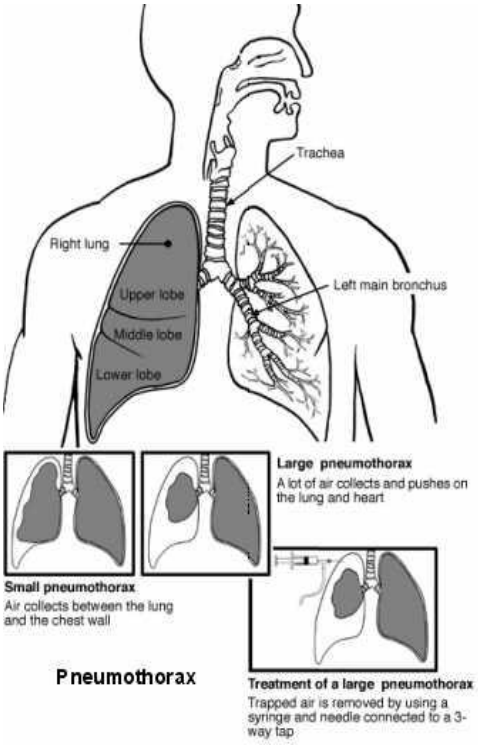


Lung Pressure

- Pleural Cavity pressure (intrathoracic) = (-) 3 → 5
  - This pressure creates a vacuum in the chest, therefore, air will always want to come in
- CVP = (+) 3 → 5
- Therefore, NO NET FLOW b/c forces are equal and opposite in direction
  - If one doesn't drop the pressure in the thorax, blood will never flow into the chest
  - Inspiration = ↓ intrathoracic pressure → ↓ lung pressure = ↑ Blood Flow to the chest
    - Must create a gradient

Pleural Cavity Pressure	**CVP**	**Result**
(-) 3 → 5	(+) 3 → 5	No net flow
(-) 10 → 12	(+) 3 → 5	Normal inspiration (Gradient made)
(-) 20 → 24	(+) 3 → 5	Deep Breath in
(-) 75	**(+) 3 → 5**	**OVER EXPAND LUNGS → Restrictive disease**

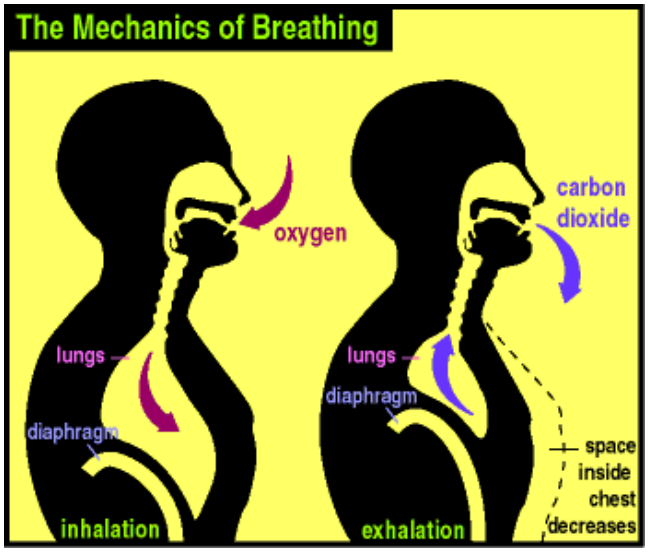
- IF there is positive pressure in the chest no gradient can be established
  - Lose pulse, blood pressure and turn blue (no blood going to the right side) = Positive pressure in the thorax is present
    - Must rule out tamponade
  - Management
    - Listen → if equal on both sides of chest = Tamponade
      - Perform pericardialcentesis
    - If not → pnuemothorax
      - If it is AIR → hyper-resonance
        - Put a needle in the 2nd intercostal space, midclavicular line
      - If blood → dull to percussion
        - Place needle in the 4th/5th intercostal space, midaxillary line



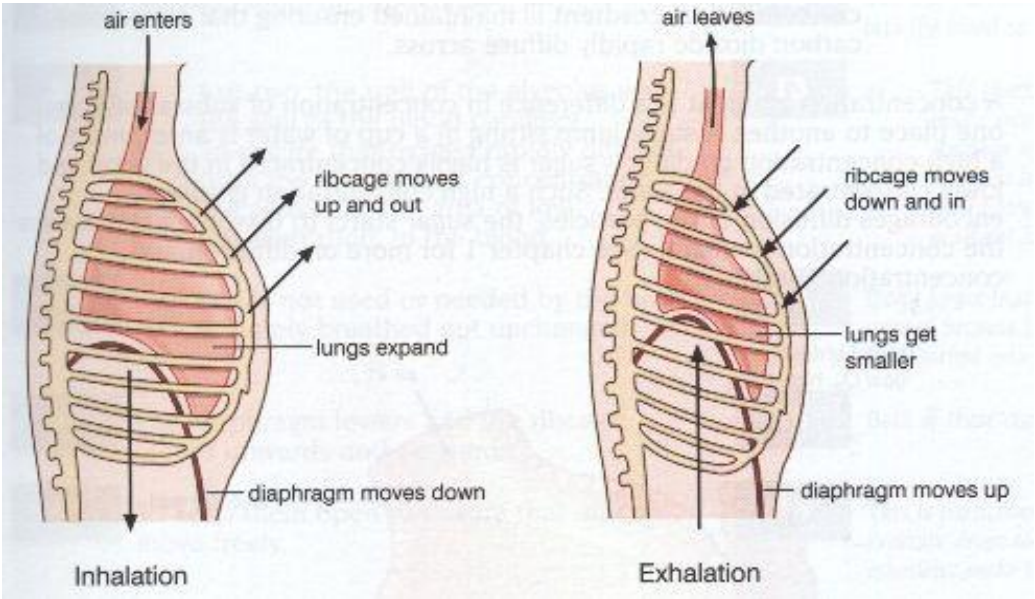
- A large negative pleural cavity pressure can create a vacuum
  - ↑ incidence of GERD/Reflux in lung disease

- **Normal expiration is passive**
  - Anything greater than 25% forced expiration is effort independent.
    - Ex. When an asthmatic breaths too hard he won't be able to get as much CO_2 out.
    - Breathing through pursed lips causes increased time in forced expiratory effort to get more CO_2 out.
  - High degree of reflux in people with restrictive and severe obstructive lung disease because very high negative intrathoracic pressure will cause stomach to go through JG junction.

Movement with Breathing:

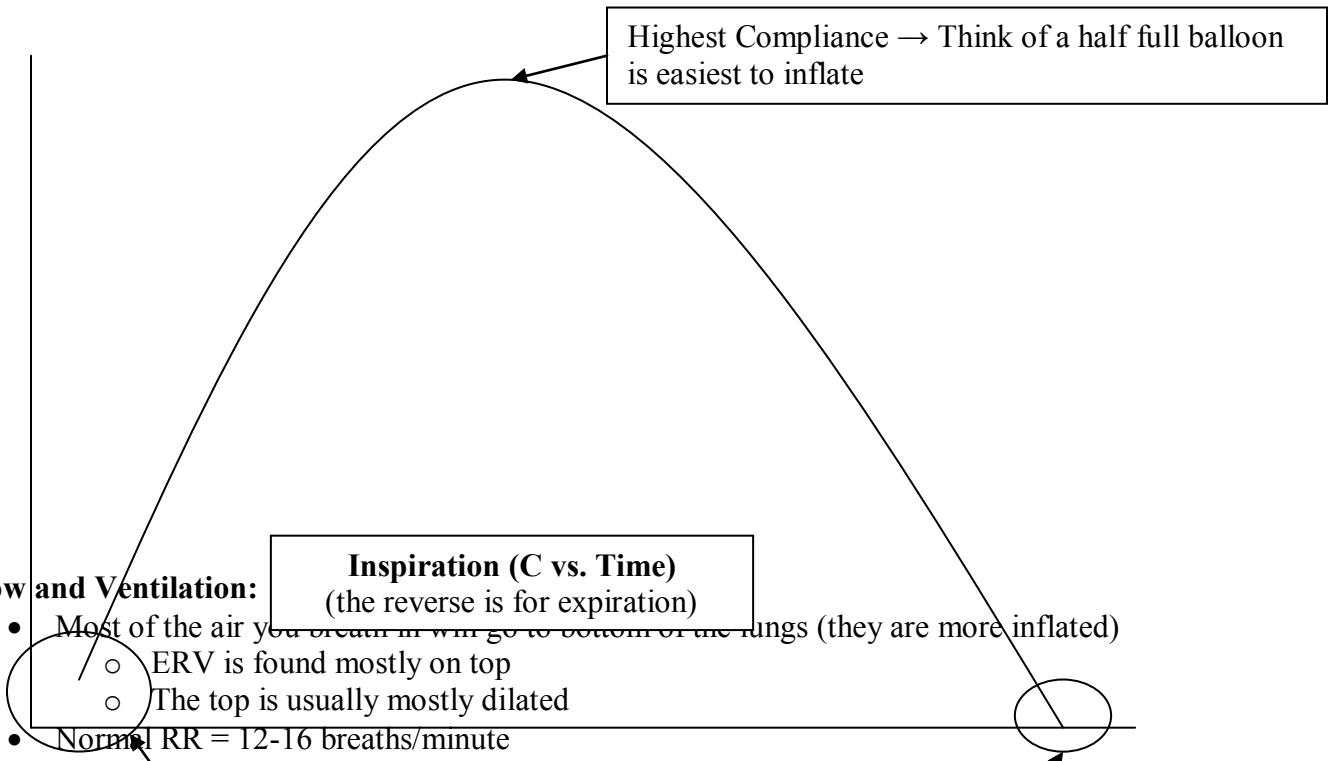


- **INSPIRATION**
  - Beginning of inspiration (1-49)– chest wall has more **expansile forces (creating the vacuum)**
  - Middle of inspiration (50-99)– lung starts chasing the chest wall (lung has more expansile forces)
  - End of inspiration – recoil of chest wall equals expansile forces of lung and that's the end of inspiration
  - If you want to ↑ TLC must overcome chest wall recoil
- **EXPIRATION**
  - Beginning of Exhalation (1-49) - ↑recoil forces of chest wall
  - Middle of exhalation (50-99%) – lung has greater recoil and separates from chest wall.
  - End of exhalation – recoil of lung = expansion of chest well → end of expiration, there is still a separation between the lung and the chest wall
  - If you want to breath in must overcome recoil of the lung



Compliance

- $C = \Delta V/\Delta P$



Flow and Ventilation:

- Most of the air you breath in will go to bottom of the lungs (they are more inflated)
  - ERV is found mostly on top
  - The top is usually mostly dilated
- Normal RR = 12-16 breaths/minute
  - Bottom of the lungs will get ventilated more, ONLY during inspiration because the lung will expand more.
  - Because there is more compliance at t… …tter ventilation norm… …as better

- Flow will always be better at the bottom
  - Because of gravity (blood will flow down from the heart)
  - Breathing in will cause ↑O2 which will dilate arterioles at the bottom → less resistance
  - Expanding alveoli at the top will compress the arterioles creating ↑ resistance.
- Flow is matched at the middle of the lung.
- V/Q is greater at the top overall because flow is less at the top.
- V/Q is greater at the bottom ONLY with inspiration.
  - **Every V/Q mismatch presents with restrictive pattern.**

<u>V/Q mismatch</u>

- ↓ pO_2
  - If bring in air with no blood flow to pick it up → ↓ pO_2
  - If bring in a lot of blood but no air → ↓ pO_2

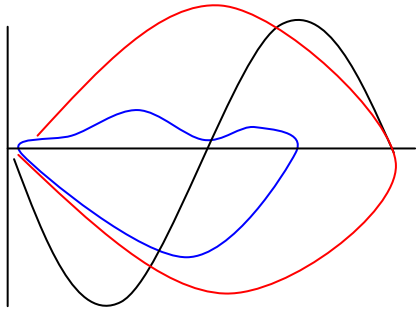
- Ex. **Neuromuscular disease will have trouble breathing in →↓pO_2 → ↑RR → ↓CO_2 →↑pH → pulmonary vasculature will constrict → ↑ pulmonary pressure → ↓ flow to the lung → ↓S_2 splitting → louder S_2 → hypertrophies RV → S_4 → ↑on inspiration → ↑ CVP, ↓ PCWP, ↓ EDV → ↓ CO & ↓ RBF**
  - Common signs: tachypnea and dyspnea.
  - Restrictive Lung disease.

A:a gradient (Alveoli:arteriole)
If ↑ = A > a = restrictive
If ↓ = A < a = Hb picking up too much O_2
PCV

- Cor pulmonale
  - RHF
- Eisenmeger Syndrome
  - Pulmonary HTN that reverses blood flow
  - Rx: Nitrous Oxide → dilates pulmonary vessels

In the Airway…

- CO_2 is not diffusion limited → Ventilation dependent
  - Top of lungs = ↓ pCO_2 in capillaries b/c blowing more off
  - Bottom of lungs = ↑ pCO_2 in capillaries b/c ↓ ventilation
    - COPDer's have a ↓ in ventilation
- O_2 is diffusion and perfusion limited
  - Mess with either of these = Hypoxia
  - Oxygen diffuses this way: Alveolar endothelium → interstitium → capillary endothelium
    - Carbon dioxide will diffuse the other way.
  - Oxygen is the most potent vasodilator
- Oxygen will flow through alveoli according to concentration gradient.
  - Ex. If pO_2 in blood is 75 → O2 in the air is 150 FIO_2)
    - Mixed expiratory O_2 is 75.
  - Person will exhale CO_2 the same as in the blood (think concentration gradient) → 40
    - As long as body doesn't make more than 80mmHg of pCO_2 40 will diffuse across, 40 will stay in the blood.
    - Double the ventilation → pCO_2 will drop in half
    - So pO_2 will increase by the same amount
    - So to get rid of CO_2, need to ↓ O_2 so that CO_2 will have more room to come out.
      - Giving O_2 to COPD patient can kill them, because it won't allow CO_2 to come out.
    - Bronchodilators are used to create more space so that CO_2 will come out more.
- At IRV $P_A = P_{ATM}$
- Pulmonary atmospheric pressure is greater than airway pressure $P_A << P_{atm}$
- End of inspiration $P_A = P_{ATM}$ at new set point
  - Airway is the only pressure than gets positive in opposition to the pleural cavity pressure.
  - Ex. Airway pressure of 20-25 is TLC of someone.
- Breathing out will cause $P_A >> P_{ATM}$
- End of expiration will go back to original $P_A = P_{ATM}$
- Red = obstructive leaving air inside
- Blue = emphysema, trouble breathing in and breathing out.
  - emphysema always presents as obstructive lung



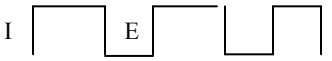
ROLE OF THE BRAIN IN RESPIRATION

- Carotid Body
  - measures
    - pO_2
    - pCO_2
    - pH
    - H+ concentration
- Aortic Body
  - Measures everything except pO_2
    - Therefore, Brain is more sensitive to pCO_2

- Hypoxia and ↑ pCO_2 are synergistic to the brain
    - These situations tell you when to take a breath or when you haven't taken a breath
- Interstitium of the lung
    - J-bodies
        - Sense stretch → fibrosis/particles in interstitium (restrictive lung disease)
        - **Stimulate Tachypnea**
- Ribs/Sternum
    - Slow adapting receptor
        - Measure expansion of chest cavity → senses stretch of ribs

- Brain is affected more by pCO_2
- Periphery is affected more by pO_2, more sensitive to hypoxia.
    - Response to hypercarbia is worse with hypoxia
    - Ex. high pCO2 and low pO2 → patient is not breathing
- Afferent (CN IX) and Efferent (CN X) for carotid body
- Afferent and Efferent are both CN X for Aortic body.
- Pons responds to the environment
- Medulla sets respiratory rate: 8-10
    - When sleeping, everything above the medulla is "asleep"
    - Therefore, one is able to breathe when "brain dead" → Thanks to MEDULLARY BREATHING
    - Brain death
        - Prove all cortical function is gone (sensory stuff)
        - Prove they will not respond to anything (pons)
            - Won't respond to ↓pCO2
        - Prove all CNs are gone
        - Prove brain stem functions are gone
        - Flat EEG
        - 2 Doctors have to agree
- ↑ obstruction during sleep → ↑TPR → RHF
    - Pickwickian = obesity causing R sided hypertrophy and HF
        - Treatment: weight loss
        - Progesterone to breath faster
        - CPAP – cont. positive airway pressure
            - (to keep airway open while sleeping, need to sleep on back.)
        - UPP – uvulopalatoplasty (hole in the back of throat that will allow airway to remain open.)
    - Obstructive Apnea = when snoring will cause R sided hypertrophy and HF
- Pons
    - Responsible for modulation →responds to environment
    - Pneumotactic
        - prevents pneumothorax makes you **breath out**
        - measures pCO_2
        - will fire when pCO2 is high
        - Obstructive lung disease
    - Apneustic
        - Senses Hypoxia → makes you **breath in**
        - Prevents apnea
        - measures pO2

        - Will fire when pO2 is low
    - pCO2
        - 90% of acid is in the form of HCO_3^-
        - ↑HCO_3^- → metabolic alkalosis → low volume state
        - 0.03 x pCO_2 is dissolved in blood → detected by pneumotactic center
        - ↑pCO_2 → high dissolved pCO_2 → will desensitize the pneumotactic center.
            - Chronic COPD → desensitize pneumotactic center, this causes pO_2 to take over the driving force for them to breathe → make themselves hypoxic on purpose
        - If you give O_2 will knock out apneustic center and kill the patient
            - Need to ↓O_2 immediately.

Normal Respirations: 

Tachypnea: 

Kussmaul Breathing: rapid deep breathing
- Metabolic acidosis → ↑ pCO_2 = breathe rapidly
- GABA connection = Slow down → deep breathing

Apneustic Lesion
- How does he breath?
    - Passive recoil

Cheyne-Stokes
- knock out the medulla
- Occurs when ↓ glucose and ↓ blood supply
    - Remove ATP from medulla (when hungry)

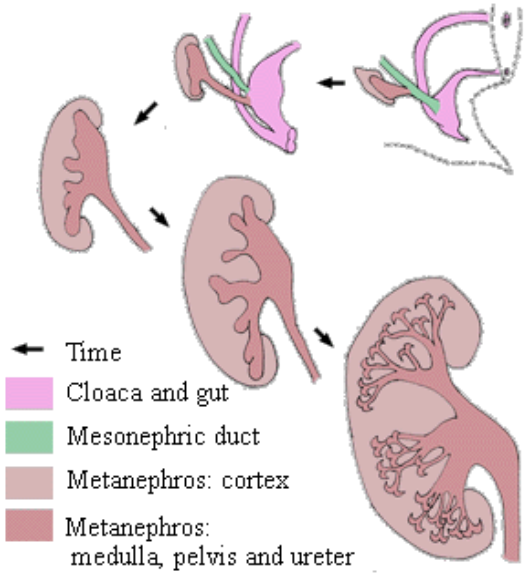
Vertebral spasm
- ↓ blood supply to medulla
- Taking a blow to the back of the head → get knocked out
- Vulcan Death Grip → Spock

Thoracic Outlet Syndrome
- Born with a extra, high cervical rib
    - When the child turns his head the cervical rib will impinge on the subclavian → a vacuum forms and forces blood to stop being shunted to vertebral artery

Subclavian Steal Syndrome
- atherosclerosis of proximal subclavian
- Once they raise their arms cut off subclavian artery → pass out
- Seen in elderly

Renal Physiology

Embryology
- Renal System develops in the 1st trimester
    - Fully functional b/c it produces amniotic fluid (20%)
- Kidney evolves from the Metanephric duct
    - Differentiate from Mesonephros which evolves into the genitalia
- The collecting system evolves from the Ureteric Bud
    - Collecting system:



        - Major/minor calyces, collecting duct, hilum, ureter
    - RULE:
        - **Uteric bud must make contact with metanephros to form the kidney**
        - Otherwise can have renal agenesis
    - Renal Agenesis
        - Metanephros not made, therefore, uteric bud did not make contact with it to form the kidney
- Bladder comes from the **allantois → urachus→ bladder**

Genitalia

- **Mesonephros**
    - Testes
    - Vas deferens
    - Seminal vesicles
    - Epididymis
- **Paranephros**
    - Ovaries
    - Fallopian tube
    - Uterus
    - Upper vagina

Male	Embryo sturcture	Female
Prostate Prostatic urethra Bulbourethral Gland	**Urogenital Sinus**	Labia vagina Labia minora
Penis	**Urogenital tubercule**	Clitoris
Scrotum	**Labioscrotal swelling**	Labia majora

- Mullerian Inhibiting Factor = MIF
    - A male requires MIF in order to develop **INTERNAL GENITALIA**
    - Any XY with internal female genitalia has an MIF deficiency
- A male must have testosterone to have **EXTERNAL GENITALIA**
    - If XY with external female genitalia has testosterone problem
- Testicular feminization
    - Penis one day → gone the next!!!
    - Disorder of the androgen receptor
- True Hermaphrodite
    - The internal genitalia does not equal the genotype
        - MIF problem
            - XX with male internal genitalia
- Pseudohermaphrodite
    - External genitalia does not match genotype
        - XX with external genitalia
- **Remember male/female is based on GENOTYPE**

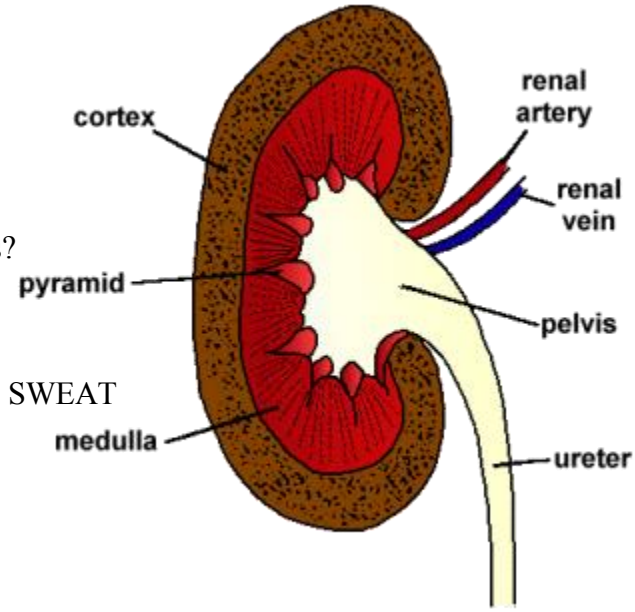
- Cryptochordism
    - Testes never descended → commonly found in the inguinal canal
        - If not descended into scrotum by 15 months = permanently injured
    - NO Leydig cells → no external genitalia → sterile
    - Management
        - Observe for 6 months
        - IF not descended refer to urologist for GnRH injections

        - IF not down in 1 year → go to surgery
            - Staple the teste down → **orcypecsy**.
            - Risk of testicular cancer
                - Yolk Sac cancer ➔ most common testicular cancer in a child
                    - (↑ α-feta protein)
- Mumps
    - Orchitis
        - d/t no more testosterone

- Testosterone
    - Needs 5 α reductase
    - **Deficiency of 5αreductase is inherited as autosomal recessive disease**
        - DHT receptor not working
    - Will present with **testicular feminization**
        - **Drugs that could cause the same thing:**
            - **Fenesteride (for BPH)**
            - **Ketoconazole**
            - **Spirolactone**
        - These drugs also can cause gynecomastia
        - **Block DHT (dihydrotestosterone) receptors**
            - **Flutamide (used for testicular CA)**
            - **Cypropterone**
        - Testicular Feminization
            - Blind pouch vagina
            - Problem will not occur until puberty
            - (Sexual identity is set by age 3)
                - Jamie Lee Curtis
    - Sertoli Only syndrome
        - No Leydig cells to make testosterone

Kidney

- Cortex
    - Keeps isotonic urine
- Medulla
    - Keeps hypertonic urine
- Why do we sweat differently in different regions?
    - Midwest → cooler climate = short nephron
        - Dilutes urine → gets rid of H_2O
    - California/any Hot area → Hot climate = SWEAT
        - Longer nephron
        - Need to hold on to water



        - There is a high solute concentrated urine therefore, need to conserve water
- The nephron will adjust and compensate in a week
    - That is why when you travel to a hot country you sweat a lot and then get adjusted as the time goes on
- In sickle cell anemia
    - The patient has smaller vessels in the medulla → lose the ability to concentrate urine and therefore, one can infarct the kidneys sooner
- Kidney Size
    - 3 x 6 x 9 inches
    - Left kidney is located at L1 (hilum)
    - Right kidney is located at L2 (hilum)
- Big Kidneys

  PCKD = polycystic kidney disease

Infantile	**Adult**
AR	AD
Unilateral	Bilateral
No Renal Failure	Renal Failure
No Hypertension	Hypertension
	↑ incidence of Berry Aneurysms → **Posterior communicating artery in circle of Willis is most commonly affected in these patients (recall that the MC is Anterior communicating artery)** CN III is the most commonly affected → subarachnoid hemorrhage(worse Headache of life)

- Congenital

Medullary Cystic	Medullary Sponge
low volume state High pH will cause Ca to ppt → kidney stones. Polyuria, polydypsia, HTN Same electrolyte abnormalities	
Sonogram will show bubbles	Sonogram will show holes
	Will have more stone formations

- Alkalotic state causes Ca^{2+} to precipitate → Hypocalcemia and Stone formation
- Small Kidneys
    - Think low flow→ **renal artery stenosis**
        - Renin splits Angio I → Angio II
        - ↓Na due to dilution effect
        - ↓Cl
        - ↓K
        - ↓H^+
        - ↑pH
        - ↑ TPR → hypertension
    - Think Low volume state
    - Common Causes
        - **Fibromuscular Dysplasia**
            - Under age 30

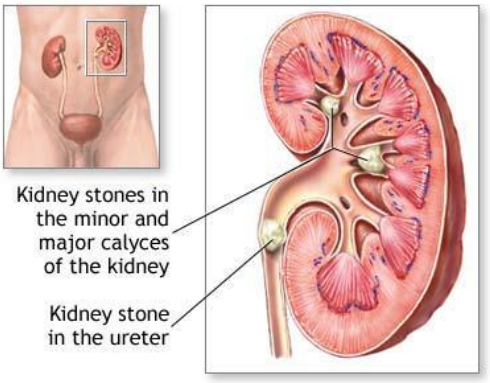
        - **Atherosclerosis**
            - Over age 40.
    - Renal Artery Stenosis
        - ↓ Blood flow because of ↑ resistance d/t vasoconstriction from the Renin system
            - Therefore, velocity ↑ in order to get through occlusion, but the contralateral kidney is not protected = Goldblatt's kidney
        - **Goldblatt's Kidney**
            - contralateral kidney is destroyed first when you have renal artery stenosis because renin will cause healthy kidney to be blasted with blood, while the affected kidney will have a clot protecting it.
            - "Flea bitten kidney" → d/t burst capillaries
            - Treatment:
                - Remove contralateral kidney (nephrectomy)
                - Remove ipsilateral blood clot (atherectomy)
            - Most common cause of secondary hypertension
    - Flow to the kidney is angiotesin II dependant
        - Severe stenosis→ can't give ACE inhibitor because they will lose both kidneys
            - Ex. Patient on ACE Inhibitor will have ↑ creatinine indicating that the reason for hypertension is renal artery stenosis.
            - ACE Inhbitors
            - Cox II inhibitors with sulfur
                - Celecoxib
            - Loop diuretics
            - Sulfonoureas
        - All have sulfur- can cause allergy
            - interstitial nephritis
            - hemolytic anemia
            - G6PD
    - ↓Angiotensin → ↓aldosterone →↓Na reabsorption → ↑Urine Na → ↓ Serum Na → ↑ depolarization
        - Also cause ↑ K → ↓ depolarization
            - Look for T wave
        - ACE also breaks bradykinin
            - Causes cough
                - Don't need to stop unless are it bothers patient.
            - Benefit of bradykinin is vasodilatation
        - Also causes proteinuria.

C1 esterase inhibitor is affected in angioneurotic edema

- Dissecting Aortic Aneurysm
    - 90% occur below the renal arteries
    - MCC = Atherosclerosis
    - Patient complains of a "ripping/tearing pain down the lower back"
    - Follow – up
        - Sonagram/CT scan → if < 4 cm in size = follow every 6 – 12 months
        - If > 6 cm = control the HTN
- Thoracic Aneurysm
    - Occurs in the aortic arch

- MCC = Trauma >> Collagen Disease
- Patient complains of upper back pain
  - Type A → Ascending
  - Type B → Descending
- Physical finding → Widened mediastinum on chest X-ray or Spiral CT
- Always control the HTN

- When a aneurysm explodes
  - Clamp the aorta and pump the heart by hand = Open heart massage
  - DO not do Chest compressions
- Ureter
- 3 Anatomical Narrowings where stones can develop
  - Hilum
  - Over the pelvic rim
  - Uretero – vesicular junction



Kidney Stones:

- Common symptoms
  - Painful hematuria
  - Colic (pain comes in waves)
    - waves are from spasms
- Common reasons
  - dehydration
- Kinds of Stones:
  - #1Ca^{2+} (oxalate phosphate)
    - Hypercalciuria
    - Normocalcemic hypercalciuria
      - Treatment = thiazides
  - #2 Struvite
    - triple phosphate, Staghorn, Ca^{2+}, Mg^{2+}, **NH_4**, Phos
    - **Urease positive bacteria**
      - **P**roteus
      - **P**seudomonas
      - **U**reaplasma
      - **N**ocardia
      - **C**ryptococcus
      - **H**. pylori
  - #3 Uric acid
    - Doesn't show up on x-ray
    - Severe flank pain (colicky pain) → pain comes in waves
    - Most common cause = **Dehydration** b/c things start to crystallize
    - Any disease with high cellular death will predispose to uric acid stones
  - #4 Cystine stones
    - Caused by 4 amino acids = **COLA**
      - **C**ystiene
      - **O**rinthine
      - **L**ysine
      - **A**rginine
    - Envelope shaped crystals
    - Look for family history

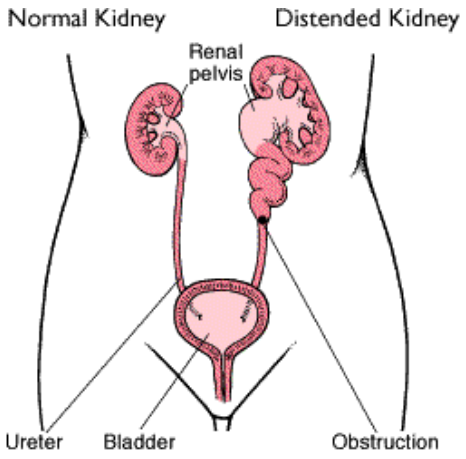
Causes for Abdominal Severe pain:

1. Pancreatitis → alcohol
2. Kidney stones → painful heamturia
3. AAA
   a. Sever pain in lower back
4. Ischemic bowel
   a. There embolus to SMA
   b. Bloody diarrhea d/t ischemia
   c. AFib

        - Prevention
            - Hydration!!!
    - #5 Oxalate
        - oxalosis
            - Normal person will not have oxalate because:
                - Usually comes from proteins break down in diet
                - Ca will bind it and will defecate it out
            - Malabsorption will cause Ca^{2+} to get stuck in the fat and won't be available to bind oxalate = saponification
            - Ex. Oxalate stones in a 3 yo white male child indicates malabsorption due to CF. In blacks its celiac sprue.
            - Ex. In a 32 yo female the most common cause of malabsorption is Crohns. Look for diarrhea in history.
    - Remember that with Chemotherapy can develop uric acid stones because of rapid cell turnover

HYDRONEPHROSIS

- **Normally**
    - Detrusser muscle acts as a functional sphincter
    - When it contracts urine cannot go back up the ureter
- Hydronephrosis
    - dialation of the ureter due causes urine to reflux and back up
    - Newborns → mal-implantation of the ureters
        - Will cause oligohydramnios
        - Treatment is surgery right away.
    - Children → UTI is the most common cause
        - 3-4 weeks post-URI → reflux
        - **Rule: 1st UTI in male or 2nd UTI in female do a GU workup not kidney**
    - Older women >40 → Most common causes
        - uterine prolapse
        - Cystocele
    - Older Man>40 → obstruction
        - BPH → bilateral



- Bladder
    - Composed of Smooth muscle
        - Acts as a physiological sphincter
    - Histology
        - TRANSITIONAL CELL EPITHELIUM
    - Able to hold 100 cc of urine before sending signals to urinate (Ca^{2+}/Calmodulin – distention)
        - If there is > 100 cc of urine in the bladder = obstruction
    - When a patient complains of "frequency and urgency" = Bladder problem
    - Embryology
        - Allantois → urachus → Bladder
    - Exstrophy of Bladder
        - Fusion of lateral abdominal walls can catch the urachus and it gets stuck
            - Therefore, a little piece of the urachus can extrude from the umbilicus

- Urachus will protrude out of lateral abdominal fold = URACHAL CYST
- Predispose to bladder CA even after surgery
- Need surgery right away

- At the tip of the bladder is the prostate
  - Which explains why BPH patient complains of "frequency and urgency"
  - Recall that the sphincters have α_1 receptors
- MC Bladder Mass = Diverticulum
  - 2 Problems
    - UTI
    - Stone development
  - Management: Surgery
- MC Bladder Tumor = Leiomyoma
  - Mid line mass
- MC CA = Transitional cell CA
  - **PAINLESS HEMATURIA**
  - **Have multiple primary lesions**
  - Treatment
    - Cystectomy and radiation
- Schistosomiasis
  - (+) Squamous cell CA d/t chronic irritation
- Posterior Urethral valves
  - **Most common cause of congenital bladder outlet obstruction in the newborn**
  - Every time bladder contracts, the valves close up
    - These valves should be in the urethra to prevent reflux.

Urethra/Penis

- Hypospadias
  - Most common urogenital/congenital abnormality
  - Normally the penis forms from dorsal → ventral (top → bottom)
    - It closes from the tip to the base of the penis (penis fuses and zips all the way down)
  - 90% of hypospadias occur in at the base of penis right next to the anus
  - Most common complication:
    - UTI (E. Coli, Proteus, Klabsiella)
      - Enterococcus is the only nitrite negative UTI

FORESKIN

Infections

- Ballanitis
  - Infection of the head of the penis. (Staph aureus)
    - Rx: Clindymycin
    - Macrolides
    - Amoxicillin and clauvanic acid
- Phimosis
  - Infection and **scarring of the foreskin at the head of the penis (tip)**
- Paraphimosis
  - Infection and **scarring of the foreskin at the bottom of the penis (base)**
    - Most common cause of circumcision:
      - Cosmetic

        - Decreased risk of UTI, and penile CA
        - Best time to circumsize is 48 hours after birth because nerves haven't developed yet
- Urethritis (UTI)
    - Infection of the urethra
    - **Dysuria by itself as a symptom**
    - Most common cause is Chlamydia (90% asymptomatic, Gonnorhea is symptomatic)
    - Rx:
        - 1 dose treatment for Gonorrhea
            - Ciprofloxacin – 500 PO
            - Ofloxacin – 400 PO
            - Gatafloxacin – 400 PO
            - **Ceftriaxone – 250 IM - DOC**
            - Cefixime – 400 PO
            - Cefoxitine – 250 IM
        - 1 dose treatment for Chlamydia = Azithromycin

If you have Gonorrhea must cover for Chlamydia

- Cystitis
    - Symptoms of:
        - Dysuria
        - Frequency
        - Urgency
            - Last two can only come from the bladder.

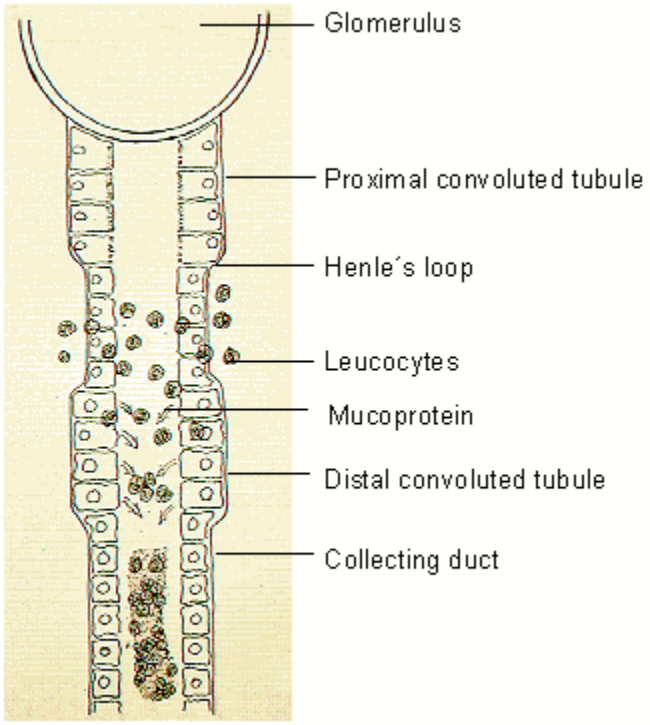
MCC for Cystitis and Pyelonephritis
- E.coli
- **Proteus → Urease (+), Struvite stones, high urine pH, swarming motility**
- Klebsiella

- Pyelonephritis →infection goes up through the kidney and into bloodstream
    - Sepsis
    - WBC casts
    - Ascending infection
- 3 Types of Nephritis (inflammation of nephron)
    - Pyelonephritis = WBC casts and sepsis
    - Glomerulonephritis = vasculitis → hematuria & RBC casts
    - Interstitial nephritis = allergy to kidney (think about drugs)

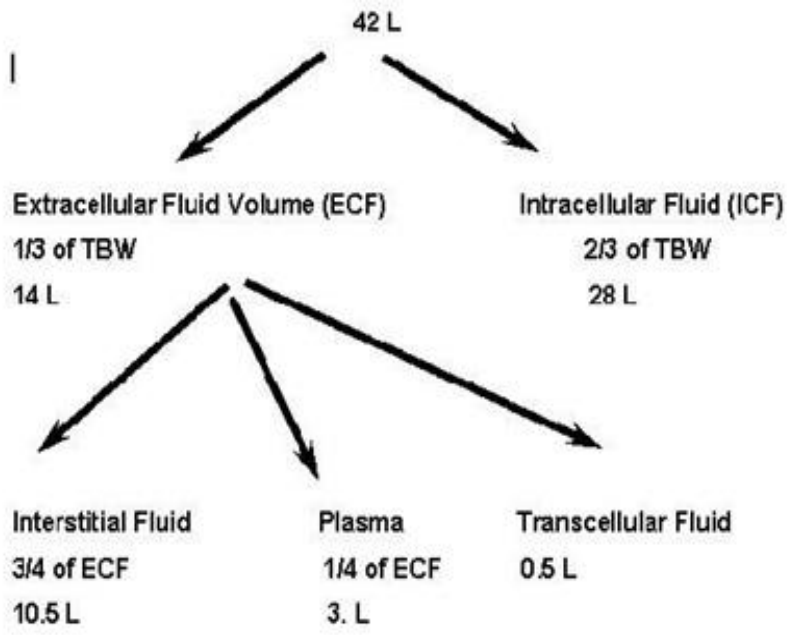
Casts:

WBC Casts	Nephritis
Pyelonephritis	Sepsis
Interstitial nephritis	Eosinophil casts
Glomerulonephritis (MCC is a vasculitis)	RBC casts Hematuria
Fat Casts (Hyperlipidemia)	Nephrotic syndrome
Waxy casts	Chronic renal failure
Normal casts 1. Hyaline casts 2. Epithelial casts	Rapidly dividing cells sloughing off. Found in the proximal tubule. NORMAL

Cresent formation	RPGN → Good Pasture's >> Wegner's



Electrolytes:



- Normal Saline
  - 154meq of NaCl/L
    - Adult**: needs 3 meq NaCl/Kg/day**
      - For 75Kg adult → 75 kg x 3 meq NaCl/kg/day= **225 meq NaCl/day**
      - Put that in 3L of urine ➔ **75meq /L needed**
        - GFR = 125 cc/hr x 24 hrs. = 3 L H_2O/day
        - 225meq/3L = 75 meq / L
      - That's why he need $D5_{1/2}NS$
        - 75 meq is ½ of 154 meq

3 L H_2O/day = 8 glasses of water/day

  - Infusion rate
    - 3 L H_2O / Day / 24 hrs. = 125 cc / hr.
    - 125 cc / hr / 75 kg = **1.5 cc / kg / hr**
  - K:
    - Adult needs 0.6-1 meq K/Kg/day
    - But it is only given in 20 meq increments, therefore, there was a need to determine a number that was divisible by 20
      - .75 x .75 = Use 60 meq/day for 75Kg adult
      - Divide by 3 L of water you need for day = 20meq of K/L
  - Run IV at $D5_{1/2}$ NS + 20 meq of K run at 125 cc/hr.
  - Pediatrics:
    - calculated weight as 35 Kg.
    - That's why give $D5_{1/4}$ NS
      - Only needs half the adult amount
  - If dehydrated you need to go to the next higher fluid

- Determining IV rate

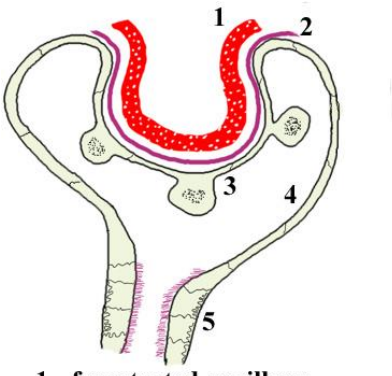
1st 10 kg →	give 100 cc / kg	40
Next 10 kg →	50 cc / kg	20
> 20 kg →	20 cc / kg	10

- If you have a 30 kg child…
  - **Give 40** for the 1st 10 kg → **add 20** for the next 10 kg → **add 10** for the last 10 kg = **70 cc / hr**

- Anyone in shock needs NS or Lactated Ringers (isotonic fluid)
  - Burn Patient
    - 1^0 = Redness → just the epidermis
    - 2^0 = Blisters → below epidermis
    - 3^0 = Neuropathy → in dermis
  - Parkland Formula
    - Determines the Deficit needed:
      - **4cc/Kg/%burn**
  - % Body burns (Rule of 9's)
    - Head and neck = 9%
    - Front Torso = 18%
    - Back of Torso = 18%
    - Each Leg = 18%
    - Each Arm = 9%
    - Genitalia = 1%
  - A burn patient's kidneys are the first to go!!!

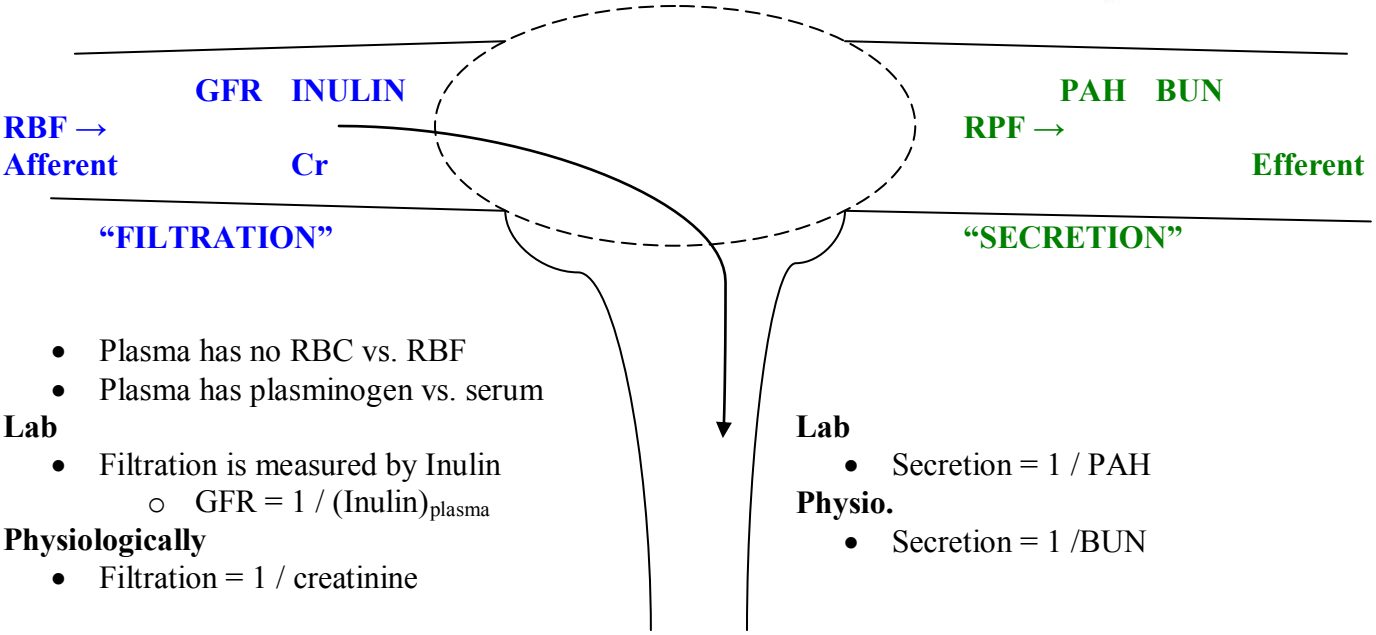
That's why burn patients need a central line
Get half the deficit in the first 8 hours
Give the other half over the next 16 hours.

Glomerulus



1 - fenestrated capillary
2 - basement membrane
3 - visceral layer (podocytes)
4 - parietal layer
5 - proximal convoluted tubule

- 2 layers of cells = Vascular endothelium with it's BM and then a podocyte and it's BM
- It has fenestrations
- Barriers in the glomerulus that prevent against proteinuria
  - **Negative charge of the BM**
    - Contains heparin sulfate
    - Albumin is a negatively charged protein there for it repels against filtration
  - **The size of the fenestrations do not allow for large proteins to get through**



- Plasma has no RBC vs. RBF
- Plasma has plasminogen vs. serum

Lab

- Filtration is measured by Inulin
  - GFR = 1 / $(Inulin)_{plasma}$

Physiologically

- Filtration = 1 / creatinine

Lab

- Secretion = 1 / PAH

Physio.

- Secretion = 1 /BUN

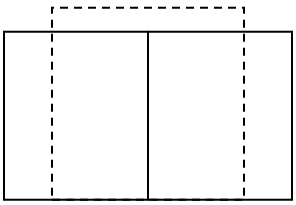
- **GFR**
  - **Measures RBF**
  - GFR = $\frac{[U_x]V}{[P_x]}$ = 20% of fluid that comes to the glomerulous.
  - 20% of 1L (RBF) = 200 cc s
  - Average Hct =45 →subtract 45% of the blood from 200 cc ➔ **125cc filtered/hour = GFR**
  - **20 – 30 L** of water comes through if left unrestricted
    - **But** the nephron can reabsorb 95% of anything that comes through → Therefore, 95% of 20 – 23 L = 3L of urine produced

Filtration Fraction (used for filtration of electrolytes)

- FF = $\frac{GFR}{RPF}$
  - RPF = Renal plasma flow

Darrow Diagrams → 1st measure the VOLUME, 2nd measure the OSMOLARITY

- Diabetes insipidus patient



Fe Na : 1-10% fraction excretion sodium
- Pre-renal <1
- renal- >10

Urine Na = 10-20 urinary sodium
- Pre-renal <10
- Renal >20

- **Renal Clearance**
  - **CL = FF – reabsorption + secretion**
    - Reabsorption – from the urine back to the plasma
  - **If CL > FF → Secretion > reabsoption**
  - **If CL < FF → Reabsorption > secretion**
- If you are secreting, you are dependant on BUN and if you are reabsorbing you are dependant on GFR. (You reabsorb what you filter)
  - Secretion and reabsorption have a V_{max},
    - Therefore, able to compete
    - Think about BUN / Creatinine ratio
  - Filtration doesn't have a V_{max}.
- We rely on filtration to get rid of most drugs
  - GFR dependant
  - To decrease toxicity of most drug
    - Need to ↑GFR
    - By ↑ RBF, by giving IV fluids.
  - Beware of giving nephrotoxic drugs to deyhydrated patients.

<u>Renal Failure:</u>

Determined by $\frac{BUN}{Cr}$

- Pre-renal Renal failure: → Low volume state
  - Initial shock
    - ↓ RBF → ↓ Clearance = NO GFR
      - Serum Creatinine ↑
      - Serun BUN ↑ because there is no secretion taking place
      - ↑ BUN / ↑ Cr = Even ratio
  - Early phase of low flow to kidney will cause ratio to ↑ overall
  - Second phase will be: Angiotensin II constricts efferent more than afferent to create back pressure to ↑ GFR
- ↓ Cr
- ↑ BUN
- BUN / Cr Ratio > 20:1 = Pre-renal problem

Renal Failure over time:

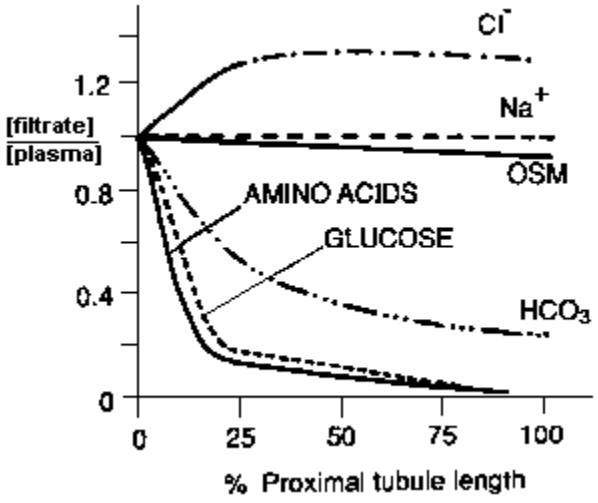
- ↓BUN
- ↑Cr
- Initially ↑ Cr but BUN will start falling.
- Then the vancomycin (or whatever is damaging the kidneys) will cause decrease filtration due to scaring and there will be **no GFR or RPF so both serum Cr and BUN will rise**. (no filtration or secretion occurring)
- Ratio is always less than 20:1
- Post renal Failure
    - "I haven't pee'd in days!!!"
    - No labs required
    - MCC in adolescent = Urethral stricture
    - Adult male = BPH
    - Adult Female = Uterine prolaspse

Renal diagnosis:

- ↑ BUN:↓ Cr = Pre-renal failure
    - 60/1.5 > 20:1
- ↑ BUN:↑ Cr = Renal Failure
    - 60/3 = 20:1
- ↑ BUN:↑ Cr = Post renal
    - 60/20 < 20:1

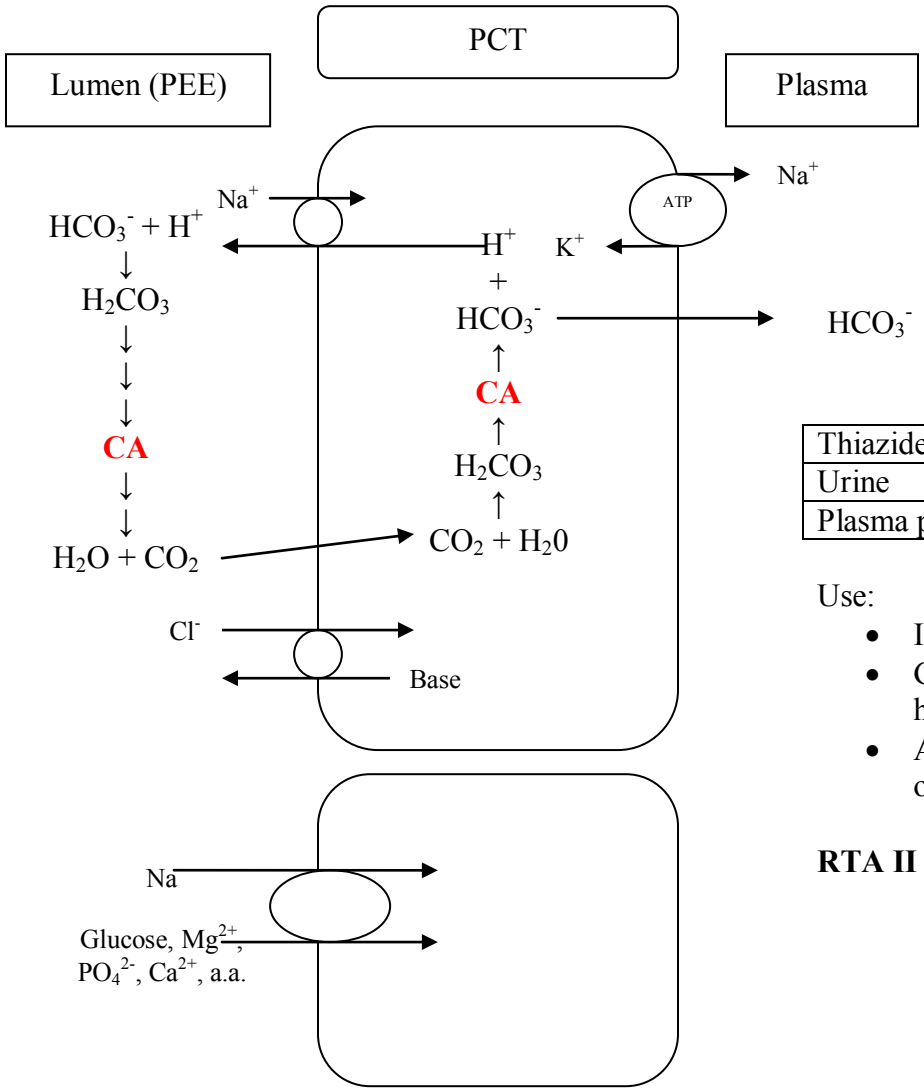
Osmolarity = 2Na + Glucose/18 + BUN/3 = 300

- Na contributes the most to osmolarity
- Directly related to osmolarity
    - Ex. High Na and low osmolarity can occur in Diabetic patient with very high BUN.
- Osmotic Diuretics
    - Methanol → forming acid → visual problems
    - Mannitol
    - Ethylene glycol → oxalate stones



Diuretics:

- **Carbonic Anhydrase Inhibitors**
  - Acetozolamine
  - MOA:
    - Nearly complete abolition of $NaHCO_3$ reabsorption in the PCT



Thiazides	NaCl	$NaHCO_3$	K+
Urine	↑	↑↑↑	↑
Plasma pH	Acidosis		

Use:

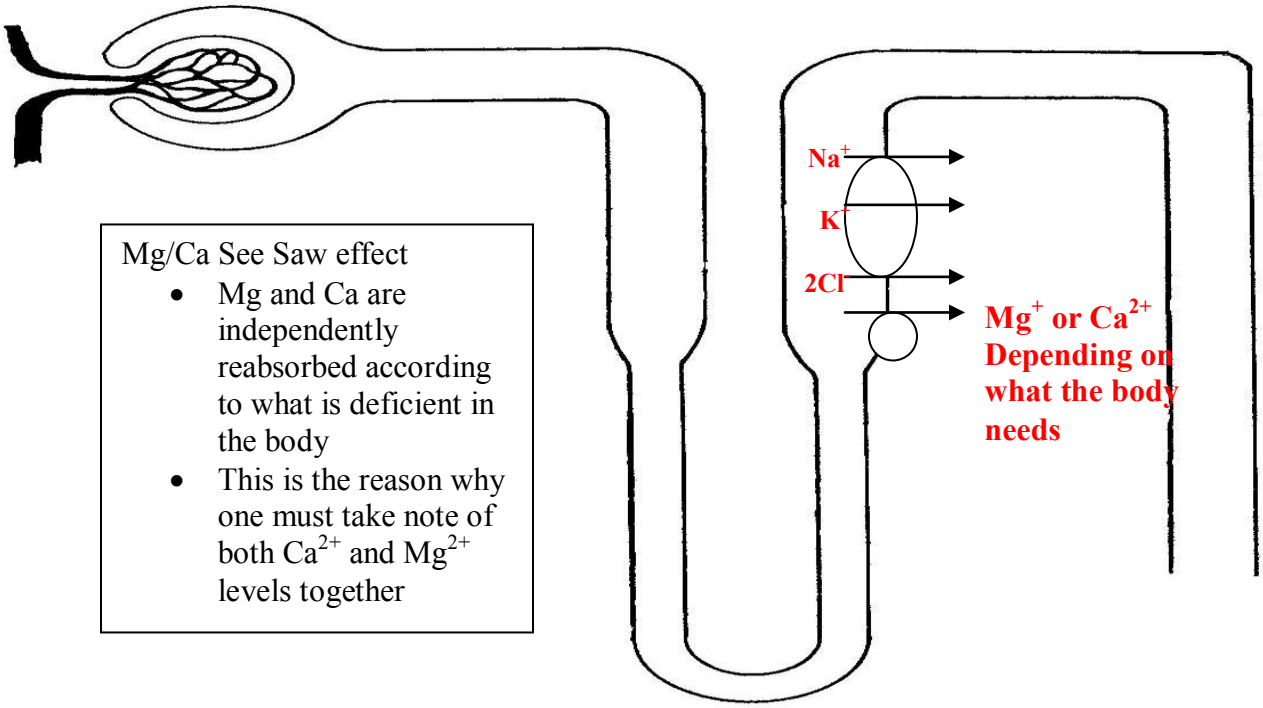
- ICP
- Glaucoma (CA involved in aqueous humor production)
- Acute Mountain Sickness (blowing off too much CO_2)

RTA II occurs here

LOOP DIURETICS = LOSE Ca^{2+}

- Must give K^+ supplements because of hypokalemia
  - Recall that at the LOOP is where 15% of ions are reabsorbed
  - Therefore, use of a loop can waste a lot of K^+
- **Furosemide (sulfonamide)**
  - SE:
    - Allergy
    - Be careful with G6 – PD patient
- **Ethacrynic Acid**
  - SE:
    - (+) Gout b/c loop diuretics are essentially acids therefore, will compete with uric acid
- **Toresamide**
- **Bumetamide**

Toxicity: **OH DANG**
Ototoxicity → reversible
Hypokalemia
Dehydration
Allergy
Nephritis
Gout



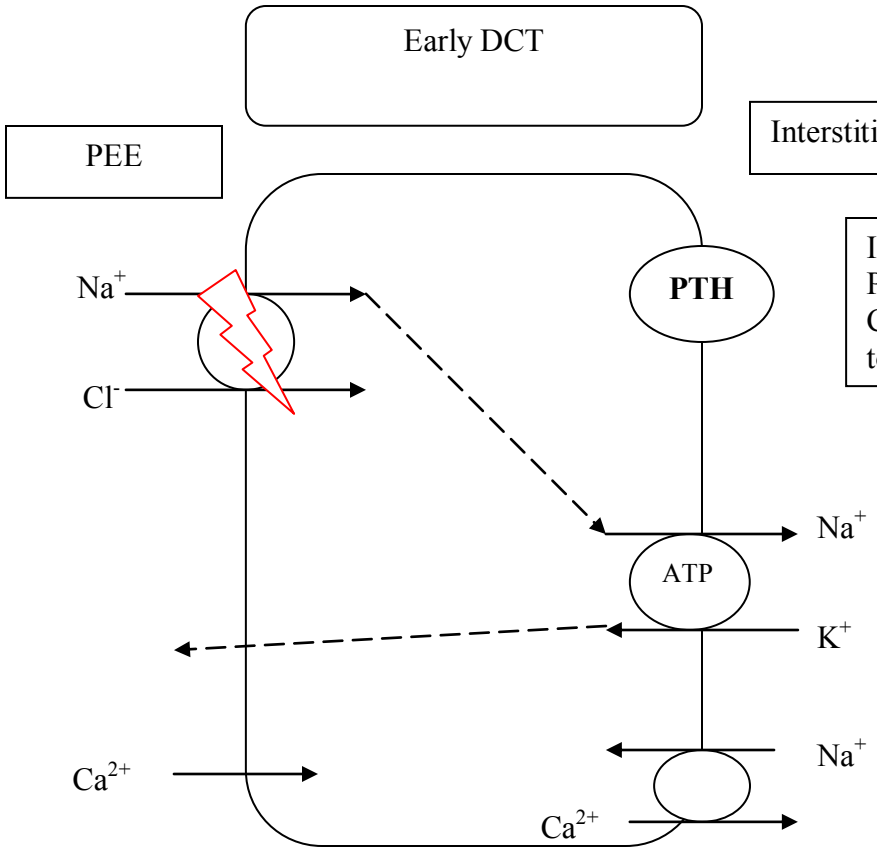
Mg/Ca See Saw effect
- Mg and Ca are independently reabsorbed according to what is deficient in the body
- This is the reason why one must take note of both Ca^{2+} and Mg^{2+} levels together

Loops	NaCl	$NaHCO_3$	K+
Urine	↑↑↑	-	↑
Plasma pH	ALKALOSIS		

- Alkalotic b/c excreting ↑ amounts of H^+ along with the others

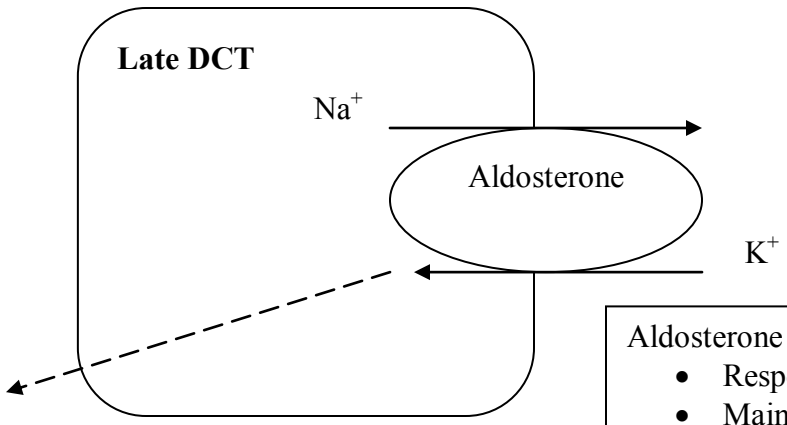
THIAZIDES

- **MOA**
  - Inhibits NaCl reabsorption in the Early DCT = ↓ diluting capacity of nephron
- **SE:**
  - Hypokalemia, Gout (these act as acids)
  - Hyperlipidemia/Hyperglycermia → Hypokalemic state inhibits insulin release (K is required for insulin)
  - Sulfonamide sensitivity
- Hydrocholothiazide (sulfonamide)
- Indopamide (sulfonamide)
- Chlorothaladone
- Metalazone



If the DCT is blocked, the work of the PCT and Loop ↑↑↑ in order to maintain Ca^{2+} → Therefore, serum Ca^{2+} ↑↑↑ due to DCT blockage

Uses: **CHIC**
CHF
HTN
Insipidus (nephrogenic)
Ca^{2+} Calculi



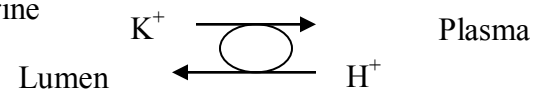
Aldosterone
- Responsible for K^+ metabolism (90%)
- Main mechanism by which hypovolemia leads to the low energy state

K^+ Sparing

- **MOA**
  - Competitive aldosterone receptor antagonist
- **Spirolactone**
  - **Inhibits 5α-reductase → gynecomastia**
- Triamterene
- Amiloride
  - Both inhibit Na/K pumps in the intercalated cells
- RTA IV is most affected in the collecting duct

<u>4 Sources of Acid</u>

- **Acid from the plasma**
  - Acidosis → hyperkalemia
  - Alkalosis → hypokalemia
    - IF these patterns differ then think about RTA!!!
    - MCC of RTA is congenital
  - **RTA I**
    - Acidosis + **hypo**kalemia (b/c can't exchange H^+ with K^+ in the **Collecting duct**
    - Can't get rid of acid in the urine because of the inability to add H^+ to the urine = ↑ Alkalotic urine
    - Predispose to…
      - UTI
      - Stones



  - **RTA II**
    - Carbonic anhydrase not working = ↓ urine pH
      - Hypokalemic b/c HCO_3^- that is not being reabsorbed is pulling K^+ with it
        - It's the charge in the lumen that draws K out!!!
  - **RTA III**
    - RTA I + RTA II BUT…
    - Urine pH is NORMAL
      - This is abnormal in the face of acidosis
      - In this case one would expect the urine pH to be low
  - **RTA IV**
    - Infarct of the JG Apparatus (usually in Diabetics) =
    - No Aldosterone release → No rennin release = ↓ Serum Na and ↑ serum K
    - Acidosis – b/c not secreting H^+ into the urine
- **Ammonia production in collecting duct**
  - Urea cycle = 10% occurring in the Collecting Duct
- **Carbonic anhydrase**
  - HCO_3^- and H^+
  - Make new bicarbonate to prevent respiratory acidosis
- **Glutaminase**
  - Breaksdown glutamine with H_2O
  - It is a source of ammonia
  - Seen in Hepatorenal Syndrome
    - Liver didn't do it's job

- **Vasculitis CONCEPT**
  - Tearing of RBC and platelets
  - Physical Manifestations
    - Petechiae
    - Purpura
    - Ecchymoses = large bruise
  - **When a blood vessel tears → CLOT FORMATION → ↓ radius of the vessel, therefore ↑ R = ↑ BP**
  - **↓ Flow to the kidney = Ischemia!!!!**

7 patterns in the kidney of vasculitis:

- **partial clot in renal artery → renal stenosis**
- **Complete clot inrenal artery → renal failure**
- **Inflammed glomerulus → glomerular nephritis**
- **Clot off medulla → interstisial nephritis**
- **Clot off Papilla →. papillary necrosis**
- **Clott of pieces of nephron → focal segmental glomerulo nephritis**
- **Clot off all the nephrons → RPGN = rapid progressive glomerulo nephritis**

The two patterns that goes with everything else:

- **Membranous → If the disease involves deposition of anything**
  - Will always be the first manifistation of disease.
- **Membranoprolifirative → deposition of anything and also autoimmune complex deposition.**
  - Ex. That's why Lupus is the only disease/vasculitis that will die from renal disease and not HF, because patient can get every possible renal complication.
  - Any chronic disease/drug use can cause depositions!!!

Berger's	IgA deposition **2 weeks after URI** **MC Nephritic syndrome in Children**
Alports	**Deafness, cataracts run in the family** IgA nephropathy
Henoch-Schonlein Purpura	IgA nephropathy **2 weeks after diarrhea** **Petechiae start from the hips/butt down** 2 Complication • GI bleeding • Intussusception – current jelly stool (blood+stool), sausage shaped mass **ONLY vasculitis with NORMAL platelet count**
Buergers	**Smoking Jewish person** **necrotizing vasculitis**
DIC	D-dimers Fibrin split products Most common cause of sepsis (endotoxin)
HUS	2 weeks after diarrhea (**E.coli/raw hamburger**) **MCC of renal failure in Children**
TTP –thrombotic cytopenic purpura	Neurological changes Triad: 1. Fever 2. Thrombocytopenia 3. Neurological changes
Polyarteritis Nodosa	pANCA Hepatitis B association in 40% of cases Affects medium sized arteries (GI/Renal)
Wegner's	cANCA involves the sinuses, lungs and kidneys at the same time #2 cause of RPGN
Post strep GN	2 weeks after sore throat **Low complement** Strain 12
DM	**Glove and stocking neuropathy** Does not have immune complexes therefore, can only progress to Focal Segmental GN
CREST =mild form of scleroderma	**C**alcinosis **R**aynaud's (spontaneous vasospasms) **E**sophogeal dismotility (due to scarring) **S**clerodactyly (tightning of fingers/toes) **T**elangectasia Clue: anti centromere antibody Mild form of Scleroderma
Scleroderma	Tightning of skin and smooth muscle Anti-smooth muscle antibody Anti – Scl70

Progressive Systemic Sclerosis	Organs are scarred up Anti - topoisomerase
Mixed Connective Tissue Disease, MCTD	combination Anti- ribonuclar protein
Goodpastures	Lungs and kidney **Anti-GBM** **#1 rapidly progressive disease** **Linear immunofluoresence**
SLE	Anti-ds DNA, Anti-smith, Anti-cardiolipin Die from renal failure Subepithelial humps
Serum sickness	2 weeks after a vaccine (especially MMR) Can be due to drugs
SBE-subachute endocarditis	septic emboli in the brain – micotic aneurysm roth spots – to retina oslors nodes – to fingers splinter hemorrhages – nail bed janeway lesions - toes Bacteria: Streptococcus Viridans Mitral valve involvement (prolapse)
MPGN	Type I → C_3 and nephritic factor in BM Type II → ↓ complement; dense deposit disease Both have a tram track appearance
Cryoglobulinemia	IgM Acute inflammation only Non-bacterial Influenza Adenovirus Mycoplasma Hep B EBV
RA	anti- IgG Most common arthritis in middle age females 1. symmetrical 2. polyarthritis (many joints affected) 3. Involves synovium/Pannus 4. Worse in A.M. 5. Periosteal erosions on side of the bone.

JRA Stills Disease	2/3 are Rheumatoid Factor negative – good prognosis Iridocyclitis – inflammation of iris and circular muscles of the eye.➔ very bad complication Need to see opthamologist every year. 1/3 who are RF positive rampant disease poor prognosis Affects Pannus (**sinovial** lining)
Feltys RA + leucopenia + splenomegaly	
Becets RA + GI ulcers	
Sjogrens RA+xeropthlmia/xerostomia	Anti- Ro, la, ssa ↑ incidence of heart block in newborns
Sicca	Without RA
Syphillis	Obliterative endarteritis d/t gumma deposition
Leukocytoclastic	Drug allerf=gy
Churg Straus	Necrotizing vasculitis d/t parasites in the lungs See ↑ eosinophils Idiopathic
Takayasu	Pulseless Japanese Woman
Kawasaki	Only one with a HIGH platelet count Japanese children Strawberry tongue Rash on the PALMS & SOLES!!!
HTN	MCC of Vasculitis in adults!!!

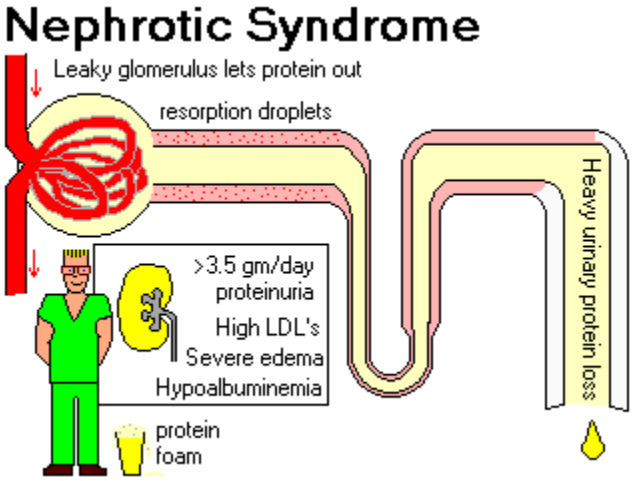
Proteinuria:

2 barriers exist to prevent proteiunuria

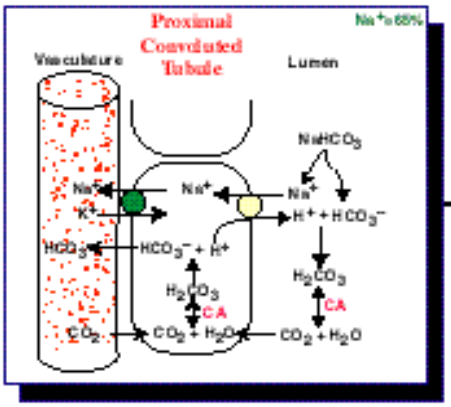
1. neg charge of basement membrane
    a. made of Heparin sulfate to repel albumin
2. Size of the pores is too small

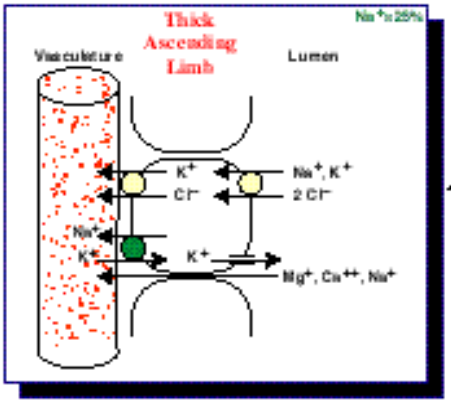
Proteinuria:

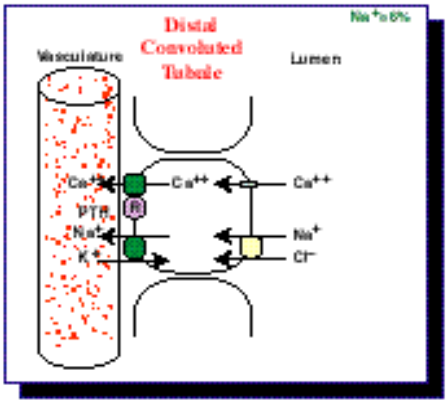
Benign (1+, 2+)	**Malignant (3+, 4+)**	
No renal disease	**Renal disease**	
Orthostasis –standing up Why first collection urine isn't wanted.	24 hr urine collection	
Exercise	Nephritic < 3.5 g/24° Lost BM charge	Nephrotic >3.5g/24° lost BM charge and BM has deposition (pores larger now)
Fever	Proteinuria	Minimal Change (0-21 year olds) -foot process fusion
	Hematuria	Membranous (adults) = MOST COMMON -any deposition disease
	RBC Casts	Focal Segmental Glomerular Nephritis, FSGN (Black/Hispanics – due to HTN) Focal Segmental is the only one with nephritic pattern
	Hypertension – due to agiotensin	6 Nephrotic syndrome with immune complexes, so use up a lot of complement: 1. SLE 2. PSGN (post strep) 3. Cryoglobulinemia 4. Serum sickness 5. MPGN (membrenoprolifirative… look for tram tracks) a. Type I – C_3 and nephritic factor are seen b. Type II – low complement level 6. SBE (Strep. viridans, staph aureus)
	Every nephritic syndrome is a vasculitis	↓ Albumin, ↓ oncotic pressure, edema, ↑ lipid/cholesterol, Fat casts

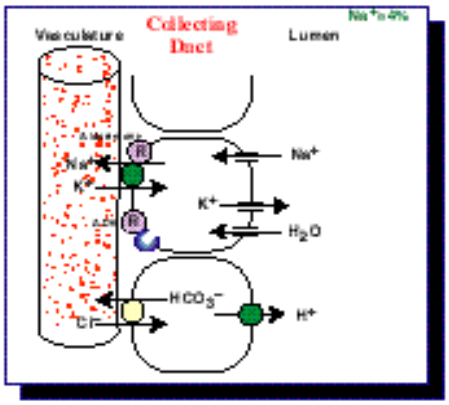


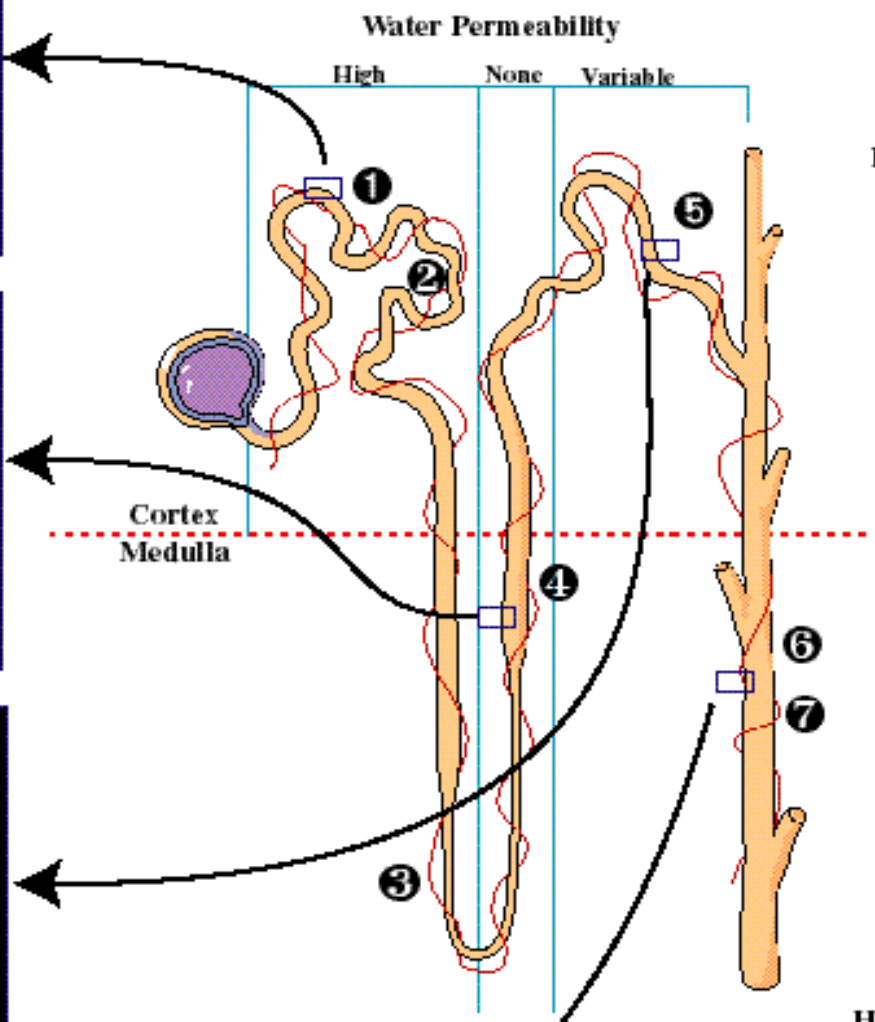
Renal Physiology and Diuretic Sites of Action





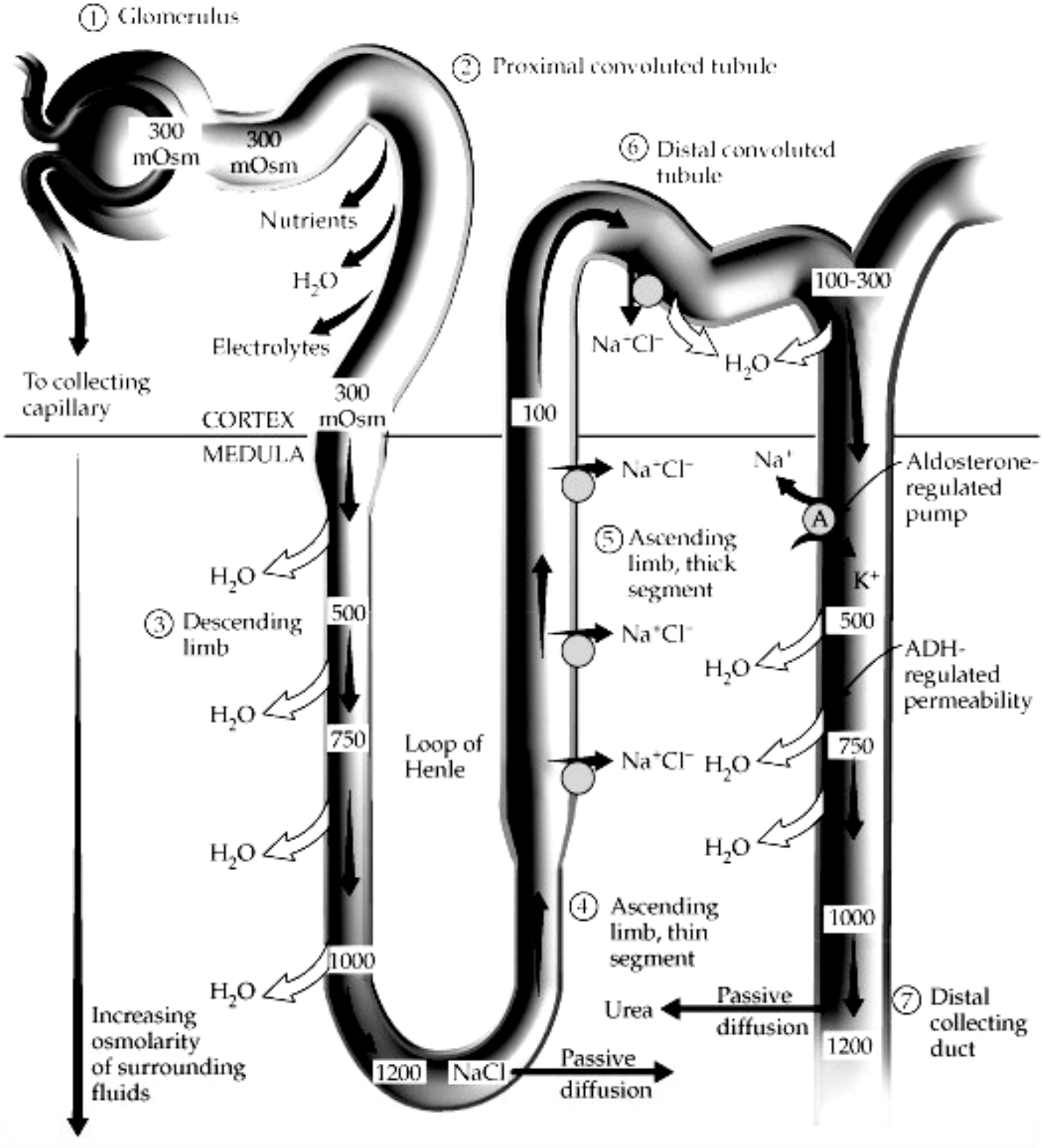






Legend	
	Vasculature
	Active Transport
	Transporter
R	Receptor
	Water "Channel"
ADH	Antidiuretic Hormone
PTH	Parathyroid Hormone
CA	Carbonic Anhydrase

Diuretic	Site(s) of Action
CA Inhibitors	1
Thiazides	5
Loop Agents	4
Osmotic	2, 3, 7
K^+ Sparing	6
ADH Antagonists	7


1 Glomerulus
2 Proximal convoluted tubule
300 mOsm
300 mOsm
Nutrients
H_2O
Electrolytes
To collecting capillary
CORTEX
MEDULA
300 mOsm
6 Distal convoluted tubule
100-300
Na^-Cl^-
H_2O
100
Na^-Cl^-
Na^+
Aldosterone-regulated pump
A
5 Ascending limb, thick segment
K^+
H_2O
500
3 Descending limb
Na^+Cl^-
500
ADH-regulated permeability
H_2O
H_2O
750
Loop of Henle
Na^+Cl^-
H_2O
750
H_2O
H_2O
4 Ascending limb, thin segment
1000
H_2O
1000
Passive diffusion
Urea
7 Distal collecting duct
Increasing osmolarity of surrounding fluids
1200
NaCl
Passive diffusion
1200

GI Physiology

All about digestion

Divide into phases:

1. Cephalic
2. Oral
3. Pharyngeal
4. Esophageal
5. UGI
6. LGI

Cephalic Phase:

- Role of the brain
  - ***Limbic System***
    - Controls urges
  - ***Cerebrum***
    - Can overcome limbic system
    - Can enhance the limbic system.
  - ***Hypothalamus***
    - **Hunger Center (lateral nucleus)**
      - Controlled by low glucose
      - Low glucose (Hypoglycemia) → ↑Firing of hunger center
        - This center can be stimulated by the sight of food → therefore can always feel hungry
      - **Stimulated 20%** of the time
        - Lesion:
          - Die of **anorexia → because no longer have "hunger signal"**
          - Could be associated with Anorexia Nervosa/Body dismorphic
            - Anorexics feel they are not thin enough
            - Patient trying to please the mom – look for executive mom type- hard to please.
            - Treat with SSRI to get at hunger center
    - **Satiety Center (medial nucleus)**
      - ↑ Glucose (Hyperglycemia) → ↑ firing of satiety center
      - Stimulated 80% of the time
        - Lesions/Abnormalities:
          - Die of Hyperphagia = overeating.
          - Could be associated with Bullimia
            - Girl trying please boyfriend.
              - Signs to look for:
              - Abrasion of knuckles
              - Loss of enamel on teeth

Male – 5" 106 lbs
Female – 5" 100 lbs
5 lbs/in + 15 lbs → moderate frame
5 lbs/in + 30 lbs → large frame

- **Neurotransmitters**:
  - Neurotransmitters in the hypothalamus are NE and Serotonin
    - NE & Serotoin can contribute to both centers
  - **Amphetamines will cause ↑ release of preformed catecholamines so NE and Serotonin levels will go up and hit satiety center → won't be hungry**.

  - Amphetamines Examples: → release of catecholamines

All of these can undergoe Anaphylaxis = Rapid Tolerance

    - Dexatrim – OTC diet pill
    - Methylphenidate
      - **Ritalin – used in ADD**
      - Used to treat narcolepsy,
      - Used to treat depression in the elderly.
    - Pemoline – used for ADD
    - Adderal - used for ADD
    - PCP – will become violent and **(+) Nystagmus**
    - Ecstacy – abused on the street
      - Will cause patients to feel
        - Superhuman
        - Dehydrated

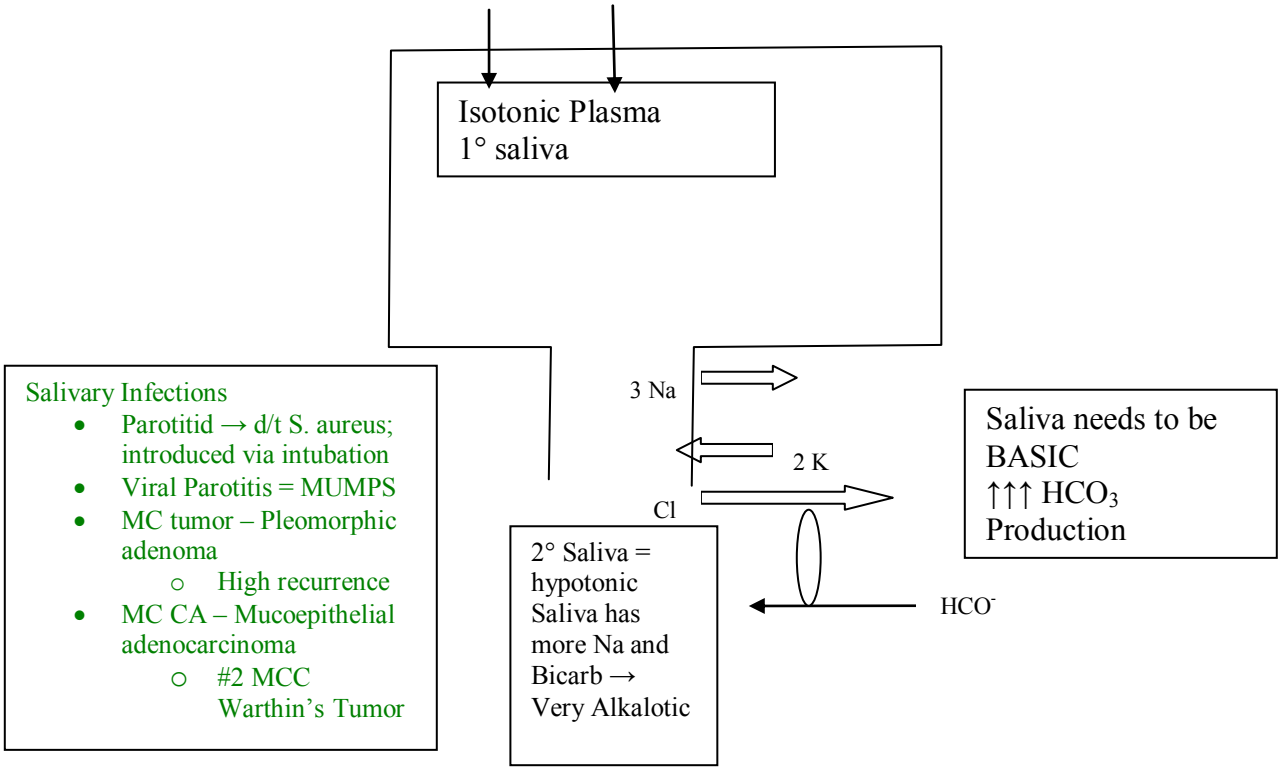
- Obesity is considered 20% over ideal body weight
- **Situations that act like a lesion to the satiety center → hyperphagia**
  - **Prader-Willi**
    - Trinucleotide repeats
    - Genomic imprinting (all paternal genes) → unipolar disomony
    - Chromosome 15
    - Huge Appetite
  - **Angelman's (all maternal genes)**
    - Inappropriate laughter
    - Acts like lesion in Satiety center.
  - **Menstrual Cycle**
    - Progesterone will ↑ hunger (↑appetite before menses)
      - Pica = taste for strange combination
    - Testosterone has the sequence of progesterone in it causing ↑ hunger in males.
  - Smell
    - Stimulates the cortex → (+) CN X → (+) GI contraction
      - All sensory input to the GI is via CN X (vagus)
    - Vagotomy → will never enjoy food again
- ***Pineal Gland***
  - Measures circadian rhythms in response to light
    - ↓ Melatonin with light
    - ↑ Melatonin with dark
  - Rhythms of the day:
    - 1st 8 hours:
    - Catabolism in the morning
      - Take vitamins
      - Exercise in the A.M. to burn most fat.

- 2nd 8 hours –
  - Mixture of catabolism and anabolism
- 3rd 8 hours: (Night time)
  - Catabolism is off
  - Anabolism is on
- Getting ready to fall asleep.
  - Explains "Jet lag", gain weight if eat in evening…

Think SZs, irritable bowel syndrome (stress response with depression, tx, with tricyclics), Cushings triad.

- **Stress Response**
  - Anytime the body senses stress, sets off the same reflex
    - **1st Parasympathetic → 2nd Sympathetic discharge**
      - "You scared the shit out of me!!!"
      - ↑ GI motility
      - ↑ GI acid output
    - Sympathetic➔↑vasoconstriction in GI and skin
      - Stress ulcer (GI doesn't have blood supply to protect itself)
      - Ex. Hospital protocol- Patients in the ICU need to be on H_2 blockers.
  - **Parasympathetic ALWAYS precedes SYMPATHETIC**
    - Ex. Point and Shoot:
      - Parasympathetic for erection
      - Sympathetic for Ejaculation.
  - Oral
    - Salivary Glands
      - Parotid (90% by weight)
        - Stenson Duct
          - Behind third molar
          - Shoot out saliva unto tongue
        - Always guess parotid involvement if there is an **infection/ tumor**
        - M/C tumor is Adenoma
        - **Mostly water/serous saliva, most watery**
        - Innervated by CN IX
          - All other salivary glands are innervated by CN VII
      - Lingual
        - **Mostly serous saliva > than the Parotid**
        - Innervated by CN VII
      - Sublingual
        - **Mostly mucous saliva > submandibular**
        - M/C cancer is Mucoepidermoid CA
        - Innervated by CN VII
      - Submandibular
        - **Mostly mucous saliva**
        - M/C cancer Mucoepidermoid CA
        - Innervated by CN VII

- How Saliva is made:
  - Saliva needs to be basic for 3 reasons: Acidic Food, Bacteria fermenting glucose to lactic acid, and reflux



    - Reflux → Normal phenomenon
      - GERD –with symptoms
      - Esophagitis
        - What you see on a scope
        - look for T cells, **macrophages in raw spots**
  - Barrett's:
    - **squamous cells become tall columnar cells**
    - Cells undergoing **metaplasia**
    - **10% Risk of Adenocarcinoma. (NOT squamous)**
  - Mallory-Weis syndrome
    - Superficial mucosal tear of Esophagus from **wretching or vomiting**
      - Alcoholic
    - If it perforates moves onto become Boorhaave's
  - Boorhaave's
    - Total perforation of esophagus
      - 90 % of perforations occur on the left side of the esophagus
    - Will get L pneumothorax and L pleural effusion
      - acid eating away in lungs
    - Hamman's Sign = Subcutaneous emphysema
      - Because trachea deviates to right
      - Esophagus deviates to left.

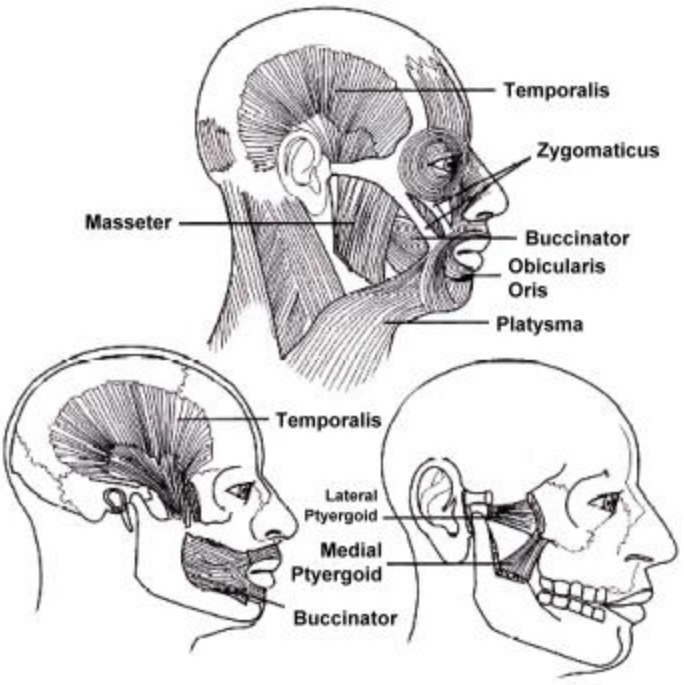
- Parasympathetic stimulation
  - will produce more saliva
  - this saliva will have ↑ osmolarity, (more salt)
    - But it can't be more than 300 mOsm
    - Can't be hypertonic → Because saliva goes through very fast
  - Drugs will do the same thing as parasympathetic stimulation:
    - Cholinergics:
      - Ach
      - Methacoline → used in diagnosis of asthma
      - Pilocarpine → glaucoma
      - Bethamecol
      - Carbachol → post-op urinary retention
- Sympathetic Stimulation
  - Vasoconstriciton = ↓ salivary production because blood is being shunted away, however, the blood will be thick and ↑ Na concentration
  - NE → α>β
  - Epi → β>α
    - Pseudoephedrine → incontinence
    - Phenyepherine → tx: for neurogenic shock → vasoconstricts arteries

- Saliva also secretes IgA
  - Used to coat bacteria in the mout from food you eat → provides protection
- Also secretes Lysozyme
  - Acts as a detergent
  - Prevents adhesion to the teeth
- Lipase
  - Fat digestion begins in mouth, but that is **negligible**
- Salivary Amylase
  - Start **Carbohydrate digestion**
  - Carbs will be digested by **brush border disaccharidases**:
    - Lactase –
      - Most common **SECONDARY dissachridase deficiency**.
      - 1st enzyme to disappear with diarrhea.
      - Will stop producing at age 4 → lactose intolerance
    - Sucrase
      - The most common **PRIMARY (congenital) dissachridase deficiency**
    - Maltase
    - α- dextrinase
  - Break down products:
    - **Lactose = glu and gal**
    - **Sucrose = glu and fru**
    - Maltose = 2 glucose and α 1,4 linkages
    - α– dextrins = 2 glucose w/ α 1,6 linkage

- ***Cystic Fibrosis:***
  - Cl/ HCO_3 protein is defective
  - Autosomal recessive inheritance
  - Chromosome 7
  - CFTR Gene
  - Present in lungs, pancreatic duct and epidydymis
  - Recurrent lung disease, diabetic, ↓ absorption, sterility.
  - Thick secretions because Cl will remain in saliva and bind Na to produce more salt in saliva
    - Check for salt
    - Normal<20
    - Hetero 30-60
    - CF >60
  - Lungs:
    - Clog up with mucous
    - Newborns will have thick meconium → meconium ileus
  - Present with:
    - maconium ileus
    - Malabsorption
    - **Predispose to Oxalate kidney stones**
    - Lung disease.
    - Steatorrhea = fatty stools/ oily diarrhea
      - Low E state
        - ↓ Serum Na
        - ↓ K
        - ↓ pH
        - ↓ Ca
  - Need to cover for pseudomonas and Staph infections.

- Teeth
  - Incisors → CUT
    - Central - 1st to come in at 10-12 months (central)
    - Lateral come in at 12-15 months (paracentral)
  - Bicuspids → CHOP
    - Come in at 15-18 months
    - 2 sets (→ 16 total teeth)
  - Molar → Grind
    - 2 years of age
    - 20 teeth by age 2.
  - Baby will start to drool when teething, Will bite nipples when breast feeding.
  - Teeth after age 8 are permanent (not desidual), need F and Ca.

- Muscles of **M**astication
  - Te**M**poralis – Moves jaw back and forth, **closes mouth**
  - **M**asseter (cheek) – close mouth
  - **M**edial Pterygoids – close mouth
  - Lateral Pterygoids – opens the mouth
    - All innervated by CN V_3
    - **Derived from the 1st Branchial arch**
  - Buccinator
    - **Slides jaw sideways**
    - Behind the masseter
    - NOT MASTICATION

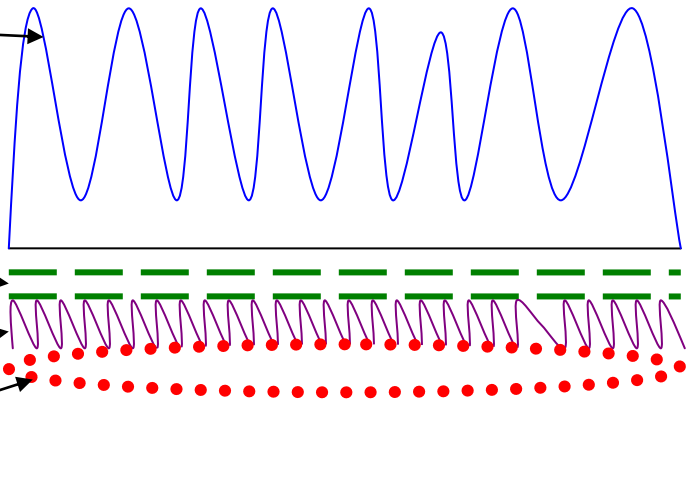


- Swallowing:
  - Tip of tongue move up
  - Sides move up and medial (form a gutter)
  - Tip goes to hard palate
    - Gravity will cause bolus to start rolling toward throat
  - When bolos reaches glottis → epiglottis closes off trachea
  - Bolus roles over the epiglottis
  - Bolus touches posterior pharynx
    - CN IX senses upper 1/3
    - CN X sense lower 2/3
  - Posterior pharynx come down and medial to finish off gutter
    - bolus enters the esophagus
    - The soft palate lifts
      - CN V – mandibular branch → (+) Tensor veli palatini
- Esophagus
  - **Upper 1/3 has skeletal muscle**
  - Voluntary activity
    - **UES – made up of 4 muscles**
  - Superior and middle pharyngeal constrictors (90% of UES)
    - A few fibers from lower pharyngeal constrictor
    - A few fibers from stylopharyngeous muscle.
      - Innervated by CN IX
    - **Gag reflex controlled by CN IX and X**
  - Smooth muscle bottom 2/3
    - Ex. nucleus ambiguous lesion will not have a gag but will have peristalsis, needs to be fed by tub (JG…)
    - Ex. Dorsal motor nucleus lesion, will have a gag but not peristalsis, can still be fed because of the **Ca/calmodulin system**. Need to eat small meals. happens in diabetic neuropathy.

UES innervation: Nucleus Ambiguous (Gag Reflex)

Innervation Dorsal motor nucleus of X

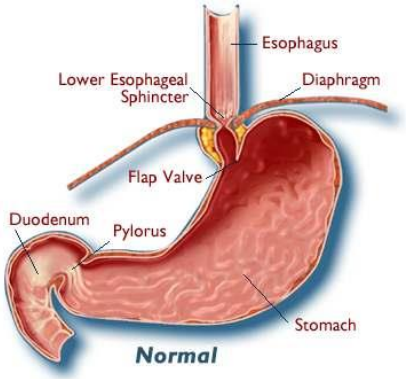
Mucosa:



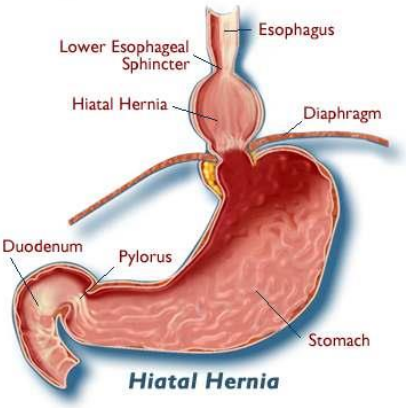
- Muscularis Muscosa
  - In contact with food
  - Also, sm. Capillaries
  - ↑ digestive Surface area
- Lamina Propria
  - Arterioles
  - Lymphoid Tissue
- Submucosa
  - Large lymphoid tissue
    - Peyer's Patches
  - Meissner's Plexus
    - Sensory Info
- Muscularis Externa
  - Inner circular → responsible for peristalsis
  - Outer longitudinal
    - Auerbach's Plexus
      - Inhibitory fxn → inhibits GI contraction
      - Uses VIP to relax
        - Transmits signal along GI tract
        - Has the most Gap Junctions
- Peristalsis
  - 2^0 Peristalsis
    - Can begin anywhere in the GI
    - It finishes "milking" the food down
  - Small Intestine
    - 1^0 peristalsis → **Segmentation**
    - 2^0 peristalsis → **Migratory Myenteric Complex**
  - Large Intestine
    - 2^0 → Haustra
  - Colin
    - 2^0 → Mass Movement
- Pathology
  - Diverticuli:
    - Zenckers
      - Above UES = Congential
    - Traction
      - Below UES and below LES → traction
    - ***Presentation:***
      - ***Coughing up undigested food.***
      - ***Malodorous halitosis.***
  - Esophageal atresia with distal TE fistula
    - Blind pouch at top of esophagus.
    - **M/C congential esophageal problem**
    - ***Presentation:***
      - ***vomiting with first feeding***
      - ***Look for big gastric bubble on X-Ray***

        - ***In utereo → oligohydramnios***
- Choanale atresia
    - membrane that **connects to pharynx** does not dissolve
    - **Choanale- space between nostrils and pharynx**
    - Presentation
        - **turn blue when they feed**
        - **turn pink when they cry**
- H-type TE fistula
    - ***Presentation***
        - ***coughing and choking <u>with each feeding</u>***
        - ***milk drips into trachea***
        - sometimes will have milk coming out of nose
- Achalasia
    - Lack of **aurebachs plexus** (ganglia) in lower esophagus
    - **GI tract will contract but won't relax**
    - ***Presentation:***
        - ***Will start chocking and gagging when start on cereal (but ok with milk)***
        - ***Look for Bird's beak on Barium Swallow***
    - Diagnosis
        - Monometry → ↑ pressure across the LES
    - Treatment:
        - Bougie used to dialate esophagus
        - partial Vagotomy (the nerve causes the narrowing)
        - Myotomy (to split tightened muscle fibers)
    - Sudden loss of Ganglia in adult causing Achalasia
        - indicates Chagas disease (6 months trip from S. America)
- Hirschsprungs:
    - Same diseases in the rectum → **loss of both Auerbach's and Meissener's**
    - **Rectum won't be able to relax**
    - Presentation:
        - Constipation
    - Diagnose with Barium
    - **Treatment: remove part of the rectum that's affected.**
- Esophageal Webs:
    - Strips of mucosa going across esophagus (congenital)
    - They can start bleeding after burns hot liquids
        - Fe deficiency anemia ➔ Plummer-Vinson
    - Diagnose with Barium swallow

- Stomach
  - Aurebach plexus uses VIP to relax LES
    - Causes food to drop into stomach ➔ **Receptive Relaxation**
  - Peristalsis begins in the middle 1/2 of the BODY of the stomach
    - ↑ pH is the signal to the G-Cells to produce Gastrin to make more acid
  - Parietal cell will produce
    - H^+
    - Intrinsic Factor (for B_{12})
  - Parietal cells:
    - take up water and CO2 from plasma
    - produce H2CO3 with carbonic anhydrase
    - Break down to H+ and HCO3
    - HCO3 will leave the cell, and float around stomach lining to protect it ➔ **Alkaline tide**
    - Fxn:
      - #1 protection from acid erosion of GI lining is Mucus → most abundant Goblet cells
      - #2 protection is Prostaglandins → (+) mucous production
        - That's why ASA which blocks PG will cause ulcers.
    - Cl^- will enter instead of the HCO3
    - H+ will pump out into stomach via **H/K ATPase** (works like Na/K pump)
    - Will make electrochemical gradient that will push Cl into the stomch
    - Make HCl in the stomach
    - Will continue to produce HCl until pH is 1-2
  - Chief Cells will release Pepsinogen
    - Will activate Pepsin
    - Main enzyme that digests **protein (protein digestion begins in stomach**)
      - sugars and fat stop digestion in the stomach
    - all digestion ends in the small bowel
  - Fat digestion is in the Small intestine
    - Dumping syndrome → eat small frequent meals high in fat!!!



- Pathology:
  - Esophageal hiatal hernia
    - mostly caused by **obesity** (due to increase intra-abdominal pressure)
    - Also caused by **restrictive lung disease**
    - 2 types:
      - **Sliding type**:
        - involves esophageal hiatus → fundus slides through hiatus
        - Treatment:
          - loss of weight
          - H2 blockers
          - last resort surgery- Nissan Fundoplication
            - Complication- lose ability to burp



- **Rolling type:**
  - involves **defect in diaphragm**
  - can strangulate bowel
    - Need surgery

- Gastritis:

Type	A	B
Location	**Body**	**Antrum**
Etiology	Autoimmune **Anti-parietal cell antibodies = ↓ Intrinsic Factor → Vitamin B12 Deficiency**	Medications, hot/spicy foods, Alcohol, ASA
Misc	Adenocarcinoma Risk → d/t inflammation Atrophic gastritis Do Biopsy	Associated with H. pylori More Benign

- Peptic Ulcer Disease
  - Duodenal
    - due to too much acid (high Ca, too much Gastrin…)
    - usually occurs in **2nd part of the duodenum**
    - **pain is worse after you eat (30-40mins) and at night**
    - **H. Pylori associated with it 95% of the time**
    - NO cancer risk
    - Type O blood association
  - Gastric
    - Break down in protection barrier
      - NOT DUE TO ACID
    - usually **located in the antrum**
    - Associated with H. Pylori 70% of the time
    - **Will predispose to cancer 20% of the time**
    - Associated with Type A blood
    - Must scope and biopsy every gastric ulcer.
    - **Pain is worse WITH eating. → need a scope.**
- 4 indications for surgery: **IHOP**
  - **I**: intractable pain (tried medications without help
  - **H**: hemorrhage (most common reason for massive GI bleed in adults)
  - **O**: Obstruction from scaring
  - **P**: perforation
- Menetrieus
  - Thick rugal folds
  - Clue: Mucosa oozes protein → "Nephritic" like

- Pyloric stenosis
  - **thickening of pyloric muscle**
  - Symptoms:
    - **projectile vomiting (usually presents 3-4 wks)**
    - Olive sign – can feel an olive in RUQ
  - Need a Barium Test- see a String sign (barium trickling down)
  - Treatment:
    - pyloric myotomy (split muscle fibers)
  - **Electrolytes: ↓Na, ↓K,↓Cl, ↑ pH → low volume state d/t vomiting**

- Bezoar
  - mass of **inanimate** objects
  - **M/C is hair**
  - Will usually cause an **obstruction in the antrum**

5 Clues to Gastric Cancer (Adenocarcinoma)
  - **Leather water bottle appearance (infiltrate the wall)**
  - **Linnitis Plastica (CA infilatrating the bowel wall)**
  - **Signet Ring Cells on Biopsy**
  - **METS to the superclavicular nodes - Virchows nodes**
  - **Seeding of the ovaries → Krukenburg tumor (NOT metasteses)**

- **Small Intestine**
  - Duodenum
    - Secretin- first hormone to be secreted
      - Stimulated by acidosis (↓ pH)
      - inhibited by alkalosis
      - Goes to:
        - gallbladder
        - pancrease
      - Causes HCO3 secretion
        - Slows down gastric emptying
        - Tightens pyloric sphincter
        - Inhibits Gastrin
    - CCK –next homrmone secreted
      - Stimulated by food – especially FAT
      - Inhibition – alkalosis - ↑ pH
      - Goes to:
        - gallbladder → secrete bile, contracts gallbladder
        - **Pancreas → contract and squeeze out zymogens**
      - **2nd messanger → IP_3/DAG**
    - Motilin
      - Stimulates segmentation
        - **Uses IP_3/DAG during meals for contractions**
      - In between meals it also controls MMC
        - **causes contraction by Ca/Calmodulin**
    - VIP (from aurbach's plexus), Somatostatin (from duodenum)
      - **job is inhibitory/regulatory**
      - to modulate the top three

        - GIP – gastro inhibitory peptide
            - **enhance insulin secretion (stimulated by presence of Glucose)**
            - **cause of reactive hypoglycemia**
        - Enterokinase – enzyme released by duodenum
            - phosphorylates using ATG
            - Uses Mg^{2+}
            - **Activate the first Trypsinogen → Trypsin reaction**

- Duodenal Atresia
    - Duodenum not connected to the rest of the intestine
    - Related to Down's
        - Vomiting 30-40 hours after eating
    - See double bubble sign on x-ray
- Pancreatic Enzymes:
    - Proteins:
        - Zymogens – **inactive enzymes in the pancrease, so won't digest pancreas**
            - α_1-antitrypson's job is to inhibit trypsin from getting loose.
                - Trypsinogen – cuts R of Lys, Arg
                - Chymotrypsinogen – cuts R of bulky AA
                - Proelastase – c
                - Proaminopeptidase –cuts to Right of amino group
                - Procarboxypeptidase – Cuts to LEFT of carboxy terminal

highly selective, parietal cell vagotomy.

        - **Na cotransport will transport the AA into the cell.**
    - Sugars:
        - Amylase – digest any sugar that is left
            - Use Na cotransport to transport the sugars across the cell wall.
            - Except Fructose-
                - has its own transport system
        - Send to liver for storage.
    - Fats:
        - Lipase is secreted by duodenum
        - Dumping syndrome = overwhelm duodenum, dump food straight into duodenum
            - Frequent small fatty meals.
- Acute Pancreatitis:
    - **Severe mid epigastric pain boring through to the back.**
    - Children M/C cause:
        1. trauma
        2. infection
            - mumps
            - coxackie B
    - M/C in adults:
        - alcohol
        - gallstones – are **stuck in the common bile duct to cause pancreatitis**.
    - Hyperlipidimia and hypercalcemia can also cause pancreatitis
        - Ex. patient with multiple myeoloma
    - Test:
        - **Amylase is sensitive not specific**
        - **Lipase is specific not sensitive**

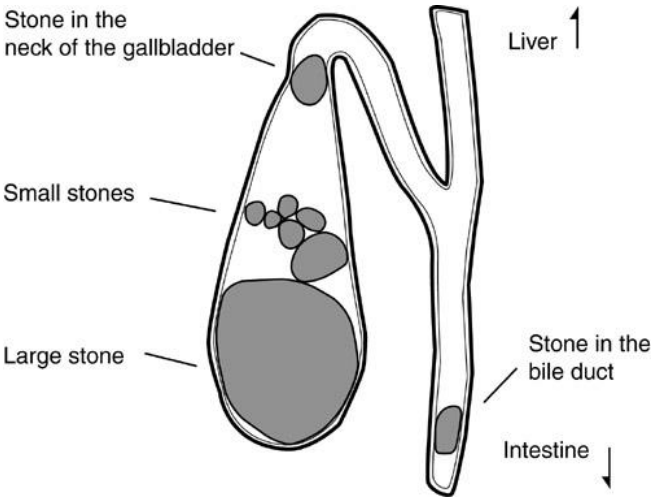
- Phlegmon
  - When there is inflammatin in the peritoneum (i.e., pancreatitis = severe inflammation), bowel will wrap around it and wall it off.
  - Will develop into an **ileus**.
    - **Therefore, Pancreatitis will cause SEVERE ILEUS**
- Saponification
  - Due to Ca^{2}+ build up as time goes on → deposits into the fat = fat necrosis
  - Can produce possible hemorrhagic pancreatitis
  - Treatment → Cut it out
- Noticable change in bowel:
  - Swelling = **3rd spacing (fluid is in the bowel wall)**
    - Will cause dehydration w/o vomiting.

Ranson's Criteria → determines progression and possible perforation

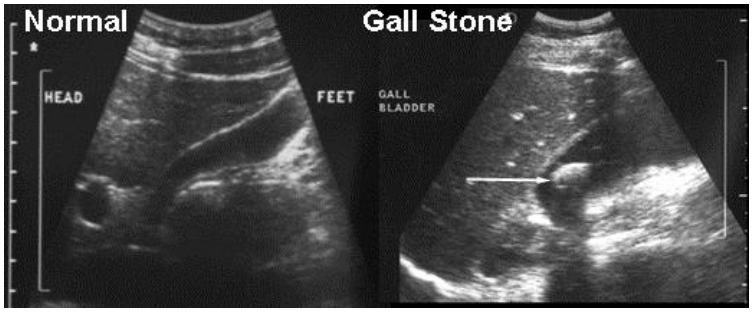
- For prognosis
  - **Age> 55**
  - **WBC > 15,000**
  - **LDH > 350 → indicates cells are dying**
  - **AST >250 → indicates cells are dying**
  - **pO_2 < 55**
    - already developed ARDS – poor prognosis
- Need to follow labs for prognosis:
  - If require > 6L of fluid over 24 hrs (NS) → DEHYDRATION-severe 3rd spacing
  - If Glucose > 200 → Developing diabetes → fried islet cells d/t inflammation
  - Ca drops < 8, being deposited in pancreas → Fat necrosis ↑ → more likely to depol
  - Hb drops by 2g → hemorrhagic pancreatitis
    - Gray Turner Sign= bleeding into the peritoneum
      - describe ecchymosis
      - bleeding into the peritoneum
    - Cullen Sign = bleeding in the center
      - periumbilical bleeding
- **Look for Fibrosis and calcifications to show chronic pancreatitis**

- Pseudocyst
  - big bubble in abdomen full of fluid
  - With high amylase
  - Can get infected and become an abcess
  - Treatment:
    - connect to GI or skin and let it drain.
- Treatment for Pancreatitis:
  - IVF
  - NPO
  - NG suction
  - Pain medication
    - Mepiridine

- Bile
  - Lecithin
    - to help absorb fat by it's emulsifying properties
  - Bile Salts:
    - In the liver
  - Between meals → Make bile
  - During meals → de novo bile synthesis

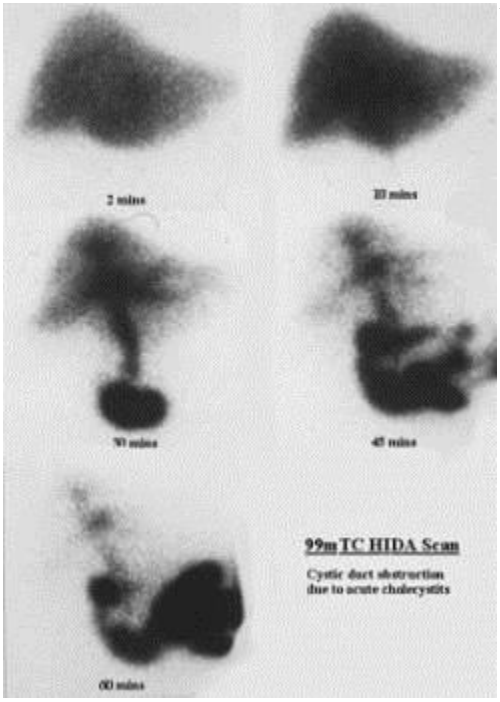


- Gall Stones
  - Virchow's Triad → precipitates stone formation
    - ↓bile salt
      - low fat diets
      - vegetarians
    - ↑cholesterol
      - fertile, fat, 40's female
      - obese
      - familial hypercholesterol
      - DM
      - Pregnancy
    - ↓ lecithin
  - Pain:
    - Colic –pain comes in waves RUQ
    - + Murphy's sign –
      - stop breathing in when palpate RUQ
  - Evaluate:
    - sonogram
      - see If its thickened



    - 80% are cholesterol stones
      - won't show up on X-Ray
      - 20% are Ca- bilirubinate
      - Show up on X-Ray
      - Have Fe-deficient anemia due to ↑ production of bilirubin

- Hida Scan
  - Most specific test
  - inject dye
  - "non visualization of the gall bladder"
  - Dye can't get into the gall bladder because of stone
- 90% get stuck in cystic duct
- 10% get stuck in common bile duct
  - pancreatitis
  - high alk-phosphatase
  - Use ERCP to drain into pancrease to avoid sepsis.



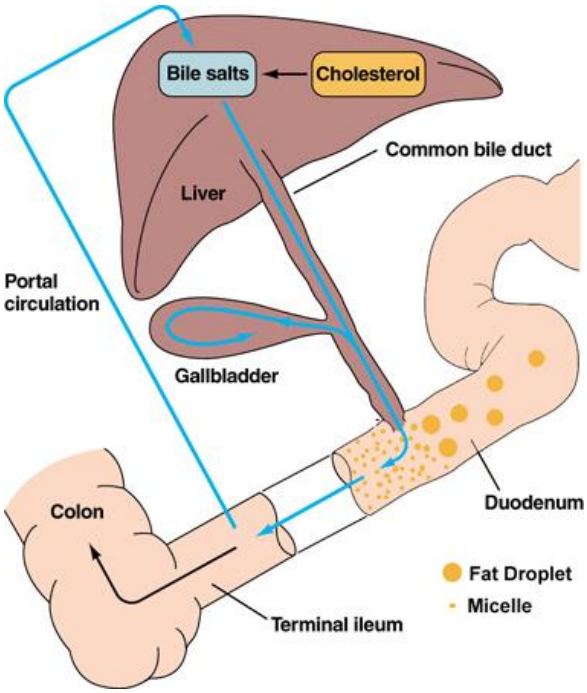
- Treatment:
  - NPO
  - IVF
  - Pain medication
  - Antibiotics
  - Surgery when stable
    - **Asymptomatic gallstones**
      - seen in obese, hypercholesterolemia
      - need to take them out with elective surgery.
        - Because will develop symptoms within 2 yrs.

- Complications
  - Gallstone illeus:
    - gallstone that eroded through gallbladder wall and fell into the duodenum and roled to ileum. Will get stuck in the ileum.
      - Pneumobilia – air in the biliary tract means a connection to GI tract

- Related Pharmacology
  - Cholestyramine/Cholestipol
    - Bind up bile salts and pull out cholesterol for excretion
    - With no cholesterol around → the liver must pull out Cholesterol from storage

SE: Steatorrhea/Problem with absorbing fat soluble vitamins → LOW ENERGY STATE

Bilirubin:



- Responsible for color of stool and urine
- Pathology
  - Starvation
    - ↓ albumin will create jaundice and hyperbilirubinemia
  - Gilbert's syndrome-
    - mild elevation of indirect bilirubin without overt hemolysis, normal liver enzymes
    - nl PE → Patient is otherwise healthy
    - Glucoronyl tranferase is saturated creating a slight backup of bilirubin
    - **Need to hydrate them.**
    - **all unconjugated bilirubin**
  - Criggler-Najjar
    - Glucoronyl transferase deficiency
    - Type I
      - Autosomal recessive
      - complete deficiency
      - **all unconjugated/indirect**
    - Type II
      - partial deficiency
      - Half will be conjugated
    - Hypoglycemia and jaundice
  - Rotors syndrome
    - Active transport out of the liver for bilirubin diglucoronide is defective
    - **Black pigmented hepatocytes only → NO GALLSTONES**
    - ↑ conjugated bilirbin
      - Because sugar is used to conjugate bilirubin, always continue feeding with sugar even after hyperbilirubinemia develops.
    - Less severe than Dubin Johnson

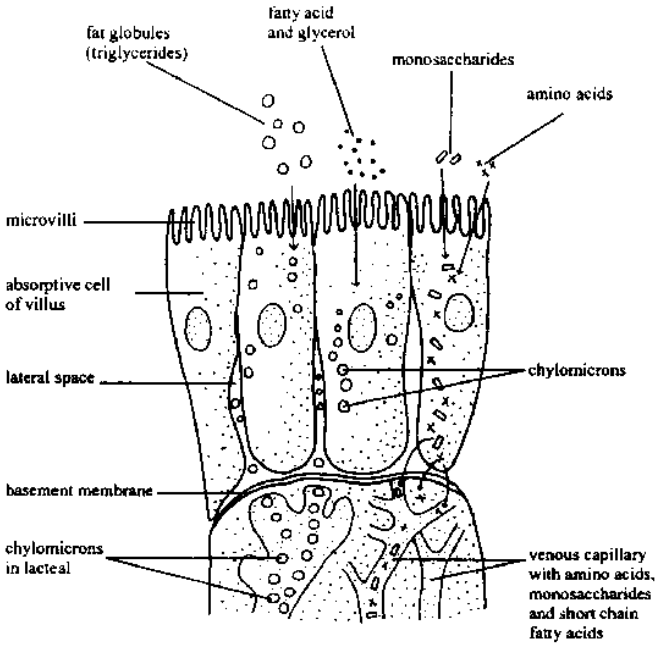
M/C reasons for cholesystectomy in children is:
Dubin-Johnson
Hereditary spherocytosis

- Dubin-Johnson (AR)
  - **Problem in the transport system out of the gallbladder**
  - **Will have black pigment in hepatocytes AND**
  - **GALLSTONES**
  - In Children the most common causes of Cholecystectomy is Dubin-Johnson and hereditary.
- **When there is an ↑ in Direct Bilirubin ➔ Think about OBSTRUCTION**
  - In Newborns:
    - Annular pancreas
      - Problem with the **ventral** piece of the head of the pancreas not coming around correctly and wraps around 2nd part of duodenum →obstruction
    - Choledochal Cyst → remove it
    - Biliary Atresia → it's not connected to duodenum
  - Older children and Adults:
    - Gallstones, Pancreatitis
  - Elderly > 50
    - Pancreatic CA
      - Head of the pancreas will cause post hepatic obstruction
- Crohns, Celiac Spru, Wipples:
  - Will have **dark urine** because there is a problem with the ileum reabsorbing the bilirubin.

- **Pancreatic Cancer: PAINLESS JAUNDICE**
  - Think about **MEN Syndrome Type I**
  - M/C pancreatic mass → cyst
  - M/C pancreatic tumor → adenoma
    - **Insulinoma**
      - High insulin, high C-peptide
    - Glucagonoma
      - High blood sugar
    - **Gastrinoma**
      - **Zollinger-Ellisen syndrome**
        - Severe ulcertions down the bowl
    - **Vipoma**
      - Watery diarrhea
    - Carcinoid
      - diarrhea
      - flushing
      - itching
  - M/C pancreaqtic cancer → adenocarcinoma
    - Presenting symptoms:
      - Painless jaundice
      - **Trousseau's syndrome**
        - **Clots in both legs (recurrent DVTs in both legs)**
          - **Always need a CT scan in the abdomen**
    - 90% are dead within 6 months diagnosis.

- **Colon:**
    - All valves are **α_1 receptors**
    - Can get diverticulosis at ileum (most common in children)
- Stool enters the:
    - Cecum:
        - First part of colon
        - Huge pocket
        - Cecal CA → poor prognosis
            - Presents as Fe-deficiency anemia b/c the patient has been bleeding over the years
            - No obstruction
    - Ascending Colon:
        - **Retroperitoneal**
        - Same reabsorptive mechanism as the kidney (PCT)
            - Intercellular reabsorption of water
            - Has the highest reabsorptive capacity
                - Uses the most Na/K pumps that are controlled by aldosterone.
            - Last chance to bring stuff back in
                - Everything else will be secretion
    - Descending Colon
        - Retroperitoneal
    - Watershed Area:
        - **MC at Splenic flexure → has the least blood supply**
        - SMA ends, IMA begins after the turn
        - Area most likely to infarct due to a clot
    - Sigmoid
        - Forms a 90° angle due to **pubococcygeus muscle** holding it to abdominal wall
            - This muscle relaxs when you start to poop, then the sigmoid will fall in line with rectum
            - Relaxation of Internal anal sphincter α_1 → external anal sphcinter (voluntary)
        - **Diverticulitis is M/C in sigmoid in adults.**
            - Because stool is stuck there for a long time due to sharp angle.
            - M/C place for CA in adults → all the toxins are now located there.
        - Uses **Ca/calmodulin** and pressure to push stool into rectum
    - Rectum
        - Stool starts pushing on internal anal sphincter (α_1)
        - Stool drops down and hits external sphincter
        - Person releases external sphincter voluntarily in order to defecate.
        - There is NO SYMPATHETIC INPUT TO POOPY!!!

- Fat Absorption
  - Emulsification
    - Form a micelle
      - Bile salts
      - Lecithin
      - Cholesterol
    - Lipase will then cut up the micelle into:
      - Short
        - Have to have lacteales (lymphatics for fats) and chilomicrons
      - Medium
        - Do not require lacteales, chilomicrons, they are transported by albumin to liver
      - Long
        - have to have lacteals (lymphatics for fats) and chilomicrons
      - Long and short
        - combine with ApoB48 to make Chilomicron
      - Chylomicron travels to:
        - Liver
          - lipoportein Lipase
            - becomes VLDL



Small Intestine Segments	Duodenum	Jejunem	Ileum
Sugars	10 %	90%	
Amino Acids	10	**90**	
Fats	10	80	10
Fat Soluble Vitamins D, E, A, K, B12			**100**
Fe^{2+}	**90**	10	
All else	10	**90**	

Cholesterol	**Triglyceride's**
Xanthomas	Xanthalesma → fat pad on eyebrow
CAD	Pancreatitis

Hyperlipidemia	Problem	Consequences
Type I	↑ Chylomicrons	LPL Deficiency
Type IIa	↑ LDL	90% LDL receptor
Type IIb **MC**	**↑ LDL** **↑VLDL**	**LPL & CII Deficiency at Adipose Tissue** **Obesity → causes down regulation**
Type III	↑ IDL	Apo E problem
Type IV	↑ VLDL	
Type V	↑ VLDL ↑ Chylomicrons	CII Deficiency MC in Diabetics

- Treatment for Hyperlipidemias
  - Statins → Inhibit HMG-CoA reductase
    - Provastatin
    - Lovastatin
    - Simvastatin
    - Atorvastatin
    - SE: Myositis, Hepatitis
  - Cholatyramine
  - Colestipol
  - Probucol → inhibits VLDL at the liver
  - Niacin → will cause itchiness and flushing
- **If a TG problem**
  - Gemfibrozil
  - Clofibiate
    - Both enhance LPL activity

- **Risk Factors for CAD**
  - **Family Hx.**
  - **Male**
  - **High Fat**
  - **↓ HDL**
- **4 Ways to ↑ HDL**
  - **Exercise**
  - **Wt. Loss**
  - **Moderate Alcohol**
  - Estrogen
- Cholesterol
  - Normal < 200
  - 200-240 → Rx: Diet/Exercise
  - > 240 → Treat everybody
- LDL
  - Normal < 130 or if have one risk factor < 100
  - 130 – 160 = Diet/Exercise
  - > 160 Treat everybody

GI Pathology

- **GI Bleeding**
  - Newborn
    - swallowed maternal blood then it comes out
    - Do APT test to test for Hg F
      - If (+) = baby is bleeding
  - Children
    - picking their nose causing epistasis
      - The blood falls back through the nasopharynx and can cause vomiting!!!
  - Older Children and Adults
    - **Gastritis**
    - Peptic Ulcer Disease
- Massive/Unexplained GI Bleed
  - Look for ↓ Hg
  - Child
    - Meckle's diverticulum
      - remnants of the pre-vitaline duct
      - **Rule of 2's**
        - **2 feet from ileocecal vavle**
        - **peaks at age 2**
        - **2% of population**
        - **2cm in size (remnants of vitiline duct)**
        - **2 types of mucosa**
      - Can also present as unidentifiable bleed
  - Adults
    - Peptic Ulcer Disease
- Lower GI bleeding → Usually d/t IBD but note the CLUE
  - Newborn – First year
    - Still swallowing maternal blood but coming out the butt
    - Do APT test
    - anal fissure- due to straining
  - Children
    - Hyperplastic polyps = **Peutz Jeugher**
      - NOT adenomatous polyps
  - After age 40
    - Angiodysplasia – varicose veins of the colon
    - Divreticul**osis** – complication of constipation
      - Children → Ileum
      - Adult → sigmoid
    - Cancer
      - recommendation for prevention
        - Baseline rectal exam starting at age 35-40
        - Starting age 40 need annual DRE (digital rectal exam)
        - Starting age 50 need annual DRE + guaiac and sigmoidoscopy
          - every year until the person has 2 normal scopes and then he can have it every 3-5 years.
        - Colonoscopy as F/U anytime there are abnormalities on sigmoidoscopy.
        - Otherwise, need colonoscopy every 7-10 years.

- Upper GI Obstruction
  - Newborn→vomit after 1st feeding
    - Esophageal atresia → distal TE atresia
    - Duodenal atresia → double bubble sign
    - Chloanal atresia
    - Pyloric stenosis →projectile vomiting
  - 1-6 months:
    - Achalasia → doesn't present until chld begins to eat solids (4 mos.)
  - 6 mos. - 2 years
    - Intussusception
      - **proximal bowel** slides into distal bowel creating an obstruction
      - **Clues:**
        - **current jelly stool**
        - **sausage mass in RLQ**
        - **Barium exam looks like stacked coins**
        - **Barium is diagnostic and therapeutic**
      - **Henoch Schonlein Purpura has high incidence of intussusception**
      - More common in **ileum in children**
      - More common in sigmoid in adults (but not common in adults)
  - Other causes of obstruction:
    - Volvulus: Bowel twists on it's own
      - More common in ileum in children
      - More common in sigmoid in adults
        - Bird's beak sign
        - upside down ace of spade sign
      - Pain is severe and sudden
  - After Age 2
    - Adhesions
      - **usually from previous surgery**
        - they might distract you by saying patient doesn't recall history of surgery, **look for scars**
      - Internal hernia d/t adhesions
      - **Blood will cause the adhesions and later fibrosis**
        - Blood is an adhesive substance
- Lower GI Obstruction
    - Newborn
      - Hirschsprung's
        - Can't pass meconium
      - Meconium Ileus
        - hints at CF
      - Imperforated anus
    - Child – Adult
      - Adhesions
      - Ischemic Bowel
        - MCC = Clots
          - MC involves SMA which supplies the splenic flexure → Water shed area = Severe abdominal pain

- After age 40
  - Adhesion
  - Obstopation
    - obstruction due to constipation
  - Diverticultis
    - causing scarring due to inflammation
  - Cancer
    - Apple core appearance
    - Pencil thin stools
    - MC CA = Adenocarcinoma

Key Words for GI problems

Heavy Chain Disease	**IgA producing Multiple Myeloma** of the bowel wall
Abetalipoproteinemia	Apo B48 is missing – low chylomicrons
Ataxia-Telangiectasia	IgA deficiency Spider veins all over body
Celiac Sprue	**Anti-glutin, Anti gelatin antibodies** Wheat allergy, diarrhea after eating bread **Biopsy:** Blunting of Villi on Biopsy in Jejunum Rash = ***Dermatitis Herpetiformis***
Tropical Sprue	Same as Celiac sprue but in the **Ileum** **Itchy rashes**
Whipple's Disease	**PAS+ macrophages** →macrophages full of fat Middle age male with **arthritis** **Gram – rods in the bowel rods causing malabsorption** TMP-SMX will cure the disease if taken for 1 year.
Spastic Colon	**Caused by Stress** Diagnosis: Inject colon with Glucagon and colon will spasm
IBS	**Cycling of diarrhea and constipation → stree response**
Selective IgA Deficiency	**Anaphylaxis with any Transfusion**

Inflammatory bowel disease:

Crohns	***Ulcerative Colitis***
Women	Men
Mouth to anus	Starts in Rectum → mouth
Transmural	Mucosal Involvement only
Granulomatous (Tcells and macs) **Cobblestones appearance to mucosa**	Pseudopolyps = two ulcers close together pushing up normal tissue to form a "polyp"
Skip lesions	Continuous
Creeping fat due to granulomas	
Fistulas Most common cause of fistulas in young Common types: Enteroenteral (MC) → Obstruction Enterocutaneous → can eat hole through anus Enterovesicular → (Bowel to Bladder) Enteroanal → (involves the anus) Enteroaortic → Erodes a hole in aorta (worst prognosis)	No fistulas Sclerosing choleangitis → scarring of the biliary tract; measure alkaline phosphatase Lead Pipe colon due to loss of haustra → scarring Toxic Megacolon → mucosa gets stretched thin and bacteria can get through and out
Melena Dark Stools	Hematochezia Bright Red Blood
3% risk for CA	10% risk for colon CA starting at 10yrs Start scoping at 7 years.
Malabsorption → Low energy state	HLA B27
	Treatment → NPO, NG tube to let gas out, triple antibiotic therapy, immediate surgery

Polyps

<table>
<tr><td>Hyperplastic
Benign</td><td colspan="3">Adenomatous
Malignant</td></tr>
<tr><td>Complication : bleeding</td><td colspan="3">Complications: bleeding
Go on to CA
Secrete K</td></tr>
<tr><td rowspan="2">Puetz – Jeghers Syndrome
polyposis
hyperpigmented mucosa
dark gums and vagina
These genes are near the genes for
Breast CA
Ovarian CA
Lymphatic CA</td><td>Tubuler</td><td>Tubulovillous</td><td>Villous
lose the most K
Risk of CA 10%</td></tr>
<tr><td colspan="3">Familial Polyposis
-Wait until teenage years to take colon out
Marsupialization
Ileostomy and then ileo-anal pull through</td></tr>
<tr><td></td><td colspan="3">Gardner syndrome:
Familial Polyposis + Sebacceous adenomas + osteomas (benign tumor of bone)</td></tr>
<tr><td></td><td colspan="3">Turcots
Familial Polyposis with Brain tumors.</td></tr>
</table>

GI Pharmacology:

- Ulcer Treatment
  - Topical
    - Calcium carbonate → TUMS
      - SE: Diarrhea, Make ulcer worse
      - 2nd Messengers activated because if ↑ in Calcium
    - Aluminum – OH → Rolaids
      - SE: Constipation
    - MOM (Mg – OH)
      - OH – buffers acid
      - Mg can cause diarrhea
    - Sucrofate
      - Coats ulcer → must be activated by acid
      - Can't be absorbed
    - Bismuth → Pepto
      - Suffocates H.pylori
    - Simethicone
      - GasEx
    - Metclopromide
      - DA blocker
      - ↑ Gastric emptying
      - SE: Think about basal ganglia
- H_2 Blockers
  - ↓ acid
    - Cimetidine
      - SE: Inhibits p450
    - Rantidine
    - Nozatidine
    - Famatidine
  - Irreversible Proton Pump inhibitors
    - Omerprazole (nexium)
    - Esomerprazole
    - Pantaprazole
    - Robeprazole
    - Lanzoprazole
    - SE: Bleeding/Bloating/Gas
- Diarrhea
  - Opiates
    - Loperamide (Lomotil)
    - Diphenoxylate
- Constipation
  - Sorbital
    - Can be found in green veggies/fruits
  - Psyllum
    - Cellulose (metamusil)
    - (+) Gas
  - Mineral Oil
    - Lubricates the bowel
  - Docusside Sodium
    - Mild stimulant of bile wall
  - Phenyphtalen
    - ExLax
    - Pulls Water
    - Jet Black Colon

Endocrine Physiology

Types of Hormone Actions:

- Endocrine: Hormone travels through the blood stream
- Exocrine: Secretion into anything but blood
  - Pancreas → Exocrine Function → Secrete zymogens
- Paracrine- works in the vicinity/surrounding area
  - Somatostatin
    - GI somatostatin only works in GI
    - Pancreatic somatostatin only works in pancreas
- Autocrine: secretion acts on the same cell that secreted it → Wherever it is released is where it works
  - Thymus and thymopoetin
- Merocrine/Apocrine: Apex of the cell is secreted with the secretion
  - Sweat glands all over body
- Holocrine: The whole cell is secreted with the secretion
  - Sweat glands in groin and axilla

Types of Hormones:

Protein	Steroid
Require second messangers because can't get through cell membrane. cAMP –used by SNS cGMP – used by PNS Catabolism activated by phosphorylations. Anabolism deactivated by phosphorylaton	**All have nuclear membrane receptor** Except: cortisol (has receptor in cytoplasm) Affect DNA transcription/translation Affects protein **No second messenger needed**

Name	Where it came from?	Direct Stimulus	Direct Inhibitor	Where does it go	What does it do?	2nd Messenger	Syndromes
Erythropoietin	Renal Parenchymal Cell	HYPOXIA	↑ pO_2	BM	Erythropoiesis	Tyr-kinase	***Polycythemia*** → ↑ RBC • 1^0 – BM doing it on it's own → CA → ***Polycythemia Rubravera*** **(Hct > 60%) & *Essential Thrombocytopenia* (All the cell lines are high but PLATELETS > 600,00)** • **2^0** – Hypoxia d/t something else → **Restrictive lung disease, Renal cell CA, Severe COPD** ***Stress Polycythemia*** → ↓ plasma – concentrating effect (normal erythropoietin levels) Tx: Hydration
Glucagon	α-cells of the Pancreas β_1 receptors	Hypoglycemia Stress	Hyperglycemia	Liver/Adrenals	Gluconeogenesis Glycogenolysis Lipolysis Ketogenesis		Glucagonoma • ↑ glucose levels but insulin can't keep up • Related to MEN I (Wermer's)
Insulin	β-cells of Pancreas β_2 receptors → + α_2 receptors → -	Hyperglycemia	Hypoglycemia	Everywhere but **BRICKLE** **B**rain **R**BC **I**ntestinal Wall **C**ardiac **K**idney **L**iver **E**xercising muscle	Enhance glucose transport ANABOLIC	Tyr-kinase	Insulinoma (Adults) • Too much insulin Nesidicblastosis (Child) • Too much insulin Labs: • ↑ Insulin • ↑ **C-peptide** Recall too little insulin → Diabetes!!! Type I • Early onset • DKA • Anti-islet cells • HLA DR3/4 • Assoc. with Coxsackie Type II • Obesity • Late onset • No DKA • Insulin Resistence
Somatostatin (Pancreas)	Delta Cells	Pancreatic Hormones	When pancreatic	Pancreas	Inhibitory/Regulatory Function	cAMP	MEN I Present with constipation

		(Insulin/Glucagon)	hormones disappear				
Pancreatic polypeptide	F cells in the pancreas				UNKNOWN		

Stress Response:

- **Glucagon responds within 20 minutes**
- **Cortisol → 2- 4 hours**
  - Stimulates Proteolysis → Gluconeogenesis
- **GH →after 24 hours**
  - Stimulus = Growth/Stress
  - Inhibited by = Hyperglycemia
  - Fxn: Proteolysis
- **Insulin**
  - Responds to all the new glucose around – osmolarity relationship
- **ADH**
  - Responds to an ↑ osmolarity of plasma d/t ↑ glucose molecules

Name	**Where it came from?**	**Direct Stimulus**	**Direct Inhibitor**	**Where does it go**	**What does it do?**	**2nd Messenger**	**Syndromes**
Epinepherine Epi cont.	Adrenal Medulla	Stress/Hypoglycemia	Hyperglycemia	Liver/Adrenals	Gluconeogenesis GLycogenolysis	cAMP	Pheochromocytoma (Adult) • Adrenal medulla tumor • Diaphoresis • Assoc with MEN II Neuroblastoma (Child) • Highest regression rate • MC abdominal CA in children • (+) Posterior Mediastinum Rule of 10's: 10% malignancy 10% bilateral 10% Familial 10% Metastatic 10% Seen in children Dx: • VMA & metanephrines in urine Rx: α_1 Blockers → Phentolamine → ↓ BP Irreversible $\alpha_1\alpha_2$ Blocker →

							Phenoxybenzanine Prazosine → HTN – 1st dose syncope, so take at night Yohimbine – $\alpha_1\alpha_2$ → used for Impotence

Adrenal Cortex

Name	Where it came from?	Direct Stimulus	Direct Inhibitor	Where does it go	What does it do?	2nd Messenger	Syndromes
Aldosterone	Zona glomerulosa	Low Volume	High Volume	Late DCT of Kidney	Stimulates production of Na/K pumps in late DCT Na reabsorption → Brings in 3x more water K excretion H excretion in Collecting duct → Alkalosis	N/A	Adrenal Insufficiency MCC: 21-hydroxylase Deficiency • Hypovolemia → ↓**Na**/↑**K** • Female pseudohermaphrodite 11- hydroxylase Deficiency • HTN → ↑**Na**/↓**K** Conn's Syndrome • Serum Na ↑ • Hypokalcemia • ↑ BP → more likely to depolarize
Cortisol	Zona fasiculata	Stress/Hypoglycemia	Hyperglycemia	Liver/Adrenal	Proteolysis	N/A	SAME AS ABOVE

GI

Name	Where it came from?	Direct Stimulus	Direct Inhibitor	Where does it go	What does it do?	2nd Messenger	Syndromes
Gastrin	G-cells of antrum and duodenum	↑ pH	↓ pH	Body of Stomach	Stimulates parietal cells	**Ca^{2+} by itself**	Gastrinoma/Zollinger-Ellison Syndrome • **Actually a pancreatic adenoma** • **Associated with MEN I** • ↑ Gastrin levels • Ulcers all throughout Small Int. • Tx: Remove it!!
Secretin	S-cells of Duodenum	↓ pH → food has now entered the sm. Int.	↑ pH	Pancreas and duodenum	Stimulate HCO_3^- release to neutralize acid	cAMP	
CCK CCK Cont.	I-cells of Duodenum and Jejunem	Fatty acids (fatty foods)	↑ pH	Gall bladder Pancreas	Squeezes gall bladder to secrete bile Stimulates pancreas to release digestive enzymes	IP_3/DAG	

					Inhibits gastric emptying		
Motilin	Duodenum	↓pH/distention/MMC	↑ pH	Paracrine action	Controls segmentation (during meals) MMC (after meals)	IP_3/DAG Ca^{2+}/Calmodulin	
GIP	Duodenum	Glucose	Lack of glu	Pancreas	Enhance insulin release		Postprandial hypoglycemia Dumping Syndrome
Somatostatin	GI mucosa	All GI hormones	When all GI hormones disappear		INHIBITORY	cAMP	MEN I

Name	**Where it came from?**	**Direct Stimulus**	**Direct Inhibitor**	**Where does it go**	**What does it do?**	**2nd Messenger**	**Syndromes**
ANP	Right Atrium	High plasma volume → ↑ Stretch of Right Atrium	Low plasma volume → no stretch	Renal Artery	Causes on to lose vol. ↑ diuresis with Na/Water by dilating renal artery → ↑ GFR Inhibits Aldosterone	NO	CHF Responsible for ↑ urination in SIADH
Thymosin Thymopoietin	Thymus	When T-cells enter thymus	When T-cells leave thymus	AUTOCRINE	Control t-cell maturation	Tyr-kinase	

Hypothalamus	**Pituitary**	**Action**	**Syndrome**
Dopamine (inhibits Prolactin)	Prolactin	Milk production	Any tumor in the Pituitary will present with **galacturia/amenorrhea** • Must check Prolactin levels • Tumor doesn't produce milk secretion itself • MC symptom: Headache (d/t ↑ ICP) • MC functional tumor - Prolactinoma

Pharmacology Connection:

Anti-psychotics:

- MOA:
  - Most antipsychotics block Dopamine
  - D_2 Receptors most often
  - **Strong Anti-cholinergic effects**
  - Therefore, Galacturia/amenorrhea are common
  - DA can induce vomiting (area postrema)
    - Therefore, if blocked → no vomiting
  - It is required by the **BASAL GANGLIA**
    - **Secreted by Substantia Nigra**
    - Responsible for the initiation of movement
    - **If DA is blocker extensively → EPS/Neuromalignant Syndrome**
      - ***Neuroleptic malignant syndrome*** **→ Rigidity (muscle contracts hard and does not release), Autonomic instability, Hyperpyrexia**
        - **Treatment??? → Dantrolene**

- **EPS**
  - Parkinsonian symptoms (drug induced)
  - Dystonia – sustained contraction
  - MC – torticolis
    - Rx: Anti-histamine or Benztropine
  - Tardive dyskinesia
  - Akathesia → non-stop restless moving

Traditional	Atypical
Dopamine	Dopamine/5HT
Positive Symptoms	Positive and Negative Symptoms
More side effects	Fewer side effects

- Drug Classes
  - Phenothiazines
    - STRONG anti-cholinergic effects
    - Weak DA effect → ↓↓ EPS
      - **Chlorpromazine →** ***block α_1 receptos by accident***
        - Hypotension & sexual dysfx
      - Fluphenazine
      - Perchlorperazone → *anti-emetic*
      - Promethazine → *anti-emetic*
      - **Thioridazine → pigmented retinopathy**
  - Thioxanthines

        - STRONG anti-cholinergic effects
        - Weak DA
        - Used for homeless and migrant workers
            - Lasts for 30 days
    - Butyrophenones
        - MOST POTENT → ↑↑↑ EPS, ↓↓↓ Anti-cholinergic effects
            - Haloperidol
            - Dropendol
    - Atypicals
        - Block $5HT_2$ and DA receptors
            - Resperidone
                - Used for **neuroleptic anesthesia**
            - Clozapine
                - Can cause **agranulosytosis and seizures**
            - Olanzapine
                - Can cause increased weight gain

- Growth Hormone

- GHRH →→→→GH→→→→Liver→→→→Somatomedian→→→→Anabolic (When it comes out regularly)

  Stress →→→ Catabolic →→ Proteolysis (Gluconeogenesis

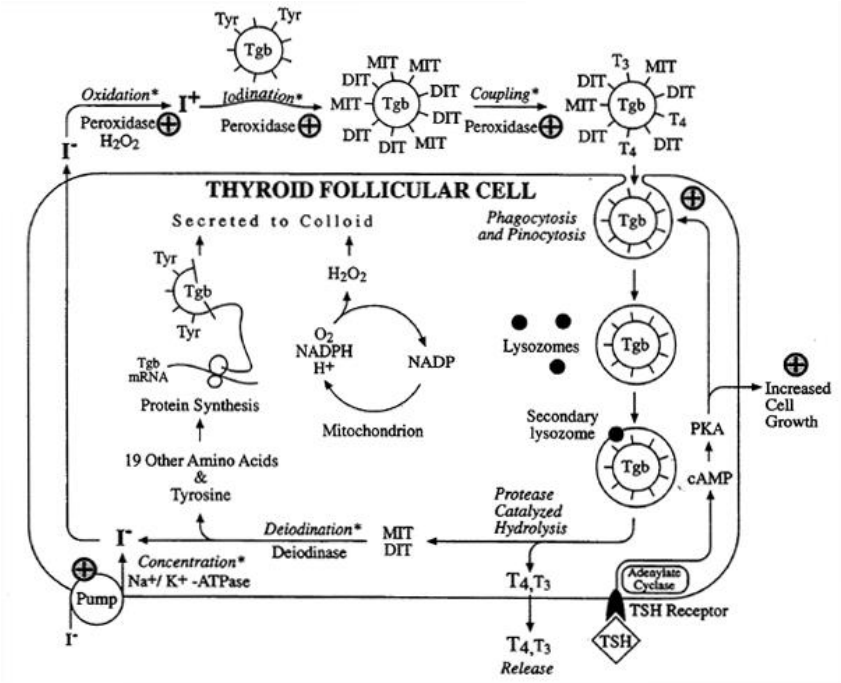
- Main Stimulus
  - Need for growth
  - Stress Growth
    - Therefore, a child with Chronic Disease is Short
    - Recall three periods of growth
      - 0-2 mos
      - 4 – 7 y.o.
      - Puberty
- 2nd Messenger → tyr-kinase
- Syndromes:
  - Don't have enough
    - Get short stature (rare cause)
    - If somatomedian did not work anywhere in the body → Pygmies

      - Achondroplasia (AD)
        - Dwarfism
        - FGF receptor 3
        - Cell signaling defect
        - Head and Trunk are normal size but have short limbs
      - Laron Dwarf
        - Somatomedian receptor insensitivity at extremities only
        - Tyr-kinase not working
        - Symmetrical everywhere
  - Too much
    - Acromegaly
      - "My clothes don't fit"
      - Growth is not symmetrical → coarse features

Acromegaly	Paget's Disease of the Bone
Coarse facial features Children = Gigantism	↑ **Osteoclastic Activity** • **Osteoblasts trying to keep up → bad remodeling** ↑ Ca^{2+} & ↑ alk. phos.
	Fluffy appearance on X-ray; Associated with **Paramyxovirus**
	Mosaic bone/Marble bone Long term: Predisposition to Osteosarcoma

Thyroid Hormone:

- TRH (Hypothalamus) →→ TSH (Pituitary) →→→ Thryroid Gland →→→ T_3/T_4
  - Thyroid hormone is required for growth and differentiation in utero
- Thyroid Hormone Deficiency
  - Cretinism
    - Poor differentiation
      - Eyes don't know where to go
    - Mother and the baby must be both hypothyroid
    - The mother's T_3/T_4 last for at least 1 month of the babies life
      - Deficiency can not be noticed until the 2nd month of life
      - If it is deficient the Brain is at danger because it is still growing → Retardation
- Thyroid Composition
  - T_3/T_4 are made from tyrosine and the have a nuclear membrane receptor
  - T_3/T_4 is responsible for the BMR
    - Therefore, it **ALLOWS** various functions to speed up
  - Permissive action
    - Lets other processes to their job
    - IF there is a deficiency everything will "shut down"
- The Thyroid Gland always **concentrates** Iodine
  - Therefore, needs a ATPase b/c it is going against a gradient
- Synthesis
  - Tyrosine →→→ MIT/DIT + colloid = Thyroglobulin →→→ Peroxidase = 20% T_3/80%T_4
  - T_3 is the biologically active form
  - T_4 is changed to T_3 by deiodinase from the liver
- Chronic Disease and Thyroid hormone
  - If a chronic disease is going on the body conserves BMR b/c/ needs energy to fight illness
    - That is why chronically sick people appear tired and worn out
- Thyroid hormone storage
  - rT_3
  - Often elevated when sick
- Sick Euthyroid Syndrome
  - Someone is hypothyroid for a reason



Most specific way to diagnose is to look at the SIGNAL
1^0 → Organ
2^0 → Pituitary
3^0 → Hypothalamus

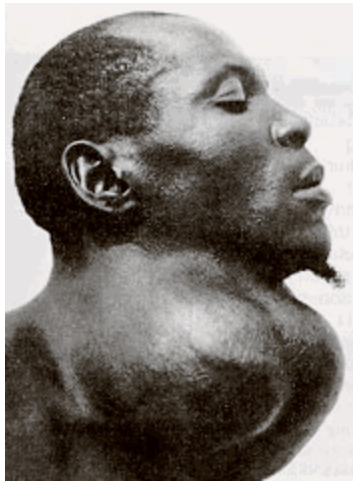
Disorders of Thyroid Hormone Secretion

	Cause	T3/T4	TSH	TRH	Goiter
Primary hypothyroidism MCC = Iodine Deficiency	Thyroid gland can't secrete thyroid hormones	↓ b/c thyroid not functioning	↑ b/c ↓ negative feedback from T4/T3	↑ b/c ↓ negative feedback from T4/T3	Yes, due to **overstimulation** of the thyroid gland by TSH
Hashimoto's Thyroiditis	Autoimmune disease See ↑ **lymphocytes/MΦ** → destroying thyroid **Anti-thyroglobulin** **Anti-microsomal**				Moderately enlarged **Non-tender**
Subacute thyroiditis ***De Quervain's***	**Viral infection** of thyroid Acute inflammation → **painful** Granulmomatous				Painful
Lymphocytic thyroiditis	Seen in **pregnant women** Short lived → lasts 6 mos.				
Reidel's Struma	**Connective tissue disease of thyroid** Tx: Repeated surgery Cause of death → suffocation				**"Woody" thyroid**
Pituitary hypothyroidism (secondary)	Pituitary can't secrete TSH to stimulate thyroid gland to produce T4 and T3	↓ b/c thyroid not being stimulated by TSH to produce the hormones	↓ b/c Anterior Pituitary not fxning	↑ b/c ↓ negative feedback from T4	
Hypothalamic hypothyroidism (teritary)	Hypothalamus can't secrete TRH	↓ b/c thyroid not being stimulated by TSH to produce the hormones	↓ b/c Anterior Pituitary not being stimulated by TRH to produce the TSH	↓ b/c hypothalamus is not fxning	
Distinct Characteristic of HYPOTHYROID ADULT: Prolonged relaxation phase of deep tendon reflexes (stretch reflex)					

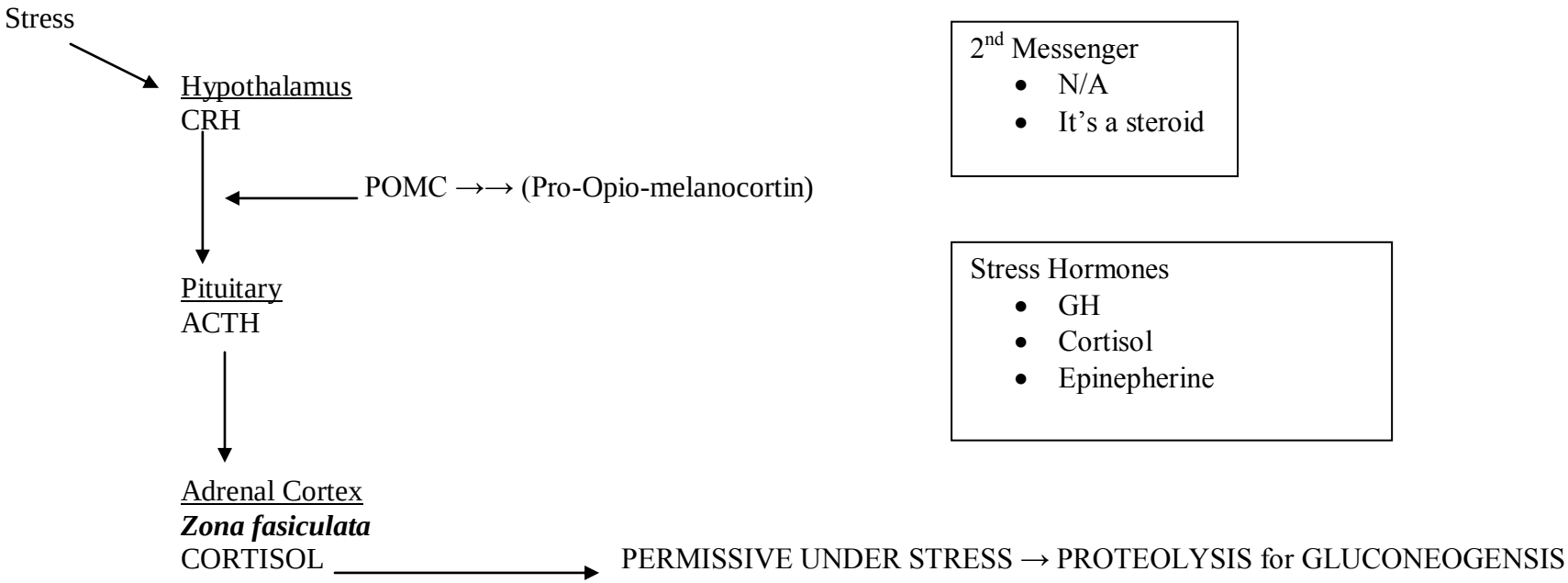
Distinct Characteristic of HYPERTHYROID ADULT: Tachycardia and increased cardiac output					
	Cause	**T3/T4**	**TSH**	**TRH**	**Goiter**
Grave's disease (autoimmune) MCC of Hyperthyroid < 50 years old	Autoimmune disorder will directly stimulate thyroid tissue **Anti-TSH receptor** Symmetric enlargement Long standing effect Heat intolerance (+) **Exopthalmos** – inflammation behind the eye (+) **Myxedema** – Edema behind leg – non pitting (Brain/Heart involved in HYPO)	↑ - in the early stages of disorder	↑ b/c ↓ negative feedback from T4	↑ b/c ↓ negative feedback from T4	
Toxic Multinodular Goiter ***MCC of Hyperthyroid > 50 years old***	Plummer's Disease				
Euthyroid Goiter	When iodine intake is deficient - thyroid gland makes more T3 & less T4	↓ in T4 levels BUT T3 remains normal	↑ b/c ↓ negative feedback from T4 which ↑ iodide trapping makes iodide available to maintain adequate T3 secretion within normal	↑ b/c ↓ negative feedback from T4	Yes, due to **overstimulation** of the thyroid gland by TSH
Pituitary hyperthyroidism (secondary)	Tumor secreting TSH	↑ b/c ↑ TSH stimulating thyroid to produce hormones	↑ b/c of tumor and is the driving force for the hyperthyroidism	↑ b/c ↓ negative feedback from T4	Yes, due to **overstimulation** of the thyroid gland by TSH

Treatments for Thyroid Conditions

- Hypothyroid
  - Thyroxine (T_4) → needs to go to the liver for activation
  - L-thyroxine (T_3) → Synthroid
- Hyperthyroid
  - Be aware that they can die from arrythmias
  - Put on Propranolol for the heart
  - Peroxidase Inhibitors
    - PTU
      - Inhibits **peripheral activation** of T_3/T_4
      - Stops rapidly dividing cells
    - Methinazole
      - Inhibits T3/T4 **release**
  - Radioactive I_{131}
    - ***Blasts Thyroid***



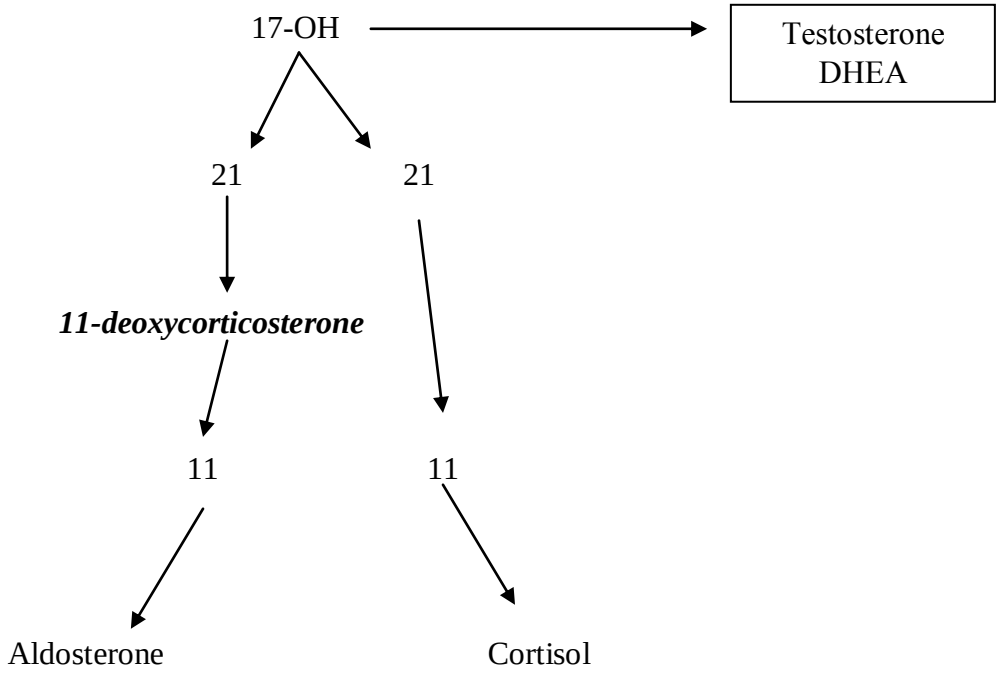
Adrenal Steroids



- POMC
  - Opio → "High Feeling"
    - Analgesia → takes pain away
    - Runner's High
  - Melanocortin
    - MSH → Hyperpigmentation with Addison's Disease
- Cortisol Deficiency
  - Can't handle stress → crash
  - Infection
  - MCC in Children → 21 β-hydroxylase deficiency
  - MCC in Adults
    - Abrupt stoppage of steroids
    - Auto-immune

Adrenal Steroid Synthesis

- Adrenal Steroid Enzyme Deficiencies
  - 21 β-hydroxlase
    - MCC in Children
    - NO Aldosterone
    - NO Cortisol
    - ↓ **BP**
  - 11 β-hydroxylase
    - NO Aldosterone
    - NO Cortisol
    - BUT →→ Have weak mineralocorticoid = ***11-deoxycorticosterone*** = ↑ **BP**
  - 17 α-hydorxylase
    - NO TESTOSTERONE → Male pseudo



- Cushing's
  - Too much ACTH → ↑↑↑ Cortisol
    - Small cell CA → ↑↑↑ Cortisol
- Cortisol tends to be the hightest in the morning (AM)
  - If extremely high do a 24 hour test → b/c if there is too much ACTH will be high all day
- **Dexamethasone Suppression Test**
  - **Give low dose to suppress**
    - **Obese**
    - **Depressed**
    - **Normal variant**
    - **Suppression occurs**
  - **Give high dose**
    - **If true Cushing's = No suppression**
    - **If suppressed = Pituitary Adenoma**
    - **If not suppressed = Small Cell Carcinoma**
      - **Measure ACTH**
        - **↑↑↑ ACTH = ectopic source**
        - **↓↓↓ ACTH = Adrenal Adenoma**

Disease = 1 organ involved
Syndrome = May places involved

Parathyroid Hormone

- PTH – Phosphate Trashing Hormone

	Signal	Serum Ca^{2+}	Serum P	Urine Ca^{2+}	Urine P
PTH	↓ Ca^{2+} ↑P	↑	↓	↓	↑
VITAMIN D	↓ Ca^{2+} ↓P	↑	↑	↓	↓
CALCITONIN	↑ Ca^{2+}	↓ Ca^{2+}		↑ Ca^{2+}	

- Be sure to check Phosphorus
  - If Ca^{2+} and P are going in different direction – Think PTH
  - If Ca^{2+} and P are going in same direction – Think Vitamin D
- 2^{nd} messenger for PTH = cAMP
- Calcitonin comes from c-cells of Thyroid → Inhibit osteoclastic activity
- Embryology
  - Superior Parathyroid glands → 4^{th} Brachial Pouch
  - Inferior PTH – 3^{rd} Brachial pouch

Actions of PTH

- OSTEOCLASTIC ACTIVITY
  - Cofactors → Vitamin A and Mg
    - Too much Vitamin A = Hypercalcemia
      - Moans, Groans → pancreatitis
      - Bones
      - Stones
- Acts on the PCT of the kidney
  - Waste P (secrete it out)
- Vitamin D Action
  - Active Vitamin D = 1,25
  - Enhances GI absorption (jejunem) and kidney reabsorption of Calcium
    - Ca^{2+} ATPase in the Late DCT

Hypercalcemia

- MCC of Isolated Hypercalcemia → Parathyroid Adenoma
  - Associated with MEN I and II
- 2^0 Hyperparathyroidism
  - MCC is Renal Failure
    - Osteitis Fibrosa Cystica → can cause renal failure
    - Renal Osteodystrophy
    - Osteomalacia
      - Demineralization of bones = soft bones
    - Osteopenia
      - ↓ bone mass b/c bone matrix fails to keep up with bone resorption

Osteoporosis

- ↑ osteoclastic activity
- ↓ Bone matrix

OsteoPETrosis

- ↓ osteoclastic activity
- Lose flexability → bones can shatter
- Lose BM

Hypoparathyroidism	PTH	Serum Calcium	Serum P
1^0 Hypoparathyroidism • Tetany • MCC = Thyroidectomy	↓	↓	↑
Pseudohypoparathyroidism • Problem is with the receptors not working • On PE → short $3^{rd}/5^{th}$ digits • Kidney Problem	⬆	↓	↑
Pseudopseudo • G protein messed up	↑	(N)	

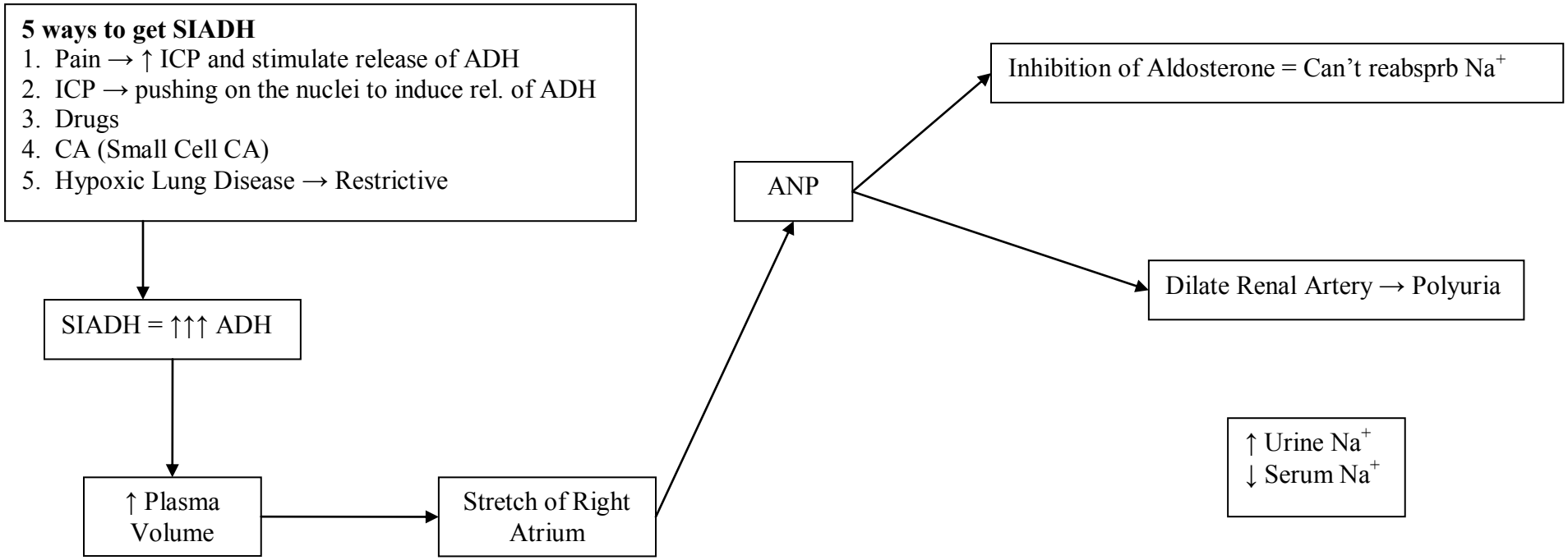
- Drugs that act like calcitonin
  - Phosphonate
    - Inhibits osteoclastic activity
    - Used for those who can not use estrogen
  - Mithramycin
    - Medullary CA of Thyroid → MEN II

Posterior Pituitary

Hypothalamus	Paraventricular	Superoptic
ADH	20%	80%
Oxytocin	80%	20%

- Understand that it is made at both
- 2nd Messenger
  - IP3/DAG

Name	Where it came from?	Direct Stimulus	Direct Inhibitor	Where does it go	What does it do?	2nd Messenger	Syndromes
ADH	Post. Pituitary	High Osmolarity	Low Osmolarity	Collecting Duct	Opens up H_2O Channels Free Water clearance ↓ d/t reabsorption	IP_3/DAG	SIADH • Too much ADH

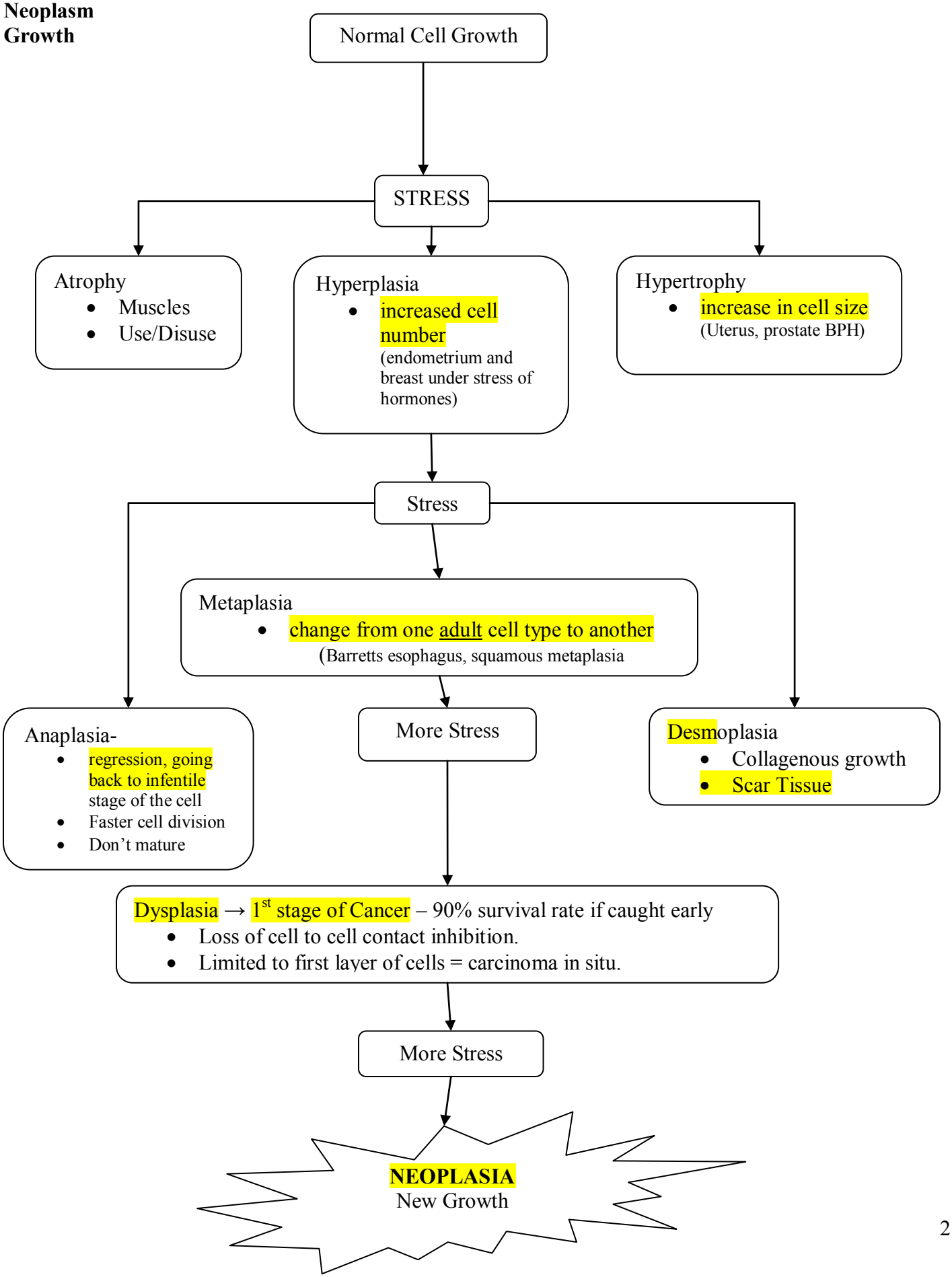


- Diabetes Insipidus
  - No ADH Activity → Free water clearance ↑↑↑
    - Plasma Volume ↑↑↑ = Serum Osmolarity ↑↑↑ → Urine Osmolarity ↓↓↓
  - Is it nephrogenic or neurogenic?
    - Water Deprivation Test
      - 1st maintain a stabilized osmolarity then add DDNP (Synthetic ADH)
        - If the concentration ↑↑↑ by 25% → Central (Neurogenic/Head injury)
        - If concentration stays the same → Nephrogenic problem (drugs)

2 Drugs that can cause DI
1. Lithium
2. Demicocycline

Name	Where it came from?	Direct Stimulus	Direct Inhibitor	Where does it go	What does it do?	2nd Messenger	Syndromes
Oxytocin	Post. Pituitray	Nipple Large uterus (preg.)		Smooth muscle Mammary Glands	Contraction of Smooth muscle Milk ejection	IP_3/DAG	Used to induce labor Too much oxytocin → Uterus contracts harder →uterus will recoil and retracts more blood upon exposure → HYPOTENSION Uterine Atony → lose tone - Reason why during delivery the woman defecates/urinates as she delivers = normal

Neoplasm Growth



Benign vs. Malignant

Benign	Malignant
Well circumscribed	Not well circumscribed (**invading borders**)
Has a capsule → doesn't outgrow capsule	Outgrows capsule (go into neighboring areas)
Obey physiology (Ex. respond to hormones → Breast CA)	Does not obey physiology
NO METS	METS
Hurts by compression Answer relates to type of compression Ex. Compressed nerve → loss of sensation	Hurt you by invasion (need to be removed before invade other tissues)
Surgery is usually for cosmetic reasons, and then for compression	Surgery due to invasion
	Need plenty of blood- vascularization for rapid growth **Angiogenin**- hormone secreted by CA that causes growth of new blood vessels. **Endostatin**- hormone to inhibit other cancers from growing. (Ex. if remove a dominant CA that produces most endostatin, other CA suppressed by this tumor will start regrowing.)
Breast and Ovary- think benign mass before malignant	Everything else should be considered a malignant mass

- Cancer likes Blood
  - Organs with most blood supply will primarily have metastases
    1. ***Brain (gray-white junction)***
    2. ***Lung***
    3. ***Bone (bone marrow)***
    4. ***Liver (portal vein, hepatic artery)***
    5. ***Pericardium (coronaries)***
    6. Adrenal Gland (renal arteries)

The most common CA in these areas is METS!!! – DON"T BE FOOLED

<u>Name your own CA:</u>

- Most common tumor of body = Most common cell type and add OMA at the end
- Name cancer or malignancy of body =
  - Most common cell type to be irritated and add CARCINOMA
  - If it is connective tissue ➔ need to add SARCOMA
    - Ex. Blood vessels/Skeletal muscle
- Any gland, will add ADENO at the beginning.
- Histology:
  - Adeno = Gland
  - Lipo = fat
  - Osteo = Bone
  - Hemangio = blood vessel
  - Rhabdo = skeletal muscle
  - Leio = smooth muscle

To determine prognosis in malignancy:

Always look for SARCOMA first – they will always have the worst prognosis.

Except: Cystosarcoma phyloides – can have a good prognosis, just need wide resection.

Organ	Name	Clue
Brain	Menigioma (Intracranial)	• Displaces brain → compression/herniation • **Psammona body** Tumors with **Psamm**oma Body o **P**apillary CA of thyroid o **S**erous cyst**A**denocarcinoma of ovary o **M**eningioma o **M**esothelioma o O o M o A
- 1^0 Brain Tumor	Astrocytoma • Glioma • Oligodendrioma →→→→→→ • Schwannoma	• **mass in whirly patten/fried egg appearance**
- 1^0 Brain Cancer	Astrocytoma Grade IV → **Gliobastoma multiforme**	
	Posterior Fossa → **Meduloblastoma** →	• **MC in Children**; actually derived from cerebellum • Usually present with **early morning vomiting** (vomiting center right there) • **pseudorosettes**
	Craniopharyngioma →→→→→→→→→	• Develops from posterior pituitary → Rathke's pouch

Organ	Name	Clue
Pineal Gland	Pinealoma (adenoma)	**Precoucious puberty**
Pituitary		
Tumor	Adenoma	
Functional Pit. Tumor	Prolactinoma (5%)	• **↑ Prolactin d/t loss of inhibitory fxn of Dopamine**
Non-Functinoal Pit. Tumor	Chromophobic Adenoma	• If suspect tumor check prolactin levels 1st
ANTERIOR MEDIASTINUM		
The 4 T's		
Thymus	Thymoma	• Associated with Autoimmune diseases – except Graves • **Highly assoc. with MG**
Thyroid		
Tumor	Follicular adenoma	
Cancer	Papillary CA of Thyroid	• #1 Risk Factor → Previous exposure to radiation in the neck • (+) **Psammoma body** Evaluation of Tumor • Soft = cystic → Sonagram/FNA • Firm + previous exposure to radiation → Remove it • Firm without exposure → Do thyroid scan (hot/cold spots)
T-cell Leukemia	Hairy Cell	• **(+) TRAP** • **Fried egg appearance** • **Sunburst appearance**
Lymphoma	Sezary (cutaneous T-cell) Mycosis fungiodes	• Invasion of blood
Teratoma		• All embryo layers present
	Hamartoma	• Abnormal growth of normal tissue • Keloid

6 CANCERS that end in "-oma"

1. Lymphoma (sarcoma)
2. Melanoma (sarcoma)
3. Hepatoma (CA)
4. Mesothelioma (sarcoma)
5. Seminoma (CA)
6. Teratoma

MEN I
- **Pituitary adenoma**
- **Pancreas**
- **PTH**

MEN II
- **Medullary CA of thyroid**
- **Pheocarcinoma**
- **PTH**

MEN III (IIb)
- **MEN II - PTH**
- **neuromass or ganglioneuromas**

Organ	Name	Clue
POSTERIOR MEDISTINUM		
Tumor of the ganglia	**Neuroblastoma (Children)**	• Most common tumor/ cancer in this area • Even though it is mostly found in the abdomen • Like pheochromocytoma (adults) → also characterized by increased epinephrine • **hypsarrhthmis – dancing eyes** • **opsoclonus – dancing feet** Labs: • **VNA in urine** • Metanephrines in urine Highest spontaneous regression rate of all cancers Usually 1-3% spontaneous regression rate
Parathyroid Gland		
MC Tumor	Parathyroid adenoma	• **MEN I → Wermer's**
MC Cancer – Parafollicular cells C-cells	Medullary CA of Thyroid	• ↑ calcitonin levels • Severe hypocalcemia

Neural Crest Origin

- **POPS CAML T**
  - **P**arafollicular cells
  - **O**dontoblasts
  - **P**seudounipolar cells
  - **S**chwann cells
  - **C**hromaffin cells (adrenal medulla)
  - **A**ll ganglia
  - **M**elanocytes
  - **L**arnygeal cartilage
  - **T**racheal cartialge

Organ	Name	Clue
MIDDLE MEDIASTINUM		
Lung		• DO surgery b/c of V/Q mismatch
MC CA	METS – don't forget	
MC Intrathoracic CA	Squamous cell carcinoma • **Involves trachea (central)**	• (+) PTH → hypercalcemia • Pink staining
MC 1^0 Lung CA	1^{st} - Bronchogenic adenocarcinoma	• Peripheral location
	2^{nd} – Bronchioalveolar carcinoma	• Alveolus involved!!! • **Only Lung CA not directly associated with smoking**
At Bifurcation	Small cell CA (central) Oat cell/Anaplastic	• **90% producing ACTH → Cushing's** • 5% ADH → SIADH • 3% PTH → hypercalcemia • < 1% TSH → rare
	Carcinoid Tumor	• **5-HIAA in urine due to seratonin break down** • **Flushing, itching, diarrhea** • Grows out like a polyp- THE ONLY ONE • Its always a metastasis: • 90% pancreas • ileum
	Large cell	• Everything is described as "Big" → giant cells
Pleural Cavity		
Risks • **Smoking** • **Radon** • **2^{nd} hand smoke** • **Pneumoconiosis (environment)**		
MCC CA of Pleural cavity	Mesothelioma **Ferruginous bodies**	• Pleural calcifications • Pleural thickening • **psamoma bodies** #1 Risk factor → Asbestos • **Shipyard workers** • **Insulation installers** • **Pipe fitter** • **Brake mechanics** • ***MC CA → Bronchogenic adenocarcinoma***

Environmental Lung Disease	Silicosis	• **Sandblaster, glass prod.**
	Berylliosis	• **Tv/sat. worker**
	Bissinosis	• **Cotton industry**
	Anthrocosis	• Carbon dust/black deposits • No predisposition to CA

Mediastinum:

<u>Cardiac</u>

- Endocardium
  - Myxoma
    - Most common tumor of the endocardium
    - Presentation
      - "diastolic/atrial plop" (90% in LA),
      - Female passes out and comes right back to consciousness, because estrogen relaxes too much.
- Myocardium:
  - Rhabdomyoma
    - most common tumor
  - Rhabdomyosarcoma
    - most common cancer
  - What syndrome predisposes to this?
    - Tuberous Sclerosis
    - Occur primarily under age 3 due to rapidly dividing muscle cells.
- Pericardium
  - MC = METS

Signs of Neurocutaneous diseases:
- Seizures
- Mental retardation
- Facial angiofibroma

Tuberous Sclerosis:
- Aslien leaf spots (**hypopigmented macules)**
- Chagrin patches (**thickened skin with hair coming out**)

Associated with:
Rhabdomyoma/sarcoma
renal carcinomas
brain tumors

Von recklinghausen - Neurofibromatosis
- Café au-lait spots (hyperpigmentation)
- Need at least >3 spots, > 1.5mm in diameter.
- High incidence of
  - neuromas
  - fibromas
- defect on chromosome:
  - type 1 = 17
    - peripheral neuroma
  - type 2 = 22
    - central neuromas
    - Bilateral acoustic schwannomas

Sturge-Weber
- Flat Hemangioma (usually on Opthalmic division of V_1)
  - Port wine stain
- Have retinal problems.

01-13-04

Liver:

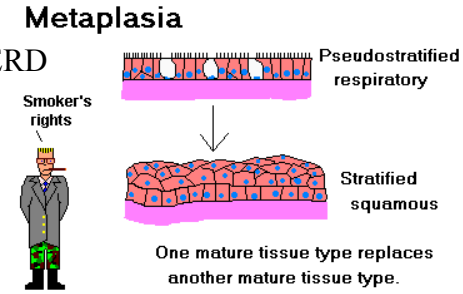
- Most common CA ➔ mets
- Most common liver mass ➔ Cyst
- Most common liver tumor ➔
  - #1 → Adenoma
    - Risk Factors:
      - Birth Control Pills
      - High estrogen
  - #2 → AVM- blood vessel tumor → ↓↓↓ AVO_2 difference
    - IF they Burst and bleed ➔ massive hemorrhage
    - Sequester platelets ➔ increasing bleeding time
    - On physical exam → continuous murmur
      - **In Abdomen and Brain = VON HIPPEL LANDAU SYNDROME**
        - **Chromosome 3/VHL deletion**
        - **High risk of Renal cell CA**
- Most Common 1° Liver Cancer➔ Hepatocellular carcinoma
- Predisposing infections:
  - Hepatits B
  - Hepatitis C
  - shistocomyosis
- Risk Factors: **HAVE CASH BS (PP clues)**
  - **#1 is alcohol**
  - smoking
  - benzene
  - aflatoxin – aspergillis
  - CCl_4 – unique for giving Angiosarcoma of the liver

GI

- Most common tumor → leiomyoma (smooth muscle)

Esophagus:

- Most common CA → Squamous Cell CA
  - Lower 1/3 ➔ Esophageal adenocarcinoma most commonly d/t Barrett's esophagus (a complication of GERD → diffuse pain)
  - Presentation
    - Painful swallowing = adynophagia (localized)



Risk Factors:

- smoking
- alcohol
- nitrites
- japanese

Stomach:

- Most common CA → Gastric carcinoma
  - Presentation
    - Early satiety

- Associations for STOMACH adenocarcinoma:
  - Leather water bottle ➔ Linnitis Plastica (infiltration of wall)
  - Virchows nodes ➔ mets to superclavicular area
  - Krukenberg ➔ **seeding** of the ovaries
  - Signet ring cells

Organ	Name	Clue
Small intestine		
MC Tumor	Leiomyoma	
MC CA	Adenocarcinoma	
At the Ileum	Lymphoma	
Appendix		
	Carcinoid – NO METS Carcinoid Syndrome → pancreas/ileum	
Colon		
MC tumor	Leiomyoma	
MC CA	Adenocarcinoma	Presentation • Bleeding → obstruction • Fe^{2+} anemia • Looks like a "napkin ring" Risk Factors • Low fiber diet • High fat intake → promotes free radicals/mutations • Polyps

POLYPS

<table>
<tr><td>Benign
Hyperplastic</td><td colspan="3">Malignant
Adenomatous</td></tr>
<tr><td>Complication : bleeding</td><td colspan="3">Complications: bleeding
Go on to CA → 100% risk
Secrete K^+ → hypokalemia (villous)</td></tr>
<tr><td rowspan="4">Peutz – Jeghers Syndrome
▪ ↑↑↑ polyposis
▪ hyperpigmented mucosa
▪ dark gums and vagina

These genes are near the oncogenes for
Breast CA
Ovarian CA
Lymphatic CA</td><td>Tubuler</td><td>Tubulovillous</td><td>Villous
• Hypokalemia
• Highest Risk of CA</td></tr>
<tr><td colspan="3">Familial Adenomatous Polyposis
- If suspected at birth with family history must perform annual colonoscopy with biopsy starting at age 5

-Wait until teenage years to take colon out
Marsupialization
Ileostomy and then ileo-anal pull through</td></tr>
<tr><td colspan="3">Gardner syndrome:
Familial Polyposis + Sebacceous adenomas + osteomas (benign tumor of bone)</td></tr>
<tr><td colspan="3">Turcots
Familial Polyposis with Brain tumors (astrocytoma)</td></tr>
</table>

Organ	Name	Clue
Gall Bladder		
MC Tumor	Leiomyoma	
MC CA	Adenocarcinoma	Thickened/calcified Gall Bladder
Pancreas		
MC Mass	Cyst	
MC Tumor	Adenoma	**Association with MEN I**
	Glucagonoma	↑ Blood sugar & lipids
	Insulinoma	↑ insulin, ↑ **C-peptide**
	VIPoma	Watery diarrhea
	Somatostatinoma	Constipation
	Carcinoid	
	Zollinger – Ellison (Gastrinoma)	↑ **Gastrin levels b/w meals** Ulcers everywhere → all the way through ileum **MEN I (Wermer's)**
MC CA	Adenocarcinoma	**Painless Jaundice** ↑ unconjugated bilirubin d/t obstruction 90 % located in the head of the pancreas **Trousseau's Syndrome** • **Migratory thrombophlebitis** • ↑ **Mucin = clots**

GENITOURINARY SYSTEM

Organ	Name	Clue
OVARY		
MC Mass	Follicular cyst	
MC Tumor	Serous cystadenoma	
MC CA	Serous cystaadenocarcinoma	Psammoma body
Misc.		
	Mucinous cystadenoma	Jelly belly Pseudomyxoma peritoni
	Granulosa Cell Tumor	Heavy Bleeding Secretion of estrogen → precocious puberty Call-Exner bodies (eosinophilic inclusion body)
	Fibroma	Meig Syndrome = ascities + pleural effusion
	Sertoli-Leydig Cell Tumor	Masculization (androgen secretion)
	Yolk – sac Tumor	(+) α-feto protein
	Teratoma	Hair and teeth in ovary
	Struma ovarii (monodermal teratoma)	Hyperthyroidism b/c composed of thyroid tissue

Organ	Name	Clue
KIDNEY		
MC Mass	Renal cyst	
MC Tumor	Renal adenoma	
MC CA	WILM's TUMOR (Children)	90% seen in upper pole Actually a teratoma → triphasic histology **WAGR** • **W**ilms tumor • **A**nuridia → colorless eyes • **G**enitourinary malformation • **R**etardation **Hemihypertrophy → d/t cancer taking blood supply away** 20% recurrence in other kidney Diagnosis • Sonagram
	Renal cell CA (Adults)	**Painless hematuria/mass in abdomen** Most vacular → think angiogenin **Likes to METS to Lung** **Cannon ball mass** PCV d/t ↑ erythropoietin **Predisposition:** **Von Hippel Landau/Tuberous Sclerosis**
URETER/BLADDER		
MC Mass	Diverticulum	2 complications: UTI & Stones
MC Tumor	Leiomyoma	
MC CA	Transitional Cell CA	**Painless hematuria** Risk Factors: • Smoking - #1 • Aflatoxin • Benzene • Schistomiasis
UTERUS		
MC Tumor	Leiomyoma (Fibroid)	**Submucosal → present with menorrhagia** **Subserosal → pain & pressure (pelvis)** Fibroid → estrogen dependent Tx: OCP >> Leuprolide (GnRH analog blocks LH/FSH) >> surgery
MC CA	Endometrial Carcinoma	Present with vaginal **bleeding after AGE 40** • **In b/w periods** #1 Risk = unopposed estrogen Tx: Hysterectomy
	Squamous Cell Carcinoma	Chronic irritation Post-coital bleeding → recommend PAP Smear Chamydia Elisa Test → #1 cause of infertility

MC Cervical Mass	Wart	HPV → Condyloma accuminatum • Mushroom shape • HPV – 16 & 18 → CA Syphillis → Condyloma lata • Fleshy

PAP Smear

- **Low Grade Finding**
  - **MCC = Infection**
  - Culture Cervical Secretions
    - **Do Hep B, RPR (Syphillis), HIV**
- **If still abnormal**
  - Do culposcopy → **Cone biopsy**
- **High Grade**
  - Not caused by Infection → straight to surgery

Organ	Name	Clue
VAGINA		
MC Mass	Bartholin cyst	Complication: Infection If recurrent • Marsupialization
MC CA Upper Mucosa	Squamous cell Carcinoma from cervix	
MC CA Lower Mucosa	Rhabdomyosarcoma * If < 3 y.o. = Sarcoma botryoides	"bunch of grapes" Skeletal muscle
MISC		
	Clear cell Carcinoma	> 90% d/t DES exposure White ridge on vaginal wall
PROSTATE		
MC Tumor	Benign Prostatic Hypertrophy	Occurs at prostatic urethra Obstruction Management: • α_1 blocker → Terazocin, Doxazocin (relax sphincter) • Fenesteride → (-) 5α reductase • Surgery (Transurethral) – if necessary
MC CA	Adenocarcinoma	↑ PSA Complication • 80% impotence d/t accidental severing of the pudendal nerve Hormone Treatment • Flutamide → blks. DHT receptors • DES → can cause irritability **OSTEOBLASTIC CA → mets to spine**

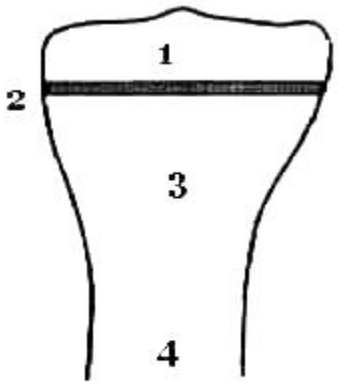
TESTICLE		
MC Mass	Hydrocele (child)	Collection of H_2O Transilluminant
	Hematoma (Adult)	
2nd MC Mass	Varicocele	Complications: • Infertility d/t impingement of spermatocord • ↑ oxygenated blood = (-) sperm production

Organ	Name	Clue
TESTICLE CONT.		
MC CA	Seminoma	RARE
Germ cell tumors	Yolk Sac	α-feto protein MC CA in youth
	Choriocarcinoma	β-hCG
SKIN		
MC Mass	Skin Tags	Tx: Tie it off → necrose right off
MC Skin Tumor	Fibromas (adult)	
MC CA	Basal Cell Carcinoma	Papular with a central ulceration No METS
MC Malignancy	Squamous Cell Carcinoma	Predisposing conditions: • Actinic keratitis = thickened skin • PKU • Xeroderma pigmentosum • Albinism • Porphyrin Cutaneous Tarda • Wiskott Aldrich #1 Risk Factor = UV light Bowen's Disease → if it is on the penis
	Melanoma	Most Malignant but Rare

- **Classification of Skin Cancers**
  - **A**rea **B**orders **C**olor **D**epth
    - Depth has the most important impact
    - If 1 mm = 90% mortality

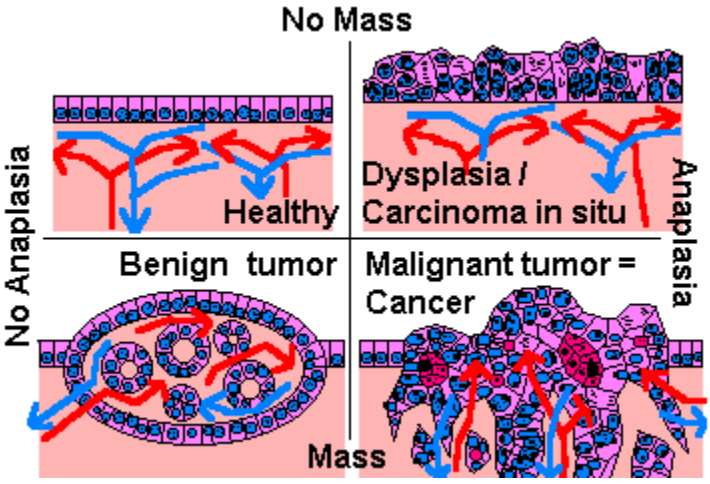
BONE

1. Epiphysis: cartilaginous end(s) of a bone.
2. Physis: cartilaginous zone in between the epiphysis and calcified cartilage (metaphysis); also known as the epiphyseal plate or the growth plate. As it "closes", it is referred to as the epiphyseal line.
3. Metaphysis: The ossified portion of an epiphysis.
4. Diaphysis: Shaft of a tubular bone.



1. Epiphysis
2. Physis
3. Metaphysis
4. Diaphysis

Organ	Name	Clue
BONE		**LOCATIONS ARE KEY**
Epiphysis		
MC Tumor	Chondroma	
MC CA	Chondrosarcoma	
	Giant cell tumor	"Soap bubble" appearance on Xray Moth eaten
Metaphysis		
MC Tumor	Osteoma	
MC CA	Osteosarcoma	Codman's Triangle Paget's Disease
Diaphysis		
MC CA	Ewing's Sarcoma (Children)	(t11:22) Onion-skinning of the bone One - hit Locations: • Distal femur • Proximal tibia • Distal humerus
MISC		
	Multiple Myeloma (Plasmacytoma → lytic lesion)	↑ Serum Ca^{2+} → d/t bone destruction ↑ IgG = M spike Bence Jones Protein (kappa) Punched out lesions on x-ray



Organ	Name	Clue
BREAST		
MC Tumor < 25 y.o.	Fibroadenoma	Due to **estrogen** **Enlarges AFTER menses**
MC Tumor > 25 y.o.	Fibrocystic Change	Due to **progesterone** **Enlages BEFORE menses**
MC CA	Infiltrating/invasive ductal CA	MC location = upper outer quadrant Osteoblastic
Benign	Intraductal papilloma	Bleeding from the nipple
Other Malignant tumors		
	Lobular CA	**Indian filing = clusters of cells fill** intralobar ductules
	Comedocarcinoma	Multiple areas of focal ulcers "black heads"
	Cystosarcoma phylloides	Grows LIKE a fungus **Good prognosis**
	Inflammatory	Peau d'orange **WORST prognosis** Lymphatic involvement

Management of Breast Cancer Treatment

Age	Management
35 – 40 years	Baseline Breast Exam
> 40 years	Monthly self exam Annual physician exam
50 years	Annual mammogram
> 50	Annual mammogram

Findings:

- Cyst/Soft Breast Mass → Do H & P → Perform sonogram → fine needle aspiration
- Firm Breast Mass → Do H & P → Mammogram → Surgery for lumpectomy → Send to pathology → if benign do nothing → if malignant do a resection and leave the Pectoralis Major

Treatment for Breast Cancer:

- Tamoxifen → can stimulate progesterone at the endometrium → risk for endometrial cancer
- Roloxifine
    - MOA:
        - Anti – estrogen at the pituitary and breast → the breast will shrink but also it will stimulate osteoporosis → blocks binding of estrogen
        - Recall that the liver breaks down estrogen, if there is more estrogen circulating it will stimulate the liver to "work" → the liver produces proteins such as, Angiotensinogen → ↑ BP and also makes the clotting factors → clot formation and DVT/PE