REVIEW PG 84-86

- **Circulatory System**
  - **Stretch** receptors in carotid sinus
    - Most important for short term BP reg
    - High BP activates the Carotid Sinus nerve
      - Activation of parasympathetic nervous system and inhibition of sympathetic to drop BP
      - Stimulation leads to **decreased** heart rate, **decreased** arterial blood pressure and **decreased** venous return
      - Increased pressure in the carotid sinus increases the discharge of efferent fibers that travel in the 9th CN
        - Then through local medullary circuitry, descending fibers are activated that inhibit sympathetic neurons associated with the heart
    - Respond to actual stretching, not chemicals
  - Stretch receptors in the atria
    - Elicit **Bainbridge reflex --- Think Bridging the gap from the heart to the Lungs**
      - Initiated by excess blood volume in R atrium
      - Sensitive to both Pressure and stretch
      - Goal is to get heart to pump harder to transfer excess blood from pulm circ to systemic circ
      - **A sudden increased inflow into the R atrium will cause an increased blood flow to the lungs in 2-3 heart beats**
    - Afferent to the medulla via the vagus nerve
      - Stimulation of the heart by the vagus nerve keeps the HR down
        - The effect on basal HR of cutting successively the vagus & the sympathetic nerves in an animal reveals predominance of vagal over sympathetic innervation in determining HR
      - Increased vagal activity also results in decreased cardiac oxygen consumption
        - Increased vagal activity does not result in "decreased transit time through the AV node
    - Then efferent sympathetic increases the HR and strength of contractions
  - Chemoreceptors
    - **Central (Think C for Central and CO2)**
      - Medulla
      - MAJOR regulators of ventilation
      - Kaplan states central receptors are sensitive to low pH
        - Detect H^+ changes in CSF (cerebrospinal fluid)
        - NO detection of PO2
        - Detect increase in PCO_2
          - When PCO_2 goes up, also increases H^+ because $CO_2 + H_2O$ forms carbonic acid, which then disassociates to H^+ and bicarbonate
          - Breathing a gas mixture with 5% CO_2 ultimately leads to a stimulation of central chemoreceptors
          - Normally, air is 78% N2, 21% O2, and traces of other gases like CO2
          - CO2 affects central chemoreceptor the most
    - Peripheral
      - Located in carotid and aortic bodies
      - Detect change in blood PO_2 (if <60mmHg), PCO_2, and H^+ (or pH) ion concentrations
      - Transmit to resp. center in brain to reg.
      - A marked fall in the **oxygen** tension in arterial blood would stimulate the receptors in the **aortic & carotid bodies**
      - Normal Hemoglobin concentration is about 15gm/dl blood and normal arterial oxygen content is about 20ml/dl blood. An anemic individual breathing room air with a hemoglobin concentration of 10 gm/dl blood is expected to have
        - Normal arterial oxygen tension and reduced arterial oxygen content (because low hemoglobine, the less oxygen in each ml of blood)
          - **Hypoxic hypoxia** in which oxygen tension of arterial blood is reduced
          - **Anaemic hypoxia** in which the arterial oxygen tension is normal but the amount of haemoglobin(Hb) available to carry oxygen is reduced.
      - Breathing a gas mixture containing 10% O2 and 90% N2 will stimulate respiration because low oxygen tension has an Excitatory effect on the peripheral chemoreceptors receptors
        - Different Q, but it reads administration of 90:10 N20 to O2 will DEPRESS RESPIRATION??? And it will result in Respiratory Acidosis
        - NOTE → Subanesthetic doses of nitrous (20-40% N2O) cause increased respiration
  - Blood Volume
    - 64% in systemic veins
      - By far the most

- 13% in systemic arteries
- 7% in arterioles and capillaries
- 7% in heart
- 9% in pulmonary vessels

- Liver
  - Largest share of systemic CO
- Kidney
  - Highest blood flow per gram of tissue
- Heart
  - Large arteriovenous O2 difference
  - Increased O2 demand is met by increased coronary blood flow, NOT by increased extraction of O2
- Total Peripheral Resistance (TPR)
  - Regulates the flow of blood from the sys. arterial to venus circulation
  - Resistance to blood flow from the entire circulatory system
  - Caused by accumulation of vasodilator local metabolites (lactate, K^+ ions, & adenosine)
    - Organ — Factors determining Autoregulation of blood flow
    - Heart — O2, adenosine, NO (Unique in that when hypoxic causes vasoconstriction)
    - Brain — CO2, pH
    - Kidneys — Myogenic and tubuloglomerular feedback
    - Lungs — Hypoxia causes vasoconstriction (* Unique like the heart)
    - Skeletal Muscle — Local metabolites, Lactate, Adenosine, K+ (vasodilators)
      - Adenosine causes vascular smooth muscle to relax
    - Accumulate due to increasing metabolism of exercising muscle
  - Posseult's Law
  - = Viscosity (of blood) x length (of vessel) / $(Radius)^4$
    - Factors affecting blood resistance
      - Vessel Radius
        - Most Powerful relationship (Vasoconstriction is King)
        - Resistance is inversely proportional to the 4^{th} power of vessel radius (= $1/r^4$)
          - **If you Half the vessel, then resistance goes up 16 times**
        - Larger the vessel, the less resistance
      - Viscosity
        - Directly proportional to resistance
        - The vena cava contains the highest viscosity blood in the body (95% sure from the other answer options of aorta, vasa recta, pulmonary vein, pulmonary artery)
        - Viscosity increases with polycythemia, Hyperproteinemic states (Multiple Myeloma), and Hereditary Spherocytosis
        - May vary with hematocrit
      - Vessel Length
        - Directly proportional to resistance
        - Constant
    - Increasing the radius produces the greatest decrease in resistance in a single artery (versus changing the length or reducing viscosity) – due to the 4^{th} power relationship
- Cardiac Output (CO)
  - Regulates flow of blood from veins back into arterial side
  - CO (5 liter/min) = HR (70 per min) x SV (70 ml)
    - During exercise, CO increases initially as a result of an increase in SV
    - After prolonged exercise, CO increases as a result of an increase in HR
    - If HR is too high, diastolic filling is incomplete and CO drops (i.e. ventricular tachycardia, pulse >200)
  - Most important factor in relation to circulation
  - Average resting is 5.6 L /min for men
    - 10-20% less for women
  - Heart Rate (HR)
    - The parasympathetic NS regulates HR
  - Stroke Volume (SV)
    - = End Diastolic Volume – End Systolic Volume
    - Average is 70-80ml
    - **CAP**
      - **C**ontractility (increases SV)
        - Increased with
          - Catecholamines (increased activity of Ca2+ pump in sarcoplasmic reticulum)

- Sympathetic action of increasing HR, conduction velocity, and contractiility
- Increased intracellular Ca2+
- Decreased Extracellular Ca2+
- Digitalis (increased intracellular Na+, resulting in increased Ca2+)
  - Resulting in bigger contractility, and slows down (more efficient)

➢ Decreased with
- B1 Blockers
- Heart Failure
- Acidosis
- Hypoxia/Hypercapnea

♦ **A**fterload (decreases SV)
➢ Diastolic arterial pressure (proportional to peripheral resistance)
➢ Vasodilators decrease afterload (i.e. hydralazine)

♦ **P**reload (increases SV)
➢ Ventricular EDV
➢ Venous Dilators decrease preload (i.e. nitroglycerin)
➢ Venous Return ➔The blood returning to the heart via the inferior and superior venae cavae.
- **Most important determinant of CO**
- A drop in BP results from decreased venous return
- Assisted by:
  - Contraction of skeletal muscles (especially in legs)
  - Pressure changes in thorax and abdomen during breathing
  - Increase of thoracic/abdominal pressure will decrease Venour Return
  - Valsalva Maneuver
    - VR would be reduced by a forced expiration with the glottis closed
    - technique for increasing the intrathoracic and intra-abdominal pressure by trying to breathe out forcibly (using the diaphragm and abdominal muscles) when the glottis (the opening between the vocal cords) is closed. The manoeuvre is often performed during isometric exercises and weight-lifting. Air is trapped and pressurized in the lungs, **causing blood pressure to rise.** The great veins may collapse, reducing the flow of blood returning to the heart. Immediately after the manoeuvre, a reflex bradycardia can occur that may cause dizziness and fainting.
  - Pressure of venous valves
  - Decrease venous compliance
  - Sympathetic action decreases compliance, and increases VR
  - NOTE: Peripheral vasodilation reduces venous return to the heart

♦ Frank-Starling
➢ Initial length of cardiac muscle fibers affects the strength of contraction
➢ Matches CO with venous return
➢ Greater the filler, the harder the contraction because of more linking of actin and myosin
➢ Increased filling of the ventricle during diastole causes a more forceful heartbeat
- This is due to the increase in end-diastolic fiber length
- NOTE: in a denervated heart, adjustments to increased workload are mediated by mechanisms associated with increased end diastolic volume
- Another Q:In the completely isolated, blood perfused mammalian heart, adjustments to increase workload appear to be mediated primarily by mechanisms associated w/ increased diastolic volume
- Increase workload = increase diastolic volume

➢ Mean Arterial Pressure (MAP) = CO x TPR (Total Peripheral Resistance)
➢ *MAP* is considered to be the perfusion pressure seen by organs in the body. MAP 60 is good to get blood to all part, below that is problematic. 2/3 of diastolic and 1/3 of systolic.
- Similar to Ohm's law = Voltage = Current x Resistance
- ALSO MAP = Diastolic + 1/3 pulse pressure
  - Pulse Pressure = Systolic – Diastolic

- Pulse Pressure ≈ Stroke Volume
- Example 120/80 → MAP = 80 + (120-80)/3 → 93.33
- **This is why doctors say the Diastolic BP is more important to monitor**

- Ejection Fraction
  - = (EDV – ESV/ EDV) = SV/ EDV (What's leaves/ what you started)
  - An idex of of ventricular contractility
  - Is normally 60-70%
- Ventricular Filling
  - Rapid Filling Phase
    - Rapid flow of blood into the ventricle actually produces a decrease in atrial and ventricular pressures, but a sharp increase in ventricular volume
  - Diastasis (Slow Filling Phase)
    - Gradual rise in atrial, ventricular, venous pressures and ventricular volume
  - The volume of the ventricle is greatest at end diastolic volume
  - End diastolic volume = The volume of blood in the left ventricle at the end of diastole, just before systole (contraction)
- Compliance (Larger compliance, larger the dilation)
  - A measure of how much a vein reacts to an change in pressure
  - Highly compliant veins dilate a lot
  - Determines the amount of blood flow in the veins
  - Sympathetic decreases venous compliance and returns more blood back to the heart
  - **Vascular compliance = Increase in volume/increase in pressure**
- Blood Flow
  - = Pressure difference/Resistance
    - The greater the pressure gradient, the greater the flow
    - The flow rate decreases with increased resistance
    - **CO = BP/TPR → V = IR = → (BP) Pressure = Flow (CO) x Resistance (TPR)**
- BP
  - Measuring BP → What indicates systole when using a sphygmomanometer? → First sound
  - A fall in BP causes increased activity of the vasoconstrictor center and decreased activity of the cardioinhibitory center
  - BP = CO x TPR
    - Aorta
      - The characteristic of the aorta most responsible for the maintenance of diastolic BP is elastic distensibility
    - Systemic Arteries
      - High pressure
        - Systolic BP may be abnormally high **when arterial compliance is decreased** (think arteriosclerosis)
          - Another Q: Prior to surgery, an anxious patient has a higher systolic BP than previously noted – the most likely reason is decreased arterial compliance (From the NE, sympathetics??)
      - Strong muscular walls
      - Always carry blood "A for Away from the Heart"
      - The main factors directly involved in the maintenance of systemic arterial blood pressure are
        - cardiac output, blood volume, blood viscosity and peripheral resistance
      - Another Q: A drop in BP results from decreased CO
        - *Now think of things that could cause a decrease in CO, like venous return for example*
      - The arterial blood pressure might be abnomally high in a cerebrovascular accident (not cardiac shock, heart failure, anaphylactic shock, or ventricular fibrillation)
      - Cardiac shock = inadequate pumping action of heart
    - Arterioles
      - Greatest drop occurs in the arterioles
        - In the presence of a constant HR, changes in BP may be attributed mainly to alterations in resistance in arterioles
        - Another Q: Postural hypotension is compensated by constriction of systemic arterioles (b/c blood accumulates in the lower body)
        - Another Q: The most likely cause of hypertension is generalized constriction of arterioles
      - Small vessels with diameter of 0.5 mm
      - Small lumen, but thick tunica media (almost all smooth muscle)
      - Primary resistance vessels, hence determine distribution of CO
      - Control valves for the capillaries
      - Local blood supply is regulated by tissue metabolism
      - **Humoral factors affect diameter as well as sympathetic activation**

- Capillaries
  - Where exchange occurs
  - Walls are very thin
    - Only a single layer of endothelial cells
    - Surrounded by a thin basal lamina of the tunica intima
  - The amt of blood passing through the capillaries of the systemic circulation/min = amt of blood passing through the aorta/min
  - More capillaries arranged in parallel
    - BP decreases as it flows through circulation
    - **If two vessels are connected in parallel, their total resistance to blood flow is less than the resistance of either vessel alone**
  - Capillary diameter is directly influenced by byproducts of metabolism
- Venules
  - Small veins which collect blood from caps
  - Gradually coalesce into larger veins
- Systemic Veins
  - Conduits for blood to get back to the heart
  - **The blood pressure of the circulatory system is the lowest in the veins**
    - **Greater osmolarity is in the IVC**
  - Larger lumens and thinner walls than arteries
  - Higher compliance, act as reservoirs
  - Valves, especially in limbs to prevent backflow

- The primary effect of substituting a rigid arterial system for a compliant arterial system would be that continuous flow in the capillaries would change into pulsatile flow (vibrating flow)
- Another Q: The continuous flow of blood in arteries during diastole is made possible by energy stored in arteries during systole
- Edema
  - From capillary fluid pressure and increased colloid osmotic pressure of interstitium
    - These two act in the same direction when it comes to movement of water between interstitium & plasma
  - Capillary pressure
    - Force out fluid by filtration
    - Determined by venous pressure and arterial pressure
  - Interstitial fluid pressure
    - Opposes cap pressure
  - Oncotic pressure (or colloid osmotic pressure of the plasma)
    - Pulls fluid back into the plasma (same axn as the interstitial fluid pressure)
      - Colloid osmotic pressure of the blood is important because it prevents excess loss of fluid from capillaries
      - Another Q: Plasma colloid osmotic pressure acts in the same direction as tissue pressure
    - Main protein contributing to oncotic pressue is albumin
      - Albumin
        - Is produced in the liver
          - Aldosterone (adrenal cortex) and Vasopressin (posterior lobe of anterior pituatry) are NOT
        - Smallest, most abundant protein in the blood plasma
        - Type: a simple protein
        - Important buffer in the blood and is partly responsible for blood viscosity
      - The role of the liver in edema may be the result of diminished albumin synthesis
      - Forms a complex with free FAs to be transported in the blood
    - **Kidney is main organ responsible** for reg of osmotic pressure with reg of water resorption via ADH
  - When balance is off, edema occurs and lymphatics pick up the extra fluid left in the interstitium
- **Pulmonary Circuit**
  - BP is much lower than systemic circuit
    - Pulmonary arteries are usually dilated and have little resistance are a lot of compliance
    - Compared with systemic circulation under normal conditions, pulmonary circulation is characterized by low pressure, equal flow and low resistance (Great example of paralleling capillaries)
      - *Think V = IR, aka 'pressure = current*resistance'*
  - From right side of the heart to the lungs and back to the left side of the heart
  - Only supplies the alveoli
- **Systemic Circuit**
  - To all tissues except the **alveoli**

- *****Volume flow for BOTH circuits is 5 L/min (vol. flow/min is the same for both the systemic & pulmonary circulations)**

- **Blood**
  - BY Total Body Weight
    - 92% Body Fluids and Tissues
    - 8% Blood
      - **55% Plasma**
      - 45% Formed Elements
    - Serum
      - **= Plasma – Clotting Factors (i.e. fibrinogen)**
      - Clear, thin, sticky fluid portion after removal of fibrin clot and blood cells
      - No platelets, RBCs, or Fibrinogen
    - Plasma
      - **= Serum + Fibrinogen**
      - **= Blood – Formed elements**
      - Liquid portion of the blood
      - 55% of the blood
      - **No cells**
      - Contains
        - Proteins (7%) – albumins 55%, globulins 38%, and fibrinogen 7%
        - Water (91%)
        - Other Solutes (2%) – Metabolic end-products, food materials, respiratory gases, hormones, and ions
      - Fibrinogen, prothrombin, calcium ion, and ascorbic acid are all found in plasma (thrombin is not)
    - Formed elements
      - The other 45%
        - RBCs
        - Leukocytes
          - PMNs 40-70%, Lymphocytes 20-40%, Monocytes 2-10%, Eosinophils 1-6%, Basophils <1%
        - Platelets
  - RBCs
    - Biconcave discs
    - 7.5 microns in diameter
    - Function to transport O_2 and CO_2
    - No nuclei or mito
    - The membrane of the RBC
      - Composed of hemoglobin & other soluble proteins necessary for gaseous respiratory exchange
      - Has lipid membrane of A, B, or O antibodies
      - Blood Type

Blood groups	Antigens on RBC (Agglutonogens)	Antibodies in Plasma (Agglutinins)
O (Universal dOnOr)	-	Anti-A and Anti-B
A	A	Anti-B
B	B	Anti-A
AB (Universal Recipients)	A and B	-

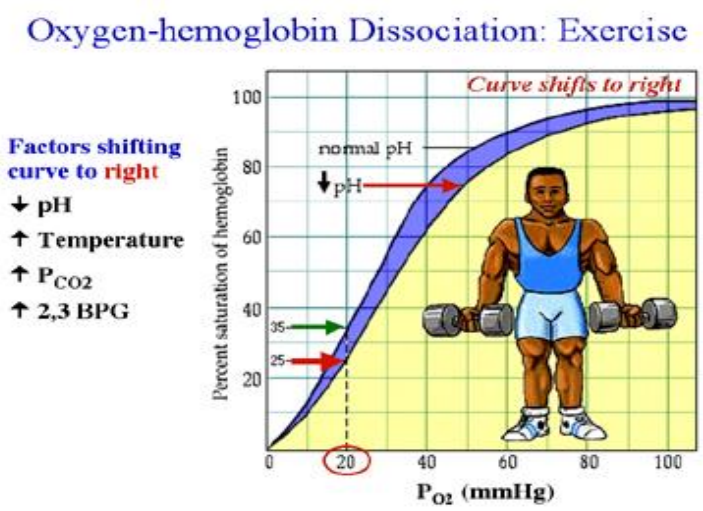
    - Hematocrit
      - Proportion of RBCs in a sample of blood
        - 46.2% -- Males
          - **Hematocrit of 45% is a typical finding for a normal 23-year-old man**
            - **Abnormal: venous pH = 7.2, WBCs = 10,000/mm^3, RBCs = 7 million/mm^3, pulse pressure = 80 mmHg**
              - Normal Venous pH
                - Venous = 7.36
                - Arterial = 7.41
        - 40.6% -- Females
      - Bile excretion is a good indicator of RBC destruction per day
  - Hemoglobin (Hb)
    - Constitutes 33% of the cell weight in RBCs
    - **1 RBC contains up to 300 million Hb molecules**
    - **Hb synthesis involves iron & copper**

- Heme synthesis occurs in the liver and bone marrow
- The committed step is Glycine + Succinyl CoA → gamma-aminolevulinate (ALA)
  - This is done by the NZ aminolevulinate synthase (inhibited by product heme)

- Another Q: Some parts of a hemoglobin molecule – iron, protein, histidine, pyrrole ring (**not magnesium)**
- Globin portion
  - Consists of 2 alpha and 2 beta chains
  - Exists in 2 Forms:
    - Taut (T) has low affinity for Oxygen
      - Increased Cl-, H+, Temp, CO2, and DPG favor the T form (Unloading O2)
      - CO2 binding favors the T form
        - CO2 transport binds to the amino acids in the globin chain (at the N-terminus) and not at the Heme site
    - Relaxed (R) has high affinity for Oxygen (300x)
- Heme Portion
  - Consists of 4 ring-shaped heme molecules
    - N-containing organic pigment molecule that has single atom of Fe^{2+} (ferrous) in its center, which can combine one molecule of O_2
      - Hb is important due to its ability to combine reversibly with O_2 at the **ferrous Fe2+** (O for oxygen carrying)) heme prosthetic group
    - Attached to Globin polypeptide chains
    - Each Fe can bind reversibly with 1 molecule of O_2, so Hb molecule can associate with 4 O_2 molecules (oxyhemoglobin)
      - **Remember that O2 binds with positive cooperativity and negative allostery, meaning that the binding of the first O2 helps with the binding of the other 3**
      - This accounts for the sigmoid shape dissociation curve (unlike myoglobin)
    - Hb can bind CO_2 and that decreases amount that can bind to O_2
    - Carbon monoxide has a 200x greater affinity for hemoglobin than does O2
    - Carbon monoxide (CO) decreases the amount of O_2 that can be transported by hemoglobin
      - CO competes w/ O2 for hemoglobin for hemoglobin binding sites – this makes CO toxic
    - MetHemoglobin
      - **Has its iron in Fe^{3+} (ferric) state and cannot function (NOT reduced hemoglobin)**
        - Remember ferrOus (O for oxygen carrying)
      - So, the consequence of appreciable conversion of hemoglobin to methemoglobin is a noticeable decrease in the ability of blood to transport oxygen
      -
  - Fe
    - $2/3^{rds}$ of the body's Iron is in Hb
    - Other $1/3^{rd}$ is in liver, spleen, bone marrow, etc. in the form of ferritin or hemosiderin
    - Body normally has about 4 gms
    - Absorbed in the upper part of small intestine, primarily in duodenum
      - Combines in blood plasma with beta globulin apotrasferrin to form transferrin, which is then transported to plasma
    - The major storage form of iron is ferritin
    - **Dominant factor controlling GI absorption of iron is saturation of mucosal cells**
- Hb Types
  - Hb A – Normal type
  - Hb C – Abnormal in which Lysine has replace glutamic acid causing reduced **plastiCity** of the RBCs
  - Hb H – Abnormal composed of 4 beta chains (resulting in alpha-thalassemia)
  - Hb M – Abnormal Hbs in which single amino acid substitution favors the formation of methemoglobin
  - Hb A1C – Hemoglobin of a diabetic pt (hemoglobine combine with glucose also know as **Glycosylated Hemoglobin.**
  - Hb S – (Sickle Cell anemia)
    - Abnormal Hb in which **valine** replaced **glutamic acid** in the **beta chain**
      - **This causes Hb to become less soluble under low O_2 tension** & to polymerize into crystals that distort the RBCs into a sickle shape (sickle-cell anemia)
      - Major effect of sickle cell anemia is from decreased solubility of the deoxy form of hemoglobin
      - **This would cause an increase of the isoelectric pH**
        - The pH at which number of positive charges equals the number of negative charges
    - Another Q: Sickle-cell anemia is caused by the presence of a valine substitution for glutamate in the sixth amino acid from the N-terminal end of the hemoglobin B-chain. This amino acid substitution is the result of a base change in the DNA of the B-chain gene

- Involves a missense mutation
- Another Q: The substitution of valine for glutamic acid is a result of a change in DNA coding (due to a genetic mutation)

- Hb test
  - Measures the grams of Hb contained in 1dl of whole blood and provides an estimate of carrying capacity of RBCs
  - Normal Concentrations
    - Women – 12 to 16 gm/dl
    - Men – 14 to 18 gm/dl
    - Infants – 14 to 20 gm/dl
  - Value depends on # of RBCs and amount of Hb in each
    - Low value indicates anemia
    - An **anemic** patient breathing room air is expected to have **normal arterial O_2 tension** & **reduced arterial O_2 content**
      - ***Remember that arterial O_2 tension has nothing to do with Hb & accounts for only 2% of total O_2 content***
        - ***It has to do with arterial saturation w/ O_2, which occurs quickly in the blood***
- Oxygen transport
  - O_2 picked up in the lungs forms oxyhemoglobin (HbO_2)
  - **Then in tissues, O_2 splits away from Hb and creates reduced hemoglobin (HHb) or deoxyhemoglobin**
    - A dental patient presents with a bluish discoloration of the mucous MBs indicative of cyanosis – most likely the result of increased levels of reduced hemoglobin
    - NOTE: Cyanosis, by definition, is a bluish discoloration of the skin due to the presence of deoxygenated Hb in BVs near the skin surface
  - Axn is reversible
    - Depends of PO_2
      - When PO_2 is high, (in pulmonary caps), Hb has higher affinity for O_2
        - Among the larger blood vessels, O_2 tension is highest in the pulmonary veins
      - When PO_2 is low, (in tissue caps), Hb has lower affinity and unloads O_2
      - **Conversion of HbO_2 to Hb is the most important process in preventing a decrease of >0.2 units in blood pH when CO_2 enters**
    - Causes of O_2 unloading (Decreased affinity for O_2) – Curve shift to the Right
      - Low PO_2
      - Bohr effect
        - The equilibrium expression for oxygen association to hemoglobin includes participation of H+ ions
        - **Decreased pH = increased arterial $[H^+]$ = decreased affinity for O_2**
      - Increase in arterial PCO_2
        - Has the most effect in stimulating respiration
      - Increase in Diphosphoglycerate (DPG)
        - Hypoxia increases the formation of DPG
      - Increase in tissue temperature (exercise)
        - So basically, when CO_2 enters the blood, pH drops, causing unloading of O_2, which then keeps the blood pH from dropping too much
        - In question form: The hemoglobin dissociation curve is shifted to the right by an increase in arterial pCO_2 & an increase in arterial H^+ concentration
    - Curve shift to the left
      - This would be area representing times of Hypoxemia or cyanosis



- Oxygen dissociation equation:
  - $y = (pO_2)^n/[(pO_2)^n + (P_{50})^n]$
    - y is the fractional occupancy of O_2-binding sites
    - P_{50} is the pO_2 at which 50% of sites are filled
    - n = 2.8 for hemoglobin (I have no idea where the 2.8 comes in)
      - Notes:
        - At 100mm Hg , Hb is essentially fully saturated (98%)
        - The PO2 must drop below 70 mmHg before there is a significant lowering of the total bound O2
        - At 40 mmHg, (venous blood), approximately 75% of heme sites or occupied (or 3 bound molecules)
        - **P_{50} (pressure where half the sites, or 2 molecules, are bound) is 27 mmHg**
  - EX: Given P_{50} = 26 torr & pO_2 = 30 torr, the average # of O_2 molecules bound per Hb is 'greater than 2', since the equation yields y = 0.6 or 60%
- **Blood leaving lungs is 98% saturated in O_2**
- **Blood returning is 75% saturated in O_2**

- Carbonic anhydrase
  - CO_2 is carried from tissue to the lungs in 3 ways
    - 90% Bicarbonate
    - 5% Bound to Hemoglobin as carbaminoglobin
    - 5% Dissolved CO_2
  - $[CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO3^-]$
  - Present within tubular cells, and it catalyzes the formation of carbonic acid from carbon dioxide and water
  - Carbonic acid dissociates into hydrogen ion and bicarbonate
  - One of the fastest known enzymes and is found in great concentration in erythrocytes
  - Zinc is an essential component
  - The steps:
    - Waste CO_2, released from respiring tissues into the blood plasma enters the erythrocyte
    - Within the erythrocyte, carbonic anhydrase facilitates the combination of CO_2 and water to form carbonic acid $[CO_2 + H_2O \rightarrow H_2CO_3]$
      - Carbonic acid dissociates into hydrogen ions and bicarbonate ions $[H_2CO_3 \rightarrow H^+ + HCO3^-]$
        - Carbonic anhydrase in erythrocytes increases the rate of dissociation of H2CO3
        - HCO_3^- reenters the blood plasma for transport to the lungs
        - **Because the RBC membrane is not very permeable to cations, the HCO_3^- efflux is balanced with a Cl- influx, which is known as the Cl- shift**
        - Chloride passes from the plasma **into the cell as HCO_3^- passes from cell into plasma**
        - Because HCO_3^- is much more soluble in blood plasma than CO_2, this roundabout route increases the blood's capacity to carry carbon dioxide from the tissues to the lungs
    - **In the lungs, HCO_3^- reenters the erythrocyte and combines with hydrogen ions to form carbonic acid, which is split by carbonic anhydrase into CO_2 and water**
      - This CO_2 diffuses into the alveoli and is exhaled
      - So, carbonic anhydrase in erythrocytes increases the rate of dissociation of H_2CO_3
  - Haldane Effect
    - **In the lungs, oxygenation of Hb promotes dissociation of CO2 from Hb**
  - Carbonic anhydrase in the kidney tubular cells is associated with reabsorption of bicarbonate ion

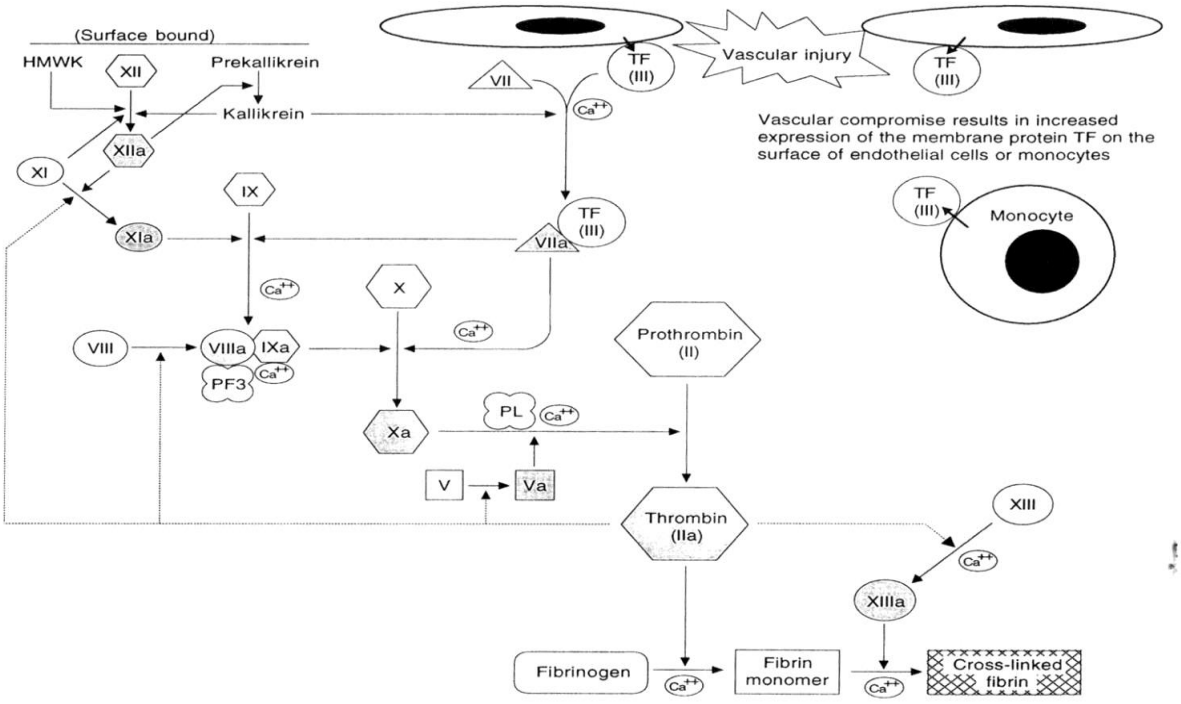
- Although not required for CO_2 and water to form carbonic acid, it greatly increase the reaction in both respects
  - Absence of carbonic anhydrase drastically reduces blood CO_2 carrying capacity
- Most of the CO_2 is transported in the blood as bicarbonate ion (HCO_3^-)
  - It is converted to carbonic acid more rapidly in whole blood than in plasma
  - The reason: whole blood contains erythrocytes w/ carbonic anhydrase, while plasma does not contain RBCs
- The greatest concentration of carbonic anhydrase is found in erythrocytes
- The bicarbonate buffer system of blood is very efficient because CO_2 is rapidly eliminated through the lungs

▪ Oxygen Tension vs. Oxygen Content
- A marked fall in the oxygen tension in arterial blood would stimulate the receptors in the aortic & carotid bodies
- Normal Hemoglobin concentration is about 15gm/dl blood and normal arterial oxygen content is about 20ml/dl blood. An anemic individual breathing room air with a hemoglobin concentration of 10 gm/dl blood is expected to have
  - Normal arterial oxygen tension and reduced arterial oxygen content
- NOTE: Hb concentration is about 15 g/dl, and each gram can combine with 1.36 ml O2, so blood can carry 20 ml/dl of O2, compared with only 0.3 ml of physically dissolved O2
- Breathing a gas mixture containing 10% O2 and 90% N2 will stimulate respiration because low oxygen tension has an excitatory effect on the peripheral receptors

▪ Carbaminohemoglobin
- Hb that is carrying CO_2
- Hb carries 97% of O_2 transported

➢ Hemostasis – preventing or minimizing blood loss

▪ Chain
- Vasoconstriction
- Platelet aggregation
  - The important role that platelets play in hemostasis is that they agglutinate and plug small, ruptured vessels
  - **Thromboxane A2 is released by platelets & causes platelets to stick together**
  - Increased bleeding (in a patient w/ leukemia) is most likely due to thrombocytopenia (when anemia, leukopenia, Ca2+ deficiency, and Factor VIII deficiency are your other options
    - Basically all the blood progenitor cells are too busy making WBCs and so no energy to make platelets
- **Coagulation Cascade (picture)**



  - Extrinsic pathway
    - Remember something else started it
    - Upon injury to endothelial cells → tissure factor (factor III) rlsd
    - Which combines w/ factor VII & Ca^{+2} to form activating complex for factor X
    - Then activates factor IX to activated complex → which becomes common pathway
    - **3- 7- 10**

- Common:
  - Then activate factor X then factor II activated (prothrombin → thrombin)
  - **10- ProT(2)- Throm- Fibrinogen- Fibrin- x-linked fibrin**
  - Also 10- ProT(2)- Throm- 13- Fibrin Monomer- x-linked fibrin
- Intrinsic pathway:
  - When platelets adhere to injured subendothel region → factor XII rlsd which becomes activated by kallikrein and HMWK (high MW kininogen)
  - Which activates factor XI → which activates IX → then common pathway
  - 12- 11- 9- 10
- Notes
  - Factor X upon activation is first slow → once thrombin made factor V is activated (back door from Thrombin) → speeds up Factor X's rsn (prothromb → thromb)
  - **Speeds up HUGE (800,000 FOLD when V and Ca2+ added)**
  - Also speeds up back door via activation of factor VIII from thrombin which joins IX making it stronger
  - Thrombin
    - Catalyzes: fibrinogen → fibrin monomer rxn
    - In other words, fibrinogen represents the normal substrate of thrombin
    - Research has shown that **thrombin acts upon the *arginyl-glycine* linkages in fibrinogen to produce a fibrin monomer**
  - Factor XIIIa catalyzes: fibrin monomer → cross-linked fibrin reaction
  - When BVs are ruptured, usually both intrinsic and extrinsic pathways are activated
  - In severe degenerative disease of the liver (such as advanced alcoholic cirrhosis), prothrombin and fibrinogen levels will be markedly deficient
- **Thromboxane A2**
  - Release by platelets and causes them to stick together or aggregate
  - PGI2 acts to inhibit Platelet aggregation

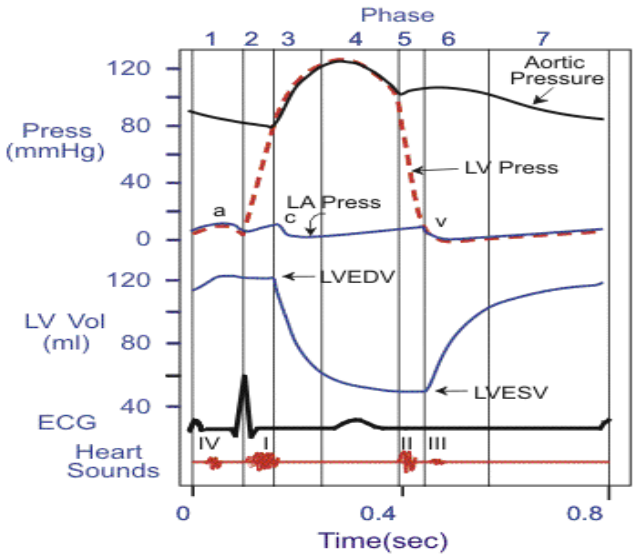
- Things required for normal blood clotting:
  - Ca^{2+}, thrombin, vitamin K, phospholipid, proteolysis
- **Vitamin K is cofactor 2 (prothrombin), 7,9,10**
  - (Plasmin breaks down clots)
  - Another Q: Fe^{2+} is not involved in coagulation of blood
- Anticoagulants:
  - Heparin, dicumarol, **sodium citrate**, any antithrombin substance
- Plasmin
  - Mediates dissolution of the fibrin clot during vessel repair
- Bleeding disorders –
  - Hemophilia A represents a bleeding disorder due to lack of factor VIII

- Erythropoeitin
  - Stimulates RBC production in bone marrow
  - **Glycoprotein hormone** produced in the kidneys
  - Negative feeback mech sensitive to the amount of O_2 in blood
  - Site of action
    - Hemcoytoblast (a pluripotent stem cell)
  - Can have hypo (anemia) or hyper (polycythemia) secretions of erythropoietin
- Plasma Calcium Levels
  - 8.5 to 10.5 mg/dl
  - Regulated by PTH
  - Vit D_3 regulates uptake in GI
  - Low Plasma Ca (hypocalcaemia) results in hyperirritability of nerves and muscles
  - In the case of hypocalcaemia, calcium ions are drawn away from their association with the voltage-gated sodium channels thus sensitising them. The upset to membrane potential is therefore caused by an influx of sodium to the cell, not directly by the hypocalcaemia. As a result, too many action potentials are sent to muscles causing spasm.==> tetany
  - High Plasma Ca results in CNS and Cardiovascular depression
- Plasma Phosporus levels
  - 3.0 to 4.5 mg/dl
  - Regulated by PTH
    - Causes kidneys to increase the rate of phosphate excretion
- Blood glucose levels
  - **80-100 mg/dl**
  - Reg. by insulin and glucagons

- Glucose normally does not appear in urine although it is filtered because it is reabsorbed in the proximal convoluted tubule

❖ Heart

- Valves
  - TPMA (Toilet Paper, My A**)
  - Tricuspid
    - Between Right A and V
    - Tough, fibrous tissue flaps of endocardium
    - Secured to papillary muscle via chordae tendineae
    - Damage to the tricuspid valve results in blood leakage from the right V to the right A
    - The three-segmented valve of the heart that keeps blood in the right ventricle from flowing back into the right atrium.
  - Pulmonary
    - Entrance of pulmonary artery
    - 3 cusps
  - Mitral (bicuspid)
    - Between Left A and V
    - Tough, fibrous tissue flaps of endocardium
    - Secured to papillary muscle via chordae tendineae
  - Aortic
    - Entrance of ascending aorta
    - 3 cusps
- Sounds
  - First Heart Sound
    - "Lub"
    - Closure of the AV valves at beginning of ventricular contraction
      - Immediately following the closure of the AV valves is the period of isometric contraction (muscle tension increased but muscle can not be shortened).
    - Louder and stronger
    - Systole starts with 1st sound
    - Diastole ends with 1st sound
  - Second Heart sound
    - "Dub"
    - Closure of semilunar valves (pulmonary and aortic)
      - Aortic closes before pulmonary, so sound can be "split"
      - The second heart sound is related to closure of aortic valve ➔ diastole starts.
    - Systole ends with 2nd sound
    - Diastole starts with 2nd sound
  - Sounds heard in the antecubital space during systole are produced by turbulent blood flow through the artery
  - All 4 valves are NEVER open at the same time
- Cardiac Cycle
  - Phases
    - 1 – Atrial Systole
    - 2 – Isovolumetric Contraction
      - Period between mitral valve closure and aortic valve opening
      - **Period of highest oxygen consumption**
    - 3 – Rapid Ejection
    - 4 – Reduced Ejection
    - 5 – Isovolumetric relaxation
      - Period between aortic valve closing and mitral valve opening
    - 6 – Rapid Ventricular Filling
    - 7 – Reduced Ventricular Filling
  - Sounds
    - 1 – Mitral and Tricuspid Valve Closure (Lub)
    - 2 – Aortic and Pulmon. Valve Closure (Dub, second sound)



Abbreviations:
LV Press, left ventricular pressure
a, a-wave; c, c-wave; v, v-wave
ECG, electrocardiogram
LVEDV, left ventricular end-diastolic volume
LVESV, left ventricular end-systolic volume

- 3 – Start of Ventricular filling
- 4 – High atrial pressure/stiff ventricle

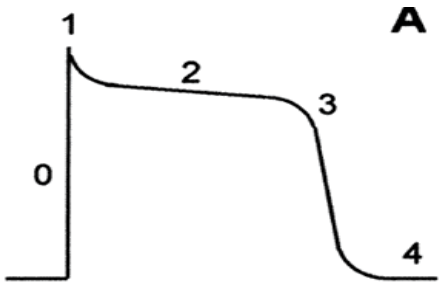
- Diastole
  - Isovolumetric ventricular relaxation
    - Pulmonary and aortic valves close
    - Ventricular pressure decreases
    - During this period, blood flow to the coronary arteries is the greatest in a resting individual
      - Another Q: During **early diastole**, blood flow to the left coronary artery is greatest
      - During contraction of the ventricular myocardium (systole), the subendocardial coronary vessels (the vessels that enter the myocardium) are compressed due to the high intraventricular pressures. However the epicardial coronary vessels (the vessels that run along the outer surface of the heart) remain patent. Because of this, blood flow in the subendocardium stops. As a result most myocardial perfusion occurs during heart relaxation (diastole) when the subendocardial coronary vessels are patent and under low pressure. This contributes to the filling difficulties of the coronary arteries.
  - Opening of tricuspid and mitral (bicuspid) valves [Passive Filling]
  - Atrial Systole
    - Following SA node depol, atria depol and contract [Active Filling]
    - The wave of depol slows in the AV node, allowing time for blood filling of ventricles
    - Ventricular volume is greatest at end of **atrial** systole = at the end of ventricular diastole
- Systole
  - Isovolumetric ventricular contraction
    - Mitral and tricuspid valves close (**All valves are closed during isovolumetric ventricular contraction**)
    - Another Q: Ventricular pressure rises rapidly and ventricular volume drops rapidly.
  - Ventricular ejection
    - Opening the aortic and pulmonary valves
    - Empty rapid at first, then rate slows and ventricular pressure drops
    - Ventricular pressure is greatest at beginning of ventricular ejection
- The largest volume flow of blood through the left coronary artery occurs during diastole
- An immediate effect of diminished oxygen tension in the myocardium is vasodilatation of coronary vessels

- Chronotropic State (Heart Rate)
  - Positive Chronotropy = Increase in Rate
    - Epinephrine administration causes both Positive Chronotropy (increase heart rate) and Inotropy (contractility)
- Inotropic States (Myocardial Contractility)
  - Term used to describe the degree to which the fibers are activated at a given preload and afterload
  - Positive Inotropy
    - Most commonly related to increased availability of intracellular Ca2+
    - Agents include:
      - Epi, NE, other Beta-1 agonsists
        - Increase the probability that a Ca channel is open
        - An injection into the left ventricular wall increases cardiac output and is a positive inotropy
      - Increased Extracellular [Ca2+]
        - **Causes an increased influx of Ca during phase 2 of the action potential**
      - Cardiac glycosides (Digitalis)
        - Inhibit the Na+/K+ ATPase, causing an increased intracellular [Ca2+]
        - **Digitalis is given to increase strength of contractions & decrease HR**
        - *I think this makes it a positive inotrope & a negative chronotrope*
  - Negative Inotropy
    - Related to decreased availability of intracellular Ca2+
      - Agents:
        - Ca channel blockers
        - Acidosis
          - Which blocks Ca2+ channels
        - Beta-1 receptor antagonists
          - Which decrease the probability that a given Ca2+ channel is open
        - Myocardial ischemia
        - Alcohol
        - Acetylcholine
          - **Decreases Ca2+ influx in the atria, but not in the ventricles**
- Exercise

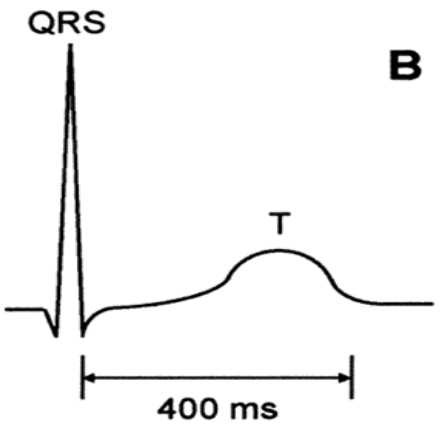
- 3 major effects are essential for proper circulation during exercise:
  - Mass discharge of sympathetic NS
    - Constricts vegetative muscles
    - Vasodilates skeletal muscles
    - Increase heart stuff, etc.
    - Moderate exercise increases HR & coronary blood flow
  - Increase in CO
    - **Skeletal muscle contraction facilitates more venous return, so stroke volume goes up, CO goes up**
  - Increase in arterial BP
    - From symp action, increasing CO

➢ Heart Muscle Refractory Periods
- Ventricular Muscle – 0.25 - 0.30 seconds
- Atrial Muscle – 0.15 seconds
  - Types of refractory periods
    - Absolute
      - Another AP is not even possible (H gate stuck)
      - Interval in which no stimulus is effective in creating an AP
      - Another Q: **Absolute refractory period is determined by duration of Na gate inactivation**
      - Limits the maximum frequency of effective nerve stimulation (maximum # of impulses a nerve can carry)
    - Relative
      - **Begins at end of absolute and continues until membrane potential returns to resting level**
      - Another AP is possible if stimulus is larger than usual
- Excitation time for total heart – 0.22 seconds
- Skeletal muscle cells have short refractory periods
  - Also can undergo tetanus, which increases strength of contraction
  - Cardiac muscle does not tetany because of its long refractory period

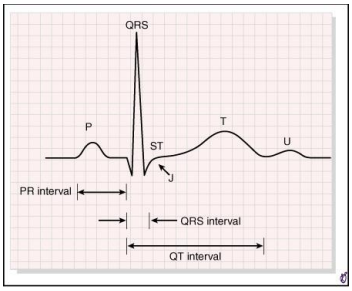
➢ Autonomic NS and the heart
- Controlled in medulla oblongata of brain stem
- Sympathetic
  - NE
  - Increase in HR
  - Fibers are from **T1-T4** (accessory nerves)
- Parasympathetic
  - Ach
  - Decrease in HR
    - Parasympathetic nervous system regulates heart rate
  - Fibers in the vagus nerves
    - Right vagus nerve – SA node (pacemaker)
    - **Left vagus nerve – AV node (slowest conductor in the heart)**
    - *****NOTE: Vagal stimulation in the mammalian heart has primarily a rate effect because there are few vagal endings distributed to the mammalian ventricles**



➢ Myocardial Action Potential (RIGHT)
- Phase 0
  - Rapid upstroke
  - Voltage-gated Na+ channels open
- Phase 1
  - Initial Repolarization
  - Inactivation of voltage-gated Na+ channels
  - Voltage-gated K+ channels begin to open
- Phase 2
  - Plateau – Ca2+ influx through voltage-gated channels balances K+ efflux
  - **Ca2+ influx triggers myocyte contraction**
- Phase 3
  - Rapid repolarization
  - Massive K+ efflux due to opening of voltage-gated slow K+ channels and closure of voltage-gated Ca2+ channels
- Phase 4
  - Resting Potential
  - High K+ permeability through K+ channels



- Cardiac Conduction
  - SA Node
    - Pacemaker
      - The following changes in the electrical properties of a pacemaker cell can slow down the rate at which the cell initiates impulses:
        - **The threshold potential becoming more positive**
        - **The rate of spontaneous depolarization decreasing**
        - **The maximum diastolic potential becoming more negative**
    - In posterior wall of R atrium by the opening of superior vena cava
    - The rate of the heart beat in a human is determined by the SA node (acts a pacemaker)
  - Internodal pathways
    - 0.04 Seconds
    - Transmit depol to L atrium and AV node
  - AV Node
    - In the lower R interatrial septum
    - Delays impulse 0.13 seconds so atria can contract first
    - The slowest rate of conduction velocity
  - AV Bundle (of His)
    - Orginates in AV node
    - Divides into 2 bundle branches to 2 sides of interventricular septum
  - Purkinje fibers
    - Originate in right and left bundle branches and extend to papillary muscles and lateral walls of the ventricles
    - Very fast depol through bundle branches and purkinje fibers – 0.03 seconds
- ECG or EKG – "Know the P, QRS, & T waves"



P wave	activation of the atria
PR segment	the duration of the AV conduction *(atrial depolarization to ventricle depolarization)*
QRS complex	activation of both ventricles
ST-T wave	ventricular recovery

Each 1 mm square represents 0.04 sec (40 ms)

Rate: 300 ÷ # of large boxes between 2 consecutive R waves

  - P wave
    - Atrial depolarization
      - **P waves occurring in ST segment indicating ectopic beats originating in the atria**
      - AV Blocks
        - 1st Degree
          - Prolonged PR interval (>200msec)
        - 2nd Degree
          - Type I (Wenckebach) shows a progressive prolongation of PR interval until a P wave is blocked and not followed by a QRS complex
          - Type II (Mobitz) shows sporadic/episodic "dropped" QRS complex
          - Extra P waves before each QRS complex on an EKG are indicative of partial heart block (second degree block)
          - Another Q: An EKG showing a consistent rhythmical ratio of three P waves to each QRST complex indicates an **AV node partial block**
        - 3rd Degree
          - Complete AV block with P waves completely dissociated from QRS complexes
          - Another Q: When the P wave and QRS complex are dissociated, it is indicative of complete (3rd degree) heart block
  - QRS Complex
    - Ventricular depol
  - T wave
    - Ventricular repol
  - S-T segment
    - **Ventricles are completely depolarized???** (Only point where this happens in ECG)
    - Isoelectric
  - P-R interval

- "What is the PR interval"
  - Length of time between depol of **atria and depol of ventricles**
  - The P-R interval is related to propagation of the cardiac impulse between the SA node and the AV node
  - Index of the conduction time between the atria and the ventricles
  - Index of the atrial depolarization and conduction through the AV node
  - Another Q: When an increased PR interval is observed, this represents slow conduction of impulses through the AV node
- **Approx 0.16 seconds (0.13 + 0.03, see above)**
- **normal if between .12 and .20 second.**

- Q-T interval
  - **Period between ventricular depol and repol**
  - Approx 0.35 seconds
- T-P section
  - **Isoelectric (aka ventricle is at resting membrane potential) – no electric signal to the heart during this section**
  - Ventricle is filling with blood
  - Shortens a lot at high HRs
- Leads
  - Standard Bipolar Limb Leads
    - I Right Arm (-) Left Arm (+)
    - II Right Arm (-) Left Leg (+)
    - III Left Arm (-) Left Leg (+)
  - Standard Unipolar Limb Leads
    - AVR Right Arm (+)
    - AVL Left Arm (+)
    - AVF Left Leg (+)
  - Doesn't matter which one you used for cardiac arrythmias, BUT it does w/ voltage abnormalities & axis deviations
  - Chest Leads
    - V1, V2, V3, V4, V5, V6
    - Represent 6 places on the anterior chest wall

➢ Heart NZs:
- **Creatine kinase (CK**) also called creatine phosphokinase **(CPK) yummy hearty pizza**
  - The first heart enzyme to appear in blood after a heart attack
- Glutamate oxaloacetate transmaminase (GOT)—the second to appear
- Glutamate pyruvate transmaminase (GPT)
- Lactate dehydrogenase (LDH) different isozyme characteristic of heart muscle
- The plasma levels of these enzymes are commonly determined in the diagnosis of myocardial infarctions
  - They are particularly useful when the ECG is difficult to interpret
- NEW GOLD STANDARD for Dx of a MI → Troponin C

➢ Congestive heart failure
- Causes bulging veins in the neck

➢ A person with left heart failure might show signs of **dyspnea** when placed in the supine position because of **edema caused by excessive pulmonary capillary hydrostatic pressure**

➢ It's sing of coronary heart disease.

➢ the left ventricle. It can be brought on by an acute heart attack, severe ischemia, volume overload of the heart's left ventricle, and mitral stenosis

❖ **Respiratory System**

➢ Gas exchange
- Oxygen passes from alveolar air into blood by diffusion
- Depends on:
  - Thickness of the membrane
    - Thin is better
    - Rate of diffusion is inversely proportional to the diffusion distance
  - Surface area of the respiratory membrane
    - Rate of diffusion is directly proportional to the surface area
    - Increasing the cross-sectional area can increase the rate of oxygen diffusion at the alveolar membrane
  - Solubility of gas
    - Gas dissolved in liquid exerts partial pressure
      - So partial pressure includes both gas particles and liquid gas particles
    - CO_2 is 20x more soluble than O_2

- Partial pressure difference between two sides of a membrane
  - Net diffusion from high to low pressure
    - In addition to the respiratory system, the exchange of gases between plasma & **tissue fluid is a function of partial pressures (NOT due to osmotic pressure differentials or differences in volume % of the gases)**
    - Another Q: The actual diffusion of gases is 1° controlled by differentials in partial pressures of the gases
  - Alveolar PO_2 is greater than pulmonary arterial pressure
  - Alveolar PCO_2 is lower than pulmonary arterial pressure
- **The diffusion coefficient for the transfer of each gas through the respiratory membrane depends upon BOTH solubility and molecular weight**
- Partially pressures of respiratory gases found in arterial blood most closely correspond to partial pressures found in the alveoli

- So, O_2 removal from the alveoli is facilitated by low PO_2 of alveolar blood, increased total alveolar surface area, and increased blood flow through alveolar capillaries
- **Another Q: As blood passes through alveolar capillaries, blood PO_2 rises, hemoglobin releases CO_2 & H^+ (blood PCO_2 does not rise)**
  - **NOTE Hb does release H+, but NOT into the blood, only to be available in the RBC to make Carbonic acid with the influxed bicarb**

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

-

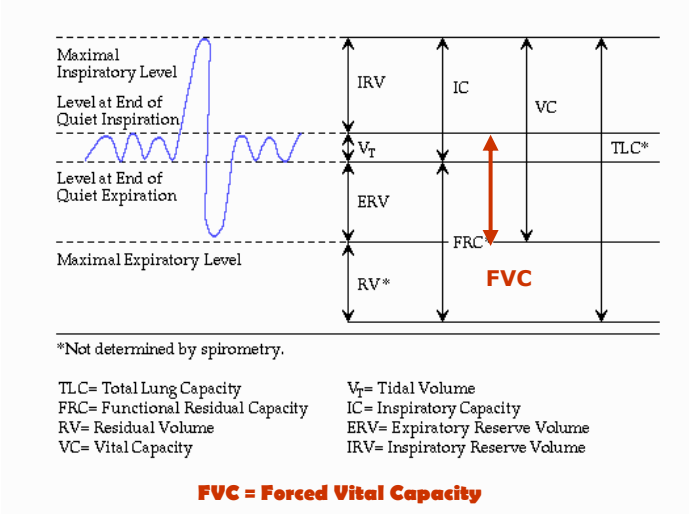
- Pulmonary Circulation
  - Normally a low-resistance, high compliance system
  - PO2 and PCO2 exert opposite effects on pulmonary and systemic circulation
    - A decrease in PAO2 causes a hypoxic vasonconstriction that shifts blood away from poorly ventilated regions of the lung to well-ventilated ones
  - **A consequence of pulmonary hypertension is cor pulmonale** and subsequent right ventricular failure (Jugular venous distention, edema, hepatomegaly)
- Pulmonary Ventilation
  - Total volume of gas per minute inspired or expired
  - Coordinated in the brain stem (medulla)
- V/Q Mismatch
  - **Ideally Ventilation is matched to perfusion such that V/Q = 1**
    - **Actual is 0.8**
  - Lung zones
    - Apex of the lung = V/Q = 3 (wasted ventilation)
      - **Just think blood is flowing through the base of the lungs, so base of the lungs, and air rises so V is greater in the apex**
    - Base of the lung = V/Q = 0.6 (wasted perfusion)
      - **BOTH ventilation and perfusion are Greater at the base of the lung than at the apex**
    - V/Q = 0 (means airway obstruction)

- V/Q = infinity (means blood flow obstruction)

➢ Minute ventilation
- Volume of air moved in to the respiratory passageways in one minute
- **= Tidal volume x Breaths/min**

➢ Alveolar ventilation
- Is the actual air that reaches the alveoli and can participate in gas exchange
- Expressed in per minute OR per breath
- **= Respiratory Rate x (Tidal volume – Dead air space volume)**
  - Dead air space
    - Air that is filled in the non-gas exchange areas of the lung (all but alveoli)
    - ~150ml
- Is the best criterion for effectiveness of breathing

➢ **Lung Volumes and Capacities**



- Tidal volume (V_T)
  - Amount of air entering the lungs with each breath
  - Normal is 12/min
  - ~500ml
- Inspiratory capacity (IC)
  - Amount of air entering lungs with maximal inhalation
- Vital capacity (VC)
  - Maximum volume a person can exhale slowly
  - = **Vt + IRV + ERV**
- Functional residual capacity (FRC)
  - This is the volume left in lungs at the end of a **normal quiet expiration**
  - **At FRC the tendency of the lungs to collapse is exactly balanced by the tendency of the chest wall to expand**
  - = ERV + RV
  - **One should expect Nitrous sedation to take longer than normal in a person with functional residual capacity larger than normal**
- Residual volume (RV)
  - Volume left in lungs at the end of a forced maximal expiration
  - ANATOMIC Deadspace
- Inspiratory Reserve Volume (IRV)
  - Extra volume of air that can be inspired in addition to V_t
  - Approx 3000ml
- Expiratory Reserve Volume (ERV)
  - Extra volume of air that can be exhaled after normal expiration of V_t
  - Approx 1100ml
- Total lung capacity (TLC)
  - Vital capacity + residual volume
- Forced vital capacity (FVC)
  - Maximum volume a person can exhale with maximal force
- Forced expiratory volume in one second (FEV_1)
  - Volume of air forcefully exhaled in one second
  - Note, this is a measure of flow whereas FVC is a measure of volume

- FEV_1/FVC
  - **This ratio is useful in differentiating obstructive and restrictive lung conditions**
- TLC =
  - IRV + V_T + ERV + RV
  - FRC + IC
  - VC + RV
- A patient with emphysema exhibits increased FRC & increased compliance
  - Compliance
    - is the measure of distensibility of a chamber expressed as a change in volume per unit change in pressure
  - Spirometry
    - **You can't measure RV, FRC, and Total lung capacity**

➢ Lung Receptors
- Lung stretch receptors
  - Located in smooth muscle of airways
  - During inspiration (when distended):
    - Stimulate Hering-Breuer reflex, which prevents overinflation
      - ➢ The adequate stimulus for the Hering-Breuer reflex is the stretching of alveoli
        - **Think Bruer Hockey Gear to keep your lungs tight**
    - Send stimuli over afferent vagus nerve to resp center in medulla
      - ➢ Lung→Vagus→Medulla→Spinal cord→Respiratory muscles
      - ➢ This results in inhibiting inspiration, allowing expiration to occur.
    - Not used much in normal breathing, only protective
    - Expansion of the lungs stimulates vagal nerve endings in the lung parenchyma & inhibits inspiration
- J Receptors
  - Located in the alveolar walls
  - When stimulated, cause rapid, shallow breathing
    - **Jake is a shallow person**
- Irritant Receptors
  - Located between airway epi cells
  - Stimulated by noxious substances
- Joint and muscle receptors
  - Are activated during exercise to stimulate breathing
- NOTE: PCO_2 is the most important stimulus for the respiratory center in medulla
  - An increase in arterial CO_2 has the greatest effect in stimulating respiration
  - Another Q: After a period of voluntary hyperventilation, respiration becomes depressed mainly due to reduced blood PCO_2
  - Another Q: **Apnea** (temporarly cessation of breathing) occurring after hyperventilation of an anesthetized patient results from **decreased CO_2 tension**.

➢ Respiratory Products
- Surfactant:
  - **Dipalmitoyl Phosphatidylcholine (Lecithin)**
  - Collapsing Pressure = 2 (tension)/Radius
  - Decreases alveolar surface tension and increases compliance
  - Difficulty breathing in neonates → due to deficient surfactant **resulting in increased surface tension**
- Prostaglandins
- Histamine
- Angiotensin Converting Enzyme (ACE): cleaves AI → AII, **inactivates bradykinin and causes cough**, angioedema)
- **Kallikrein: Activates Bradykinin**

➢ Respiratory Terms
- Apnea – cessation of breathing
- Hypercapnea – Excess CO_2 in arterial blood
- Hypocapnea – Duh
- Hyperpnea – Abnormally deep and rapid breathing
- Resp Arrest – Permanent cessation of breathing
- Hyperventilation – Increased ventilation in excess of metabolic requirements
  - Results in loss of CO_2 from blood, causing a decrease in BP and may result in fainting (Brown Bag it)
  - Results in decreased CO_2 and increased pH (decrease in H^+)
  - Another Q: Voluntary overventilation of the lungs results in decreased $[H^+]$
  - Repiratory alkalosis
- Hypoventilation –

- decreased ventilation
- **The most important test for hypoventilation is the determination of arterial CO_2 tension**
- Caused by:
  - **Drugs that depress respiratory center in the medulla (barbiturates)**
  - Obstruction paraylysis of the respiratory muscles
  - Lung Disease

➢ Pressures in the respiratory system:
- Atmospheric Pressure
  - = 760mmHg = same pressure in alveoli when lungs are at rest (aka after a normal expiration)
- Collapsing force of lungs
  - **By the elastic CT of the lungs and surface tension from surfactant**
  - **NOTE: Pulmonary surfactant acts to increase both lung compliance & vital capacity**
    - **So obviously w/o it you have decreased both compliance and vital capacity**
- Expanding force of the lungs
- ***Both forces are equilavent at FRC or the end of expiration, or the "point of rest"**
  - Here, both inspiration or expiration would require muscle involvement
- Partial Pressures (in mmHg)

	Venous Blood	Arterial Blood	Alveoli	Atm
PO_2	40	100	105	160
PCO_2	46	40	40	0.3

  - In the resting state, the average difference between O_2 content of arterial & venous blood is 5 volume percent
    - ***Jake**: how does this correlate with the 40 vs. 100mmHg thing above? Does it have to do with total content, and not PO_2, which changes drastically*
  - Another Q: When the partial pressure of oxygen in arterial blood is lower than that in alveoli, this suggests thickening of the alveolar membrane??? (Sounds normal to me)
  - Another Q: The partial pressures of respiratory gases found in arterial blood correspond most closely to those partial pressures found in the alveoli
  - Another Q: In a pulmonary AV shunt, the O_2 partial pressure in arterial blood is low
  - Another Q: Under physiological conditions the lowest partial pressure of oxygen is in Venous Blood NOT expired Air
- Intrapleural Pressure
  - Pressure w/in the pleural cavity
  - **In resting position, approx 4 mm Hg less than the atm pressure (so 756mm Hg)**
    - Intraalveolar **pressure** is the **pressure** inside the alveoli of the lungs.
    - **Intrapleural pressure (intrathoracic)** is the **pressure** within the pleural cavity.
    - Intrapulmonary pressure is the pressure withing the lungs.
  - Intrapleural pressure is always less than the intrapulmonary pressure
  - Another Q: Intrapleural pressure during normal respiration is subatmospheric
  - **Simultaneous contraction of the external intercostal muscles & the diaphragm results in a decrease in intrapleural pressure so the air can come in.**
    - *(the pressure becomes more negative – that's a decrease)*

➢ Physiologic Dead Space
- **= Anatomic dead space + any part of the lung that should be ventilated and perfused but is not**
- = the volume of the conducting pathways (trachea and Bronchio…something)

➢ Establishing a tracheostomy results in decreased respiratory work
- Non perfusing alveoli, PHYSIOLOGIC dead space
- Work, which is defined as P x V is reduced because volume is reduced
  - You would decrease anatomic dead space with a tracheostomy

➢ Another Q: The RQ for a man who uses 4 liters of oxygen and produces 3 liters of CO2 is 0.75
- **Respiratory Quotient**
  - = The rate of Vco2/ Rate of vO2 – **How much CO2 you make/ How much O2 you use**
  - RQ = CO2/O2 → remember the 0.8
  - RQ quotient for a person taking pure glucose as food source is → higher than normal (normal is 0.8, with pure glucose is 1.0)
    - NOTE the RQ may be used to calculate the basal metabolic rate via the technique of indirect calorimetry (O2 and CO2)
- **RQ: for fat = 0.7; for carb = 1.0**

- If the respiratory quotient is 0.7, the primary energy source is: fat, ketone bodies, glucose, etc.
    - ♦

➢ Asthma
- Signs/Symptoms of asthma attack
    - Airway Edema
    - Brochospasm
    - Increased Mucous secretion
    - Increased airway resistance
        - ♦ NOT Decreased Surfactant
- Tx
    - Adrenergic Beta-2
- Consequences of pt's respiratory difficulty
    - Causes, Hypoxia, Hypercapnia (increase CO_2), hyopventilation, Tachycardia, Acute Respiratory Acidosis
        - ♦ NOT Increased Renal Bicarbonate Production
            - ➢ **(Because Increased CO_2 already shifts the equation back to having lots of Bicarb, so no need for more)**

❖ **Muscle**

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

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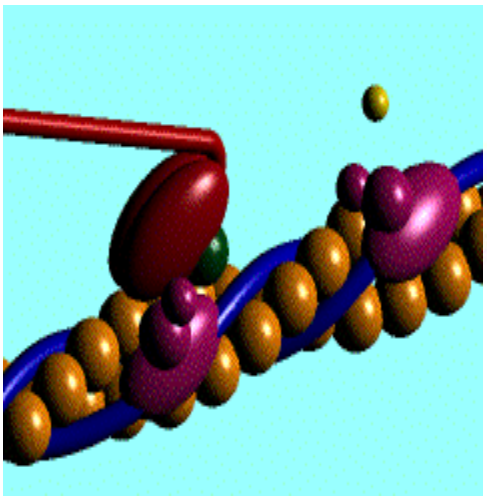
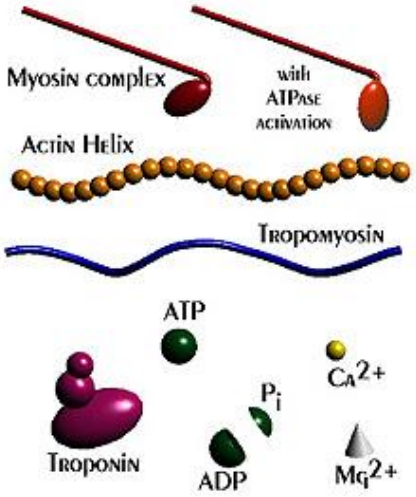
❖ ---

❖ **epimysium:** The external sheath of connective tissue surrounding a muscle
❖ **perimysium:** The sheath of connective tissue enveloping bundles of muscle fibers (fascicle)
❖ **endomysium:** The connective tissue surrounding each individual muscle fibre
❖ **myoribril:** Any of the threadlike fibrils that make up the contractile part of a striated muscle fibe
❖ **sarcomere:** One of the segments into which a fibril of striated muscle is divided

➢ Motor Unit
- Alpha motor neuron and all of the muscle fibers it innervates
    - Each muscle has several muscle fibers
    - Each muscle fiber is innervated by a single alpha neuron
    - Each alpha neuron innervates many muscle fibers
    - All of the fibers innervated by a motor neuron contract when that motor neuron fires an AP
        - ♦ In other words, when a nerve arrives at a motor unit, it will cause all of the motor unit to contract
- Size Principle
    - Motor neurons are recruited in order of size
    - If small force is needed, only small fibers activated, etc.
- Fractionation

- You do NOT need to activate all motor units in a muscle at once
- Recruitment with respect to motor neurons refers to progressive increase in the number of motor units involved





SEE http://www.sci.sdsu.edu/movies/actin_myosin_gif.html for a sweet Animation

- Muscle Contraction (ABOVE PICS)
  - Controlled by nervous system
  - The sarcomere represents the basic contractile unit of muscle myofibril
  - APs traveling down somatic alpha motor neurons cause depolarization of the skeletal fibers at which they terminate
  - Neuromuscular junction = junction between the terminal of the motor neuron and a muscle fiber
    - When an AP arrives at a neuromuscular junction, calcium ions enter the nerve terminal causing the release of Ach from synaptic vesicles within the motor neuron
      - Ach then binds to the nicotinic cholinergic receptors in the muscle fiber plasma membrane. This causes depolarization which triggers an AP (the action potential travels along the membrane t-tubules)
        - Acetylcholine esterase is the NZ that is involved in the termination of the neuromuscular transmission
        - **The depolarization of the skeletal muscle cell membrane by motor nerves is directly produced by the change in end plate potential level to a critical value**
        - Transmission of impulses from the motor nerve to the muscle cell regularly produces an action potential in the muscle cell
        - This AP triggers the release of calcium ions from the sarcoplasmic reticulum
          - **The calcium release form the S.R. into the cytoplasm is the 1st measurable event in the myofiber following generation of an AP in the sarcolemma**
          - Calcium is sequestered/stored in Sarcoplamic Reticulum
          - This leads to crossbridge formation between actin and myosin. These interactions are responsible for the development of tension and the shortening of the fibers
            - The length-tension diagram shows that the maximum active tension of a muscle occurs when there is maximum overlap of crossbridges
          - The excitation-contraction coupling is measured by the release of calcium from the sarcoplasmic reticulum
          - Troponin C (trops for movement when Ca++ binds)
          - Tropomyosin in Actin prevents connection of Mysoin to Action, when Ca++ binds to Troponin C then Tropomysoin is relocated and myosin can bind.

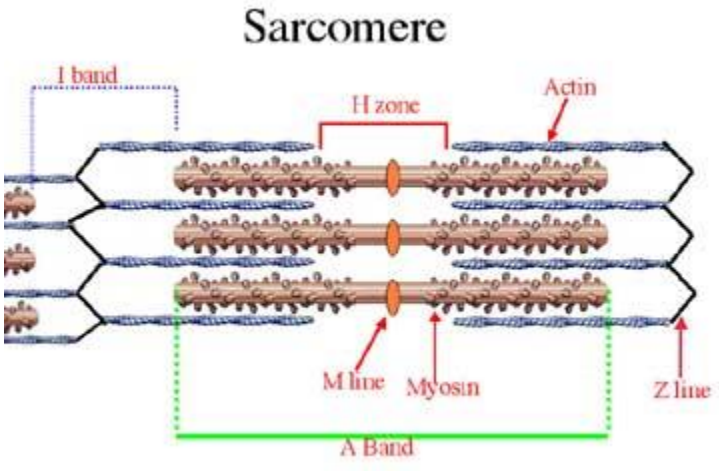
-
- Calcium binds to troponin C on the thin filaments

- Calcium ions trigger contraction of muscles when they bind to troponin
- The stimulation of muscle contraction (via calcium) is mediated via troponin C (not mediated by actin, tropomyosin, troponin I, or the sarcoplasmic reticulum)
- **Cardiac muscle only needs 1 Ca to activate, other muscles need 2 Ca2+**
- **2 sites are always filled by Mg**
- Causes a conformational change in troponin that permits Troponin I to release from tropomyosin and then tropomyosin changes allowing myosin and actin to bind
- After calcium binds with troponin, tropomyosin moves from its blocking position permitting actin and myosin to interact
- High energy myosin binds weakly to actin subunits, however, **when inorganic phosphate is released from the myosin, the myosins bind tightly to the actin subunits**
  - High energy myosin has ATP bound to it; **upon release of P_i, myosin can bind tightly to actin**
- Energy stored in the high-energy myosin is discharged, and the myosin head swivel, pulling on the thin filaments
  - **Mg2+ comes in to Activate the ATPase, which then gives the energy to stroke**
- This repeated pulling of the thin filaments past the thick filaments toward the centers of the sarcomeres draws the Z lines closer together, and the muscle fiber shortens (contracts)
- During an isotonic contraction, the A band does not change in width or length
  - HIZ contracts!!!
  - H band, I band, and consecutive Z lines, sarcomeres, & series elastic elements do change dimension
- This process is repeated as long as calcium ions are bound to troponin and ATP is available
- Once calcium ions are returned to the sarcoplasin reticulum, tropomyosin moves back into its blocking position and prevents further interaction between high-energy myosins and actin subunits
  - Then contraction ceases and the muscle fibers relax
- The dissociation of the actomyosin complex results from ATP replacing ADP on the myosin head
  - **NOT rephosphorylation of ADP**

♦ **Submaximal direct stimulus to skeletal muscle will cause some fibers to contract, but not the whole muscle**

♦ Another Q: Ratio between the amount of work done & total energy expended determines the mechanical efficiency of muscular contraction

▪ A muscle devoid of tonus (muscular tone) is atonic



➢ Muscle Energy Sources

▪ Another Q: ATP→ADP + P_i is the reaction providing the **immediate source** of energy for muscular contraction (1-2 seconds)

♦ Then, creatine phosphate is used to rephosphorylate the now unbound ADP to ATP (next 2-5 seconds)

♦ Phosphocreatine, also known as creatine phosphate or PCr, is a phosphorylated creatine molecule that is an important energy store in skeletal muscle. It is used to generate ATP from ADP, forming creatine for the 2 to 7 seconds following an intense effort.

♦ Glycogen is then the 3rd participant and is used to reconstitute both ATP and creatine phosphate

♦ At moderate levels of muscle activity (>20 minutes), the predominant source of ATP is from FAs

➢ Another Q: FAs is the predominant source of ATP at MODERATE levels (>60 min) of activity

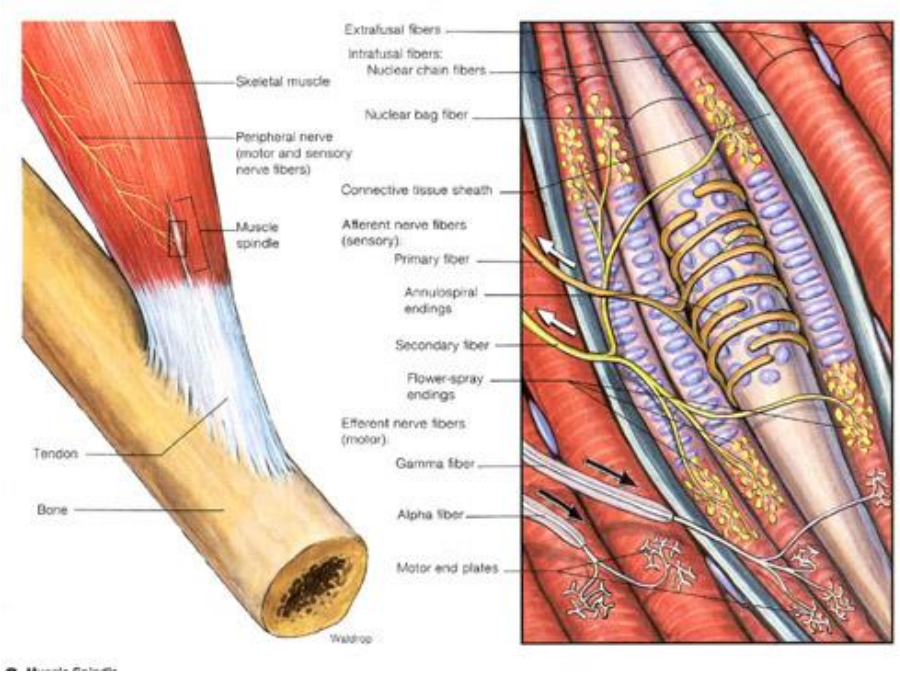
➢ During prolonged period of starvation, the primary fuel is NOT glycogen

▪ **Another Q: ATP is essential to the transformation of G-actin to F-actin**

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

- Types of muscle fibers:
  - Extrafusal fibers:
    - Fibers that make up the *bulk of the muscle*
    - Innervated *by alpha-motor neurons (efferent neurons)*
    - Provide the force for muscle contraction
  - Intrafusal fibers
    - Are encapsulated in sheaths to form muscle spindles
    - Innervated by gamma-efferent (motor) neurons
    - Two types of fibers:
      - Nuclear bag fibers:
        - Detect fast, **dynamic** changes in muscle length and tension
        - Innervated by **group 1a afferents**→fastest in body
      - Nuclear chain fibers:
        - Detect **static** changes in muscle length and tension
        - Innervated by the slower group II afferents
      - Chain gangs are slow
  - *NOTE:
    - **Discharge of impulse in small motor (fusiform (spindle)) neurons *innervating muscle spindle* serves to sustain extrafusal muscle contractions**
    - Another Q: the gamma efferent system controls the excitability of the muscle spindle
- Spinal Reflex
  - *The spinal cord is the only structure in the CNS necessary for a simple reflex
  - Two important spinal reflexes influence the contraction of skeletal muscles
    - Stretch reflex:
      - It is initiated at receptors called muscle spindles that are sensitive to muscle length and tension
      - This reflex stimulates the stretched muscle to contract
      - Stretch reflex is **monosynaptic** (not withdrawal)
      - Another Q: The sensory endings serving the **stretch reflex** are classified as **proprioceptors**
      - An example is the patellar reflex (knee jerk reflex) in which the striking of the patellar tendon at the knee causes the quadriceps muscle to contract and swing the leg forward
      - **Another example of a spinal reflex is reflex shivering upon application of a local, cold stimulus applied to an extremity but not leading to lowering of body temperature**
      - Another Q: The tone of masseter muscle is maintained by stretch reflex (via muscle spindles)
      - Another Q: Strong stimulation of spindles in the masseter muscle results in contraction

- Another Q: Tapping on the side of the face elicits a contraction of the masseter muscle; this is an example of a stretch reflex
- Fxns:
  - Maintain muscle tone for posture
  - Increase efficiency for locomotion
  - **Postural reflexes are maintain by muscle spindles**
  - Smooth out movements
  - Act as site of coordination for higher-order inputs
- Muscle spindles: (muscle length and tension)
  - Are found within the belly of muscles
  - Connective tissue sheath that encloses 2-12 intrafusal muscle fibers
  - **Consists of two afferent fibers, group Ia and group 2 fibers**



  - **Type Ia Sensory Fiber also called Primary Afferent Type 1A Fiber or Group II sensory fibers is a component of a muscle fiber's muscle spindle which keeps track of the how fast a muscle stretch changes (the velocity of the stretch).**
  - Encapsulated intrafusal fibers that run in parallel with the main muscle fibers so that the spindle will stretch when the muscle relaxes or stretches
  - Detect both static and dynamic changes in muscle length
  - The stretrching gives rise to a generator potential and ultimately to an action potential in the group Ia and 2 fibers that arise from the spindle
    - The intrafusal fibers in addition to being innervated by sensory fibers also receive motor innervation from gamma efferents
    - The activation of these gamma fibers stretches the intrafusal muscle fibers and gives rise to an action potential in the group Ia fibers
    - Relaxation of intrafusal muscle fibers decreases impulse activity in the group Ia fibers
  - Finer movements require greater number of muscle spindles in a muscle
  - 3 components:
    - Specialized muscle fibers (intrafusal) – see below
      - Separate from the exrafusal fibers, that make up the bulk of the muscle fiber
    - Sensory terminals: group Ia and II afferents
      - Wrapped around specialized muscle fibers (intrafusal fibers)
    - Motor terminalis: gamma motor neurons
      - Activation maintains the spindle sensitivity

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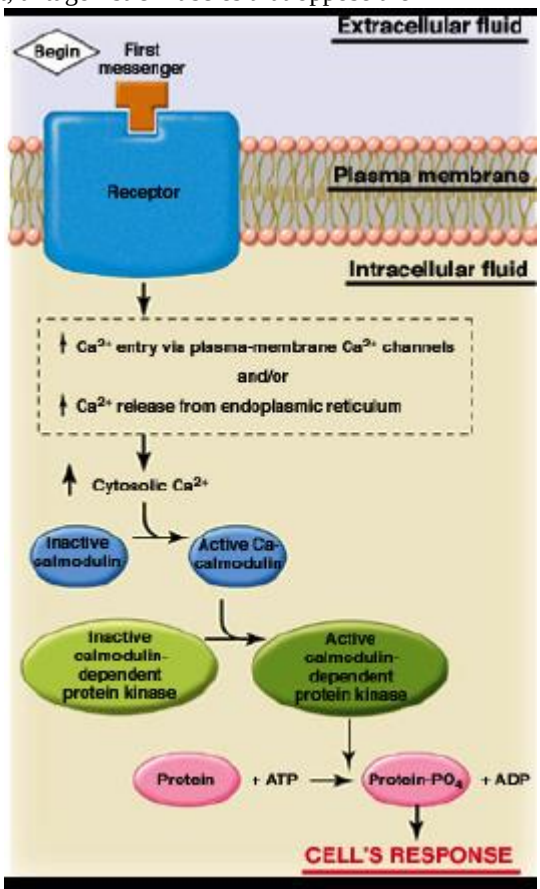
are needed to see this picture.

- ➢ **Muscle spindles** are the sensory organs concerned with maintenance of skeletal **muscle tone**
- ➢ **Another Q: The annulospiral (primary) ending of the skeletal muscle spindle is stimulated when the muscle is stretched**
- ➢ **Another Q: Frequency of impulse activity in the afferent nerve from a muscle spindle (Group Ia afferent fibers) is increased by an increased activity in gamma efferent fibers AND a passive stretch of the muscle**

♦ Spasticity – is best characterized by exaggerated stretch reflexes (normal reflexes) (state of spasm, muscle resists being stretched out)

♦ Constant stimulation of muscle spindle, leads to spastic paralysis

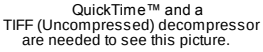
- Golgi Tendon reflex:
  - ♦ Initiated at receptors called neurotendinous organs (golgi tendon organs)
  - ♦ Sensitive to tension which occurs as a result of muscular contraction or muscle stretch
  - ♦ Stimulates the contracted muscle to relax
  - ♦ **Reverse of stretch reflex**
  - ♦ **Also depolarize in response to stretch, but this reflex inhibits alpha neuron causing the muscle to relax**
    - ➢ Golgi tendon organs (tension):
      - ▪ **Innervated by a single group Ib sensory fiber**
- Reciprocal inhibition
  - ♦ When the stretch reflex stimulates the stretched muscle to contract, antagonistic muscles that oppose the contraction are inhibited
  - ♦ The neuronal mechanism that causes this reciprocal relationship is called reciprocal innervation
    - ➢ Reciprocal innervation is the process by which motor neurons to extensor muscles acting at a particular joint are inhibited by stretch of the flexor muscles acting at the same joint



- ➢ Jaw opening reflex
  - ▪ When a person bites down rapidly on an unexpectedly hard surface while chewing, the result is cessation of motor unit recruitment in jaw closing muscles by causing a stimulation of periodontal mechanoreceptors
- ➢ Jaw Jerk reflex
  - ▪ Is an example of a dynamic stretch reflex
  - ▪ Is seen when you tap on the chin, causes the masseter to jerk close
- ➢ Reflex after-discharge????
  - ▪ Can be explained in terms of internuncial pool circuits
    - **Internunial – A neuron functionally interposed between two or more other neurons**
- ➢ Types of muscle:
  - ▪ **Smooth muscle**
    - Contraction
    - First a hormone combines with a hormone receptor and activates a G protein
      - ♦ Then the alpha subunit goes and opens the Calcium channel

        - Calcium comes in and binds to **Calmodulin**
            - Then the CaCM complex binds to Myosin kinase and activates it
                - MK attaches phosphate from ATP to myosin heads to activate the contractile process
                    - A cycle of cross-bridge formation, movement, detachment, and cross-bridge formation occurs
                    - Relaxation occurs when myosin phosphatase removes phosphate from myosin
    - Characterized by:
        - Slow Ca2+ channels
        - NO transverse T tubules
        - NO Troponin
        - Ach Stimulates → Think glands and rest and digest muscles from Parasympathetic
        - Spontaneous activity in the absence of nervous stimulation (Hormones aren't nervous!)
            - They have intrinsic nerves that are contained within plexuses (GI – myenteric plexus)
        - Sensitivity to the chemical agents either released locally from nerves, or carried in the circulation
            - They could cause the release of more Ca2+
    - Another Q: Slow wave potentials are commonly observed in smooth muscle
    - Another Q: The contractile process in smooth muscle involves actin & myosin
    - Another Q: Smooth muscle contraction can be maintained for a longer time than skeletal muscle contraction
    - Another Q: Smooth muscle contains each of the following muscle proteins:
        - **Actin, myosin, tropomyosin (but not troponin)**
    - Another Q: In smooth muscle contraction, myosin kinase is responsible for initiating cross-bridge cycling
- Skeletal muscle
    - **Has the greatest membrane potential difference across the membrane**
    - NO slow Ca2+ channels
    - Has Transverse T tubules
    - NOT inhibited by Ach
- Cardiac muscle
    - **(Calcium-induced Calcium release)**
        - Contraction is dependent on Extracellular Ca2+, which enters the cells during plateau of action potential and stimulates Ca2+ release from the cardiac muscle Sarcoplasmic reticulum
    - Cardiac is different than skeletal because:
        - Action potential has a plateau, which is due to the Ca2+ influx
        - Cardiac nodal cells spontaneously depolarize, resulting in automaticity
        - **Cardiac myocytes are electrically coupled to each other by gap jxns**
    - **A type of striated muscle containing transverse tubules, a slow rate of calcium sequestration, & is inhibited by Ach**
    - **The strength of cardiac muscle contraction is increased when extracellular Ca^{2+} is increased**

- Muscle Cells/Energy
    - Use the Phosphorylated form of creatine to store energy
    - Normal metabolism cannot supply energy as quickly as a muscle cell can use it, so an extra storage source is needed
    - The phosphate group can be quickly transferred to ADP to regenerate ATP necessary for muscle contraction
    - Autoregulation of bloodflow in muscle determined by muscle metabolites (PAL: K^+, lactate, adenosine)
        - **Adenosine causes vascular smooth muscle to relax**
            - **Your muscles relax because ATP has been broken down to adenosine**
    - Phosphate compounds found in living organisms can be divided arbitrarily into two groups based on their standard free energy hydrolysis:
        - Higher phosphate group-transfer potential than ATP:
            - Phosphoenolpyruvate
            - Acetyl phosphate
            - 1,3-diphosphoglyceric acid
            - Carbamoyl phosphate
            - Creatine phosphate
            - ***1,3-diphosphoglyceric acid & creatine phosphate are energy-rich phosphate carriers
        - Lower phosphate group-transfer potential than ATP: **(Sugars and De-Pi Creatine)**
            - Glucose-1-phosphate
            - Fructose-1,6-diphosphate
            - Glucose-6-phosphate
            - Creatine



- ATP and muscle contration
  - Hydrolysis of ATP (ATP→ADP + P_i) provides immediate source of energy for muscle contraction
  - Although muscle fibers contain only enough ATP to power a few twitches, its ATP "pool" is replenished as needed
  - Sources of high-energy P_i:
    - Creatine P_i
    - Glycolysis of glucose from stored glycogen
    - Cellular respiration in the mitochondria of muscle fibers
- Slow vs. Fast Twitch
  - Fast twitch are twice as large
    - **Twice for Type II**

Characteristic	**Slow Twitch (type I) Think O2**	**Fast twitch (type II)**
Myosin-ATPase activity	Low	High
Speed/intensity of contraction	Slow/low	Fast/hight
Resistance to fatigue	High	Low
Oxidative capacity	**High**	**Low (Burn out quickly)**
Enzymes for anaerobic Glycolysis	Low	High (depends on anaerobic glycolysis)
Mitochondria	Many (You've got time for Kreb's)	Few
Sarcoplasmic reticulum	**Less extensive**	**More extensive**
Capillaries	Many	Few
Myoglobin	High	Low
Glycogen content	Low	High

CNS

- Spinal Cord
  - Gray Matter
    - Dorsal Horn (DRGanglia)
      - Sensory impulses
    - Anterior Horn (Ventral)
      - Motor impulses
  - White Matter
    - Consists of myelinated nerve fibers, which form the ascending and descending tracts
      - A tract represents a group of axons within the CNS having the same origin, termination, and function, and is often named for its origin and termination (i.e., spinothalamic tract)
      - Sensory impulses
        - Travel via the afferent of ascending neural pathways to the sensory cortex in the parietal lobe of the brain where they are interpreted
        - Sensory information is processed on the contralateral side
        - Spinothalamic tract (anterior and lateral)
          - Travel in the anterolateral quadrant of the spinal cord and are also called the anterolateral system

- Sensations originate in the dorsal horns of the spinal gray mater, **cross to the opposite side of the cord and ascend via the spinothalamic tracts** through the anterior and lateral white columns of the cord to terminate at the levels of the brain stem and in the thalamus
  - Lateral spinothalamic tracts
    - Impulses concerned with **pain and temperature**
  - Anterior (ventral) spinothalamic tracts
    - Impulses from receptors sensitive to **light touch**

➢
➢ Dorsal Column-Medial Lemniscal System:
- Carries sensations mainly in the posterior (dorsal) columns of the cord and them, after synapsing and **crossing to the opposite side in the medulla**, upward through the brain stem to the thalamus by way of the medial lemniscus
- Conveys well-localized sensations of **touch, pressure and vibration**
- Fasciculus gracilus
  - In the medulla, nerve fibers from the fasciculus gracilis synapse in the nucleus gracilis
- Fasciculus cuneatus
  - Fibers from the fasciculus cuneatus synapse in the nucleus cuneatus also in the medulla
    - **Processes from the two nuclei cross to the other side of the medulla and give rise to a tract called the medial lemniscus
    - Nerve fibers from the lemniscus synapse in the thalamus

➢ **Spinocerebellar tract
- convey information about proprioception from spinal to cerebellum Ipsillaterlay
- Destruction of the left spinocerebellar tract at T2 would eliminate positional sense on the LEFT side of the body below T2
- **Tract is IPSILATERAL**

♦ Motor impulses
- ➢ Travel from brain to muscles via motor (efferent or descending) pathways
- ➢ Originate in the motor cortex of the frontal lobe
  - These impulses reach the lower motor neurons of the PNS via the upper motor neurons
- ➢ Two systems:
  - Pyramidal system (corticospinal)
    - Composed of lateral (70 – 90%) and anterior or ventral (10 – 30%) corticospinal tracts
    - Impulses in this system travel from the **primary motor cortex through the internal capsule to the medulla, where they cross** to the opposite side and continue down the spinal cord
    - **This system is responsible for fine, skilled, movements of skeletal muscle**
    - Section of the pyramidal tracts produces loss of fine voluntary movements
      - **Think it took fine, skilled movements to build the pyramids**
  - Extrapyramidal system:
    - Impulses originate in the **premotor area of the front lobe (and other areas) and travel to the pons, where they cross to the opposite side**
    - Then the impulses travel down the spinal cord to the anterior horn, where they are relayed to the lower motor neurons. These neurons, in turn, carry impulses to the muscles
    - **This system controls gross motor movements for posture and balance**
    - Tracts in this system include
      - Rubrospinal, reticulospinal, olivospinal, vestibulospional, and tectospinal (neck muscles)
- ➢ Flaccid Paralysis
  - **Damage to the spinal nerves or to the cell bodies of lower motor neurons resulting in reduced muscle tone, depressed stretch reflexes, and atrophy**

➢ Cerebellum
- Situated below and posterior to the cerebrum and above the pons and medulla
- Divided into two lateral hemispheres and a middle portion
- Fxns:
  - Maintain equilibrium
  - Muscle coordination (voluntary movement)
    - Another Q: The cerebellum modifies the pattern of muscular response in reflex and voluntary contractions

➢ Cerebrum
- Divided into right and left hemispheres, which are connected by nerve fibers called the corpus collosum
- Majority of the cortex is involved in associative and higher order functioning such as ideation, language, and thought
  - Frontal lobes: control skilled motor behavior (think pyramidal tract)
  - Parietal lobes: interpret **somatosensory input**
  - Occipital lobes: interpret visual input

- Temporal lobes: interpret auditory input

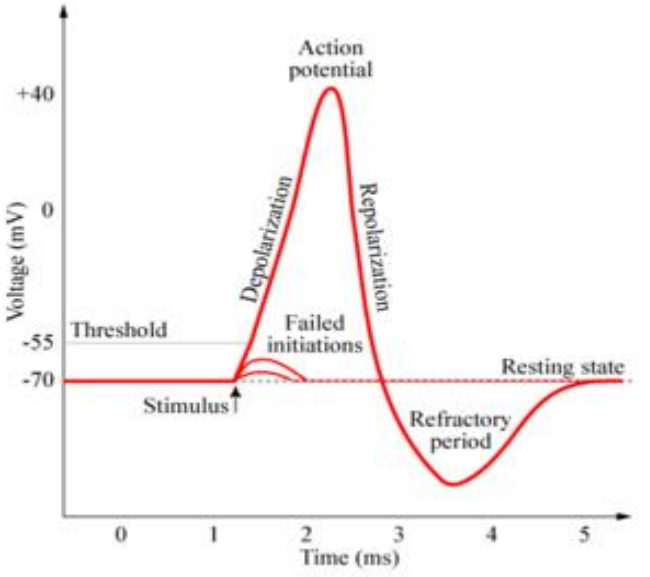
- Hypothalamus
  - Controls many homeostatic processes, which are often associated with the ANS
    - **The major center in the brain for ANS regulation is the hypothalamus**
    - Fxns:
      - Body temperature
        - A patient's internal temperature is monitored by central thermoreceptors located in the hypothalamus
        - Stimulation of the anterior hypothalamus by a reduction in core temperature will produce shivering
      - Water balance (ADH)
      - Appetite
      - Gastrointestinal activity
      - Carbohydrate metabolism (Gets out epi, which triggers glycogenolysis, etc.)
      - Sexual activity
      - **Sleep**
      - Emotions such as fear and rage
      - Growth
      - Ovulation
      - Anterior parts of the hypothalamus excite parasympathetic functions such as constriction of the pupils of the eye
        - Does **not** control respiration (medulla does)
        - Does **not** control pupillary diameter
        - Does **not** control PTH (calcium does)
  - Also regulates release of hormones of the pituitary gland – thus, it greatly affects the endocrine system
  - The hypothalamus-pituitary complex controls hormonal secretions of the corpora lutea (corpus luteum), ovarian follicles, and interstitial cells of the testes (NOT the parathyroids)
  - *supraoptic* and *paraventricular nuclei of thalamus controls ADH and oxitosin*
- **Thalamus**
  - Large ovoid mass of gray matter that *relays all sensory stimuli* (except olfactory) as they ascend to the cerebral cortex
  - Output from the cortex also can synapse in the thalamus
  - Located in the lower region of the brain
  - Contributes to the subconscioius activities of the body, like controlling BP and respiration
- Basal Ganglia
  - Includes:
    - Caudate nucleus
    - Putamen
    - Globus pallidus
    - Substantia nigra
    - Subthalamic nucleus
  - **Function is control complex patterns of voluntary motor behavior**
  - Basal ganglia & Cerebellum are large collections of nuclei that modify movements on the minute-to-minute basis
    - **Cerebral cortex sends information to both, & both structures send information back to the cortex via the thalamus**
    - **Output of the cerebellum is excitatory, while the basal ganglia are inhibitory**
    - Balance between these two systems allows for smooth, coordinated movement, and a disturbance in either system allows for smooth, coordinated movement, **(i.e., Parkinsons, Huntingtons, Dysmetria and Ataxia)**
- Hippocampus
  - Functions in the consolidation of memories and in learning
  - Sea Horse Shape
- Brain stem
  - Lies immediately inferior to the cerebrum, just anterior to the cerebellum
  - Consists of:
    - Midbrain
      - Connects dorsally with the cerebellum
      - Contains large voluntary motor nerve tracts
    - Pons
      - Connects cerebellum with the cerebrum and links the midbrain to the medulla oblongata
      - Serves as the exit point for cranial nerves V, VI, and VII
    - Medulla oblongata:
      - Lowermost portion of the vertebrae brain, continuous with the spinal cord
      - **Joins the spinal cord at the level of the foramen magnum**
      - **Contains the cardiac, vasomotor, and the respiratory centers of the brain**

- Responsible for blinking, coughing, vomiting, and swallowing, sneezing (not patellar reflex (AKA knee jerk))
- Breathing ceases upon destruction of the medulla oblongata
  - The activity of the respiratory center is **decreased** directly by **increased** pH (less H+ and less CO2, so we are hyperventilation, so less breathing good idea)
- Things that can alter the function of the medullary centers for respiration:
  - 1)The central & peripheral chemoreceptors
    - **Nucleus tractus solitarius** and nucleus retro ambiguus are the nuclei in the medulla responsible for generating the respiratory rhythm
    - Peripheral chemorectors from the aortic and carotid bodies synapse onto the NTS in the medulla to increase respiration
  - **2)The apneustic & pneumotaxic centers in the pons**
    - Apneustic center
      - Initiates respiration by activating the inspiratory center in the medulla
      - **Inhibited by lung stretch receptors (Hering-Bruer Reflex)**
        - **Remember Hockey, and the Ducks play on the PONd (Pons)**
    - Pneumotaxic center
      - Inhibitory center in the upper pons
      - **Stimulated by medullary inspiration neurons during inspiration to inhibit the apneustic center until inspiration stops and expiration begins**
  - 3)The CNS at the conscious level
- A note on swallowing (no where else to put it):
  - In swallowing, the larynx is elevated, respiration is inhibited, the epiglottis covers the trachea, & **the eustachian tubes open**
  - Before swallowing can be initiated, afferent information must be received from mucosal mehanoreceptors, indicating the consistency of soft bolus of food
    - Trouble swallowing pills

- Limbic system
  - Primitive brain area deep within the **temporal lobe**
    - Located in the mid-basal region of the brain
  - **Initiates basic drives** (hunger, aggression, emotional feelings and sexual arousal)
    - **Emotional feelings are most closely linked to the limbic system in the brain**
  - Screens all sensory messages traveling to the cerebral cortex

Nerve

- *Let's put this one 1st, in case it shows up:* **Tetrodoxin blocks sodium channels in nerve-axon MBs** *(it's the puffer fish poison)*
- Membranes
  - Action potential is initiated by a depolarizing stimulus:
    - If it reaches threshold (about 20 mV positive to resting membrane potential) an excitable cell will fire an AP
    - If neuron does not reach this critical threshold level, then no AP will occur (all or none)
    - So long as they can reach the threshold, suprathreshold stimuli produce the same AP that threshold stimuli do
      - Excitable cells include neurons and muscle cells



- Depolarization
  - Makes membrane potential less negative (interior of cell becomes less negative)
  - Following a depol, a membrane is then more permeable to Na+, which causes a further depol and the opening of Na+ channels
  - Membrane potential actually reverses (becomes positive inside – the overshoot) as the Na+ influx drives membrane potential towards Na+ equilibrium potential
    - If an axonal MB transiently becomes very permeable to Na^+ ions, the cell MB potential approaches +60mV
  - Another Q: A depolarized membrane is more permeable to ion flow
  - Another Q: The generation of an action potential is attributed to a rapid but brief increase in Na+ conductance
  - Another Q: an AP is related to the entry of Na+ followed by the exit of K+
  - Another Q: Under normal conditions, the resting potential across a muscle cell membrane is lower than the equilibrium potential for potassium because the membrane has a low permeability to the sodium ion
  - Another Q: Sodium permeability of an axon membrane is maximal during the ascending limb of the action potential
  - Another Q: The primary ionic movement during the depolarization phase of a nerve AP is best described as sodium ions moving from outside the MB to inside the MB
  - Another Q: The generation of the spike or action potential is attributed to a rapid but brief increase in Na+ conductantce
  - If a nerve can't produce ATP, then the intracellular level of Na+ will slowly rise → can't use Na+/K+ ATPase!!
- Repolarization
  - Occurs due to:
    - Rapid decrease in membrane perm to Na+ (stop flowing in)
    - Slower increase in membrane perm to K+ (start leaking out)
- Hyperpolarization
  - **Membrane potential becomes more negative**
  - Happens because K+ conductance is greater than at rest (relative refractory period)
    - if you have high extracellular potassium, what occurs?
    - **SAME AS Failed Pump**
    - **SAME as Digoxin which prolonges contraction and wrings out the heart longer and more efficiently**
    - **SAME as HyperKalemia**
      - **Gradual hyperpolarization – this is what I put – Because K+ can't rush out and make cell more neg again**
  - Case in point → Hypokalemia can produce a hyperpolarized cell membrane potential
  - Many K+ channels remain open for several milliseconds after repolarization of the membrane is complete
    - Increased K+ conductance allows for additional K+ efflux, leaving the interior of the cell more negative ('the overshoot')
      - **This opening of K+ channels, although delayed, is due to the initial depolarizing stimulus**
    - Relative refractory period
      - The phase at which Sodium activation is ending
      - In order to trigger a second AP, the depolarizing stimulus must be of a greater magnitude to achieve threshold
      - Increased K+ permeability (not change in Na+ perm) has primary control over the relative refractory period
        - **The relative refractory period of a nerve corresponds to increased potassium permeability**
    - Absolute refractory period
      - **Determined by the duration of Na^+ inactivation gate closure**
      - No matter how strong the second stimulus, the AP cannot be propagated, as H ball is stuck, inactivating the Sodium channel
      - The length of the absolute refractory period limits the maximum frequency of effective nerve stimulation

- Resting membrane potential (RMP):
  - Difference in electrical charge between the inside and the outside of the cell membrane of an unstimulated (nonconducting) neuron
  - Due to an imbalance of charged particles (ions and proteins) between the extracellular and intracellular fluids
  - More positive ions (cations) outside the membrane and more negative ion (anions) on the inside
    - The membrane is said to be polarized (a voltage exists [called the RMP] across the membrane)
  - RMP varies, but in excitable cells runs between (-) 40 and (-) 85 millivolts
    - If one could extract the cytoplasm from a resting neuron and measure it, the electrical charge would be negative
  - Comes from 2 activities:
    - There is a resting K^+ membrane potential which allows (+) charges to leave cell down their electrochem. gradient
      - In most excitable cells this is the most important determinant of RMP
    - The Na^+/K^+ pump establishes the Na^+ and K^+ gradients across the membrane using ATP

        - ♦ This pump is electrogenic, i.e., it exchanges two K^+ ions into the cell for every three Na^+ ions it pumps out of the cell for each ATP that binds to the cytoplasmic-side ATP binding site, resulting in a a net loss of positive charges within the cell
        - ♦ **Cardiac Glycosides (digitoxin) block this pump and keep the inside of the cell more positive and closer to its threshold, thus increasing cardiac contractility**
            - ➢ **Ouabain inhibits by binding to the K+ site**
    - The resting potential of a nerve membrane is maintained by active transport of Na^+ & K^+ ions
    - Another Q: an example of primary active transport is the movement of potassium into a nerve cell
- Another Q: Visceral smooth muscle & **cardiac pacemaker cells both lack a stable RMP**
    - **Another Q: The gradual (phase 4) depolarization in a pacemaker cell is generated by progressively decreasing K^+ conductance, meaning leaky K channels are becoming less leaky**
- Another Q: At rest, the potential difference across the membrane of skeletal muscle is the greatest (more than the sinoatrial node & visceral smooth muscle)
- Which changes can slow down the rate of the pacemaker cell?
    - Threshold becomes more positive (increase threshold)
    - The rate of spontaneous depolarization decreases (less firing)
    - The maximum diastolic potential (resting potential) becomes more negative

➢ Nernst Equation

$$E = E^{0'} + \frac{0.0591}{n} \log \frac{[\text{ion out of cell}]}{[\text{ion inside cell}]}$$

- n is the number of electrons transferred in the half-reaction.
- $E^{0'}$ is the formal electrode potential
- E is the electrode potential

- Allows you to compute the electric potential difference required to produce an electrical force that is equal to and opposite to the force of the equilibrium
- At the peak of the action potential, the rapid increase in sodium conductance causes the membrane to move toward the equilibrium potential for sodium
- Another Q: The limit of the peak of the AP is solely determined by the Nernst equilibrium potential for Na+ between the inside of the axon and the surrounding tissue fluid
    - **Think K+ controls the Baseline (Resting Membrane Potential)**
    - **Think Na+ controls the Changes**

➢ Local anesthetics and the membrane

- Reversibly block impulse conduction and produce reversible loss of sensation at their administration site
- Small, myelinated nerve fibers which conduct pain and temperature sensations are affected first, followed by touch, proprioception, and skeletal tone
- **Bind to the inactivation gates of fast voltage gated Na^+ channels, stabilizing them in a closed position, effectively prolonging the absolute refractory period**
    - This decreases Na^+ membrane permeability, and therefore reduces membrane excitability
    - Local chemical anesthetics block nerve conduction by preventing the increase in membrane permeability to Na+
    - When the excitability has been reduced below a critical level, a nerve impulse fails to pass through the anesthetized area
- **K^+, Ca^{2+}, and Cl^- conductances remain unchanged**
- When anesthetics are applied to a neural membrane:
    - K+ flux remains unchanged
    - **Pores of the membrane become "frozen"**
    - There is a Ca^{2+} flux through the membrane?????
    - Resting potential does not drop to a more negative value

➢ Conduction

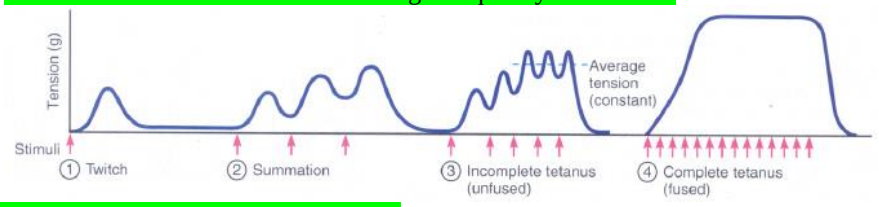
- An impulse can travel from one nerve to another in only one direction because the synapse limits the direction of travel
- **Another Q: An AP initiated at the midpoint along the length of an axon will propagate towards BOTH the soma & the nerve ending**
    - *NOTE: The impulse from the 2nd Q will terminate at the soma, because of the reasoning in the 1st Q*
- Unmyelinated neurons
    - Impulse travels along the entire membrane surface and is known as continuous conduction
    - It is relatively slow (1.0 m/sec)
- Myelinated neurons
    - **Myelin sheath decreases membrane capacitance and increases membrane resistance – Makes you jump**, preventing movement of Na+ and K+ through the membrane

- Conserve energy since the Na+ and K+ pumps have to re-establish concentration differences only at the nodes of Ranvier (spread .2m and 2mm apart)
- Travels up to 100 m/sec
- Saltatory conduction:
  - Increase the velocity of nerve transmission along myelinated fibers
  - Allow repolarization to occur with little transfer of ions
  - Depends on the presence of nodes of Ranvier
- Conduction velocity depends on:
  - Diameter of nerve fiber – an increase in diameter reduces resistance to current flow down the axon
  - Presence of myelin sheath

- Neurilemma (aka sheath of Schwann or Schwann's membrane)
  - Thin membrane spirally enwrapping the myelin layers of certain fibers, especially those of peripheral nerves, or the axons of certain unmyelinated nerve fibers
  - All axons of PNS have a neurilemma (made up of the outer layer of Schwann cells) around them
    - When a Schwann cell is wrapped successively around an axon it becomes a myelin sheath
  - Peripheral fibers can sometimes regenerate if the soma (cell body) is not damaged and some of the neurilemma remains intact
  - The neurilemma forms a regeneration tube through which the growing axon reestablishes its original connection
  - If the nerve originally led to a skeletal muscle, the muscle atrophies in the absence of innervation but re-grows when the connection is re-established
    - **Regeneration of severed axons does not take place in the CNS because of the absence of a neurilemma**
  - ***NOTE:
    - Right-sided lesions of the spinal cord result in loss of **motor activity** on the **same side,** and **pain & temperature** sensation on the **opposite side**
      - **Remember Motor crosses above in the medulla, where pain crosses right away at the spinal cord**
- Synapse
  - Anatomical junction between 2 neurons – depolarization of presynaptic cell initiates a response in postsynaptic cell
  - An axon terminal of a presynaptic neuron closely approaches a dendrite or cell body of a postsynaptic neuron
    - But, the two cells are separated by a small synaptic cleft
  - Neurotransmitters are stored within the axon terminal of a presynaptic neuron in synaptic vesicles
  - When an AP depolarizes the presynaptic MB, voltage-gated calcium channels are opened causing an increase in intracellular calcium
  - Calcium causes the synaptic vesicles to empty the neurotransmitters into the synaptic cleft
  - Neurotransmitters diffuse across the synaptic cleft and bind to specific receptors on the postsynaptic cell
    - This process is called synaptic transmission and the time required is called synaptic delay
    - Synaptic delay explains the following phenomenon:
      - When an impulse is carried by a chain of two or more neurons, the total transmission time is greater than the sum of the transmission times for each neuron
- **Electrotonic or Subthreshold potentials examples:**
  - Inhibitory post-synaptic potentials
  - Excitatory post-synaptic potentials
  - Generator potentials in Pacinian corpuscles
  - Endplate potentials at the neuromuscular jxn
- End Plate Potentials
  - Depolarization of the skeletal muscle cell membrane by motor nerves is directly produced by the change in the end-plate potential level to a critical value
  - Another Q: If AChE is inhibited, there will be prolongation of the endplate potential (neuromascular junction)
- Miniature End-Plate Potentials (MEPP)
  - **Due to the release of subthreshold amounts of Ach**
- Spatial Summation
  - Occurs when two excitatory inputs arrive at a postsynaptic neuron simultaneously converging circuits
  - This increases probability of causing an AP in the postsynaptic neuron (excitatory postsynaptic potential = EPSP)
  - Results from the convergence of several afferent impulses on the same postsynaptic nerve soma
  - Another Q: Spatial summation in spinal reflexes is dependent upon simultaneous arrival of impulses from a large number of receptors
- Temporal Summation
  - Occurs when two excitatory inputs arrive at a postsynaptic neuron in rapid succession
  - There is an increase in the frequency of nerve impulses in a single presynaptic fiber
  - The amplitude of the AP may be increased by increasing the extracellular concentration of Na+

- Tetany

- Point at which nerve signals are arriving fast enough to cause a big steady contraction, not just individual twitches
- A tetanic contraction results from a high frequency stimulation



- ****When are nerve fibers hypoexcitable**
  - **During Positive after-potential:**
    - Spontaneous or inducible increase in transmembrane potential following the completion of repolarization
      - In the heart, this usually corresponds to the U wave on the EKG
- Excitatory neurotransmitters in the CNS
  - Depolarize the postsynaptic membrane bringing it closer to threshold and closer to firing an AP
  - The altered membrane potential is known as an excitatory postsynaptic potential (EPSP)
  - **Includes: Ach, NE, Epi., Dopamine, Glutamate, Serotonin**
- Inhibitory neurotransmitters **(including glycine and GABA) in the CNS**
  - Hyperpolarize the postsynaptic membrane moving it away from threshold and farther from firing an AP
  - **An inhibitory postsynaptic potential (IPSP)**
    - **could result from either an increase in membrane permeability to Cl^-, which must run into the cell, or an increase in membrane permeability to K+ out of the cell**
  - GABA
    - **GABA increases the permeability of postsynaptic membranes to chloride ions Cl-**
    - Glutamate decarboxylase, which catalyzes formation of GABA by decarboxylation of **glutamate**, is unique to nervous tissue
    - **Cl- then hyperpolarizes the cell, making it harder to feel pain**
    - Secreted by nerve terminals in the spinal cord, cerebrum, basal ganglia, and in the cortex
  - Glycine
    - **binds to specific receptors (mainly in the spinal cord) opening chloride channels**
    - **Glycine is the immediate precursor for creatine, purines & porphyrins**
- CNS (= spinal cord + brain)
  - Peripheral Nervous System (afferents from sensory receptors to CNS + efferents from CNS to muscles, organs, glands)
    - Somatic nervous system
      - Consists of:
        - 12 pairs of cranial nerves and 31 pairs of spinal nerves
    - Autonomic nervous system: has two subdivisions:
      - Actions of the ANS are largely involuntary (in contrast to those of the somatic system)
      - Also differs from the somatic system in using two efferent neurons from the CNS to the effector
      - Preganglionic neurons arise in the CNS and run to autonomic ganglia in the body
        - Here they synapse with postganglionic neurons, which run to the effector organ (cardiac muscle, smooth muscle, visceral organs, or glands)
        - **Preganglionic** autonomic nerve fibers are exclusively **cholinergic**
      - Postganglionic neurons have their cell bodies in the autonomic ganglia and synapse on effector organs
      - Sympathetic nervous system
        - Ganglia located in the paraverterbral chain or prevertebral ganglia
        - Preganglionic neurons originate in the spinal cord segments T1–L3 (thoracolumbar)
          - Pregang symp cell bodies are found in thoracic & lumbar segments of the spinal cord
          - Uses Ach (cholinergic)
        - **Majority of sympathetic post G are noradrenergic (NE)**
          - **Exception: BVs in skeletal muscle, terminal fibers to the adrenal medulla (Ach) & sweat glands use Ach at muscarinic cholinergic receptors**
        - When the sympathetic nervous system is activated, arterial pressure, mental activity, blood glucose concentration and blood flow to skeletal muscles all increase (blood flow to the skin does not increase)
          - **NE is NOT used at the terminal sympathetic fibers to the heart**
        - High ratio of postganglionic sympathetic to preganglionic is indicative that stimulation of the sympathetic NS leads to widespread effects
        - **Sympathetic Stimulation most likely produces Bronchial Dilation**
      - Parasympathetic nervous system
        - Ganglia located in or near effector organs
        - Preganglionic neurons originate in the nuclei of cranial nerves in spinal cord segments S2–S4 (craniosacral)
          - Uses Ach (cholinergic)

- Postganglionic fibers are all cholinergic
  - Innervation of salivary gland cells in humans is predominantly parasympathetic postganglionic
- Main nerves of the PNS are the vagus nerves
  - They originate in the medulla oblongata
- Each preganglionic PS neuron synapses with just a few postganglionic
- **The synapses in the CNS are the most susceptible sites in the nervous system to acute anoxia**
  - Absence or almost complete absence of oxygen from inspired gases, arterial blood, or tissues; to be differentiated from hypoxia.

- Receptors/Neurotransmitters
  - Cholinergic receptors
    - Use Ach as neurotransmitter
    - Membrane receptor proteins located on autonomic postganglionic neurons or on effector organs regulated by Ach
    - They are always excitatory in preganglionic
    - Effects of postganglionic PS can be either excitatory or inhibitory (PS fibers innervating heart cause a slowing)
    - Preganglionic autonomic neurons (both Symp and PS) and all postganglionic PS
    - Ach is released at sympathetic ganglia, parasympathetic ganglia, somatic efferents to skeletal muscles, & terminal sympathetic fibers to the adrenal medulla (but not at terminal sympathetic fibers to the heart) – Nor is NorEpi
    - Muscarinic:
      - Located on all effector organs innervated by postG neurons of the PS division
      - Located on those effector organs innervated by postG cholinergic neurons of the Symp division (e.g., sweat glands)
    - Nicotinic:
      - Located at the ganglia of both the Symp and PS divisions
        - Neuromuscular junction:
          - Ach is the neurotransmitter released from the presynaptic terminal and the postsynaptic membrane contains a nicotinic receptor
          - Ach opens Na+ channels in the motor endplate resulting in depolarization and the opening of voltage gated Na+ channels in the sarcolemma
            - Leads to an AP in the skeletal muscle fiber which travels down the transverse tubules resulting in a release of calcium from the sarcoplasmic reticulum and muscle contraction
        - Ach Synthesis
          - Synthesized in the neurons from which it is released
            - **Choline acetyltransferase** catalyzes formation of Ach from **acetyl CoA & Choline** in the presynaptic terminal
          - Stored in the synaptic vesicles
          - Following its release form the presynaptic terminal, Ach is rapidly broken down into acetate and choline by the enzyme Actylcholinesterase (AChE)
          - AChE is responsible for the termination of neuromuscular transmission
          - Another Q: If AChE is inhibited, there will be prolongation of the endplate potential
        - Receptors: structures that are generally activated by changes (stimuli) in either the internal or external environment of the body. As a result of the activity of these receptors, nerve impulses are initiated within the sensory nerve cells
  - Adrenergic receptors:
    - Membrane receptor proteins located on autonomic effector organs that are regulated by catecholamines (Epi & NE)
    - Two main types:
      - **Think "1s" are Constriction, and the "2s" are both Relaxers**
      - **Alpha (NE, Epi)**
        - Alpha 1: located on smooth muscle, produces excitation (contraction or **constriction)**
        - Alpha 2: located in presynaptic nerve terminals, platelets, fat cells, and the walls of the GI tract; produce **inhibition (relaxation or dilation)**
      - **Beta (Epi)**
        - Beta 1: located in the heart; produces excitation **(increased HR, and contractility)**
        - Beta 2: located on smooth muscle; produce relaxation (dilation)
          - Treatment of asthma symptoms requires activation of the adrenergic beta-2 pathway
    - **NE stimulates mainly alpha receptors (remember NE doesn't go to the Heart)**
    - **Epi stimulates both alpha & beta receptors**
      - **Epi at high concentrations B 1 predominates, like Anesthesia, but at low, it's B 2 and does vasodilation**
  - Monoamine oxidase (MAO)
    - Enzyme that catalyzes the oxidative deamination of monoamines such as NE, serotonin, and Epi
      - Normally NE is uptaken into the nerve endings via active transport or diffused away into body fluids and then into the blood, but if there is some left over, MAO takes care of it

- This deamination process aids in metabolizing excess neurotransmitters that may build up at post-synaptic terminals
- **MAO is present in the nerve endings themselves**
- **MAOIs increase the available stores of serotonin, NE and epi**

- Two classes of receptors:
  - Exteroceptors:
    - Respond to stimuli from the body surface, including touch, pressure, pain, temperature, light, and sound
    - Two-point discrimination requires that two sensory receptors are innervated by two different axons
  - Interoceptors:
    - Sensitive to pressure, pain, and chemical changes in the internal environment of the body
    - Baroreceptors
      - Aortic Arch
        - Transmits via vagus nerve to medulla
      - Carotid Sinus
        - Transmits via glossopharyngeal nerve to medulla
- Specialized types of receptors:
  - Photoreceptors:
    - Specialized receptors that are sensitive to light energy
    - Located only in the retina of the eye (specifically the rods and cones)
  - Mechanoreceptors:
    - Sensitive to pressure or stretch
    - Pacinian corpuscles, muscle spindles, golgi tendon organs, Meissner's corpuscles, and hair cells which transduce the senses of hearing and balance
    - Tactile Sensation → Meissner's corpuscles, **found in demal papillae**
  - Thermoreceptors
    - Free nerve endings sensitive to changes in temperature
  - Chemoreceptors
    - Stimulated by various chemicals (in food, the air, or blood)
    - Receptors for:
      - Taste (taste receptors)
        - Sensations of taste are generated in the taste buds and conveyed to the CNS through CN VII & IX and X
        - Low threshold of taste for BITTER
      - Smell (olfactory receptors)
      - Monitoring pH & gas levels in the blood (osmoreceptors and carotid body O_2 receptors)
        - Peripheral
          - Carotid and Aortic bodies
            - **respond to decrease in PO2, increased PCO2, increased H+, and decreased pH**
            - Peripheral **carotid body** receptors are stimulated most effectively by low arterial **O_2** tension
            - Another Q: Increased pulmonary ventilation at high altitudes results directly from the effect of **hypoxia** on the carotid body
        - Central
          - Respond to changes in PCO2 and pH of CSF, which are influenced by systemic PCO2
          - **DO NOT directly respond to PO2**
    - NOTE on taste/smell: The following are similar characteristics of taste & smell: ??? from 2001 pilot
      - Receptors are replaced regularly
      - There are primary classes of taste & odor
      - Receptors are located on cilia or microvilli at the apical ends of cells
      - Molecules must be dissolved in saliva or mucus to interact with receptor membrane proteins
        - **Not correct: Receptors initiate APs directly to respective cranial nerve sensory fibers**
          - **Smell does have directly firing AP cells with ciliary sensors**
          - **BUT TASTE uses G Protein mechanism, Do NOT have axons, and do NOT generate own APs**
  - Nocioceptors
    - Free nerve endings sensitive to painful stimuli
  - Proprioceptors
    - Type of interoceptor that provides information concerning the position of body parts, without the necessity of visually observing the parts
    - Located in muscles, tendons, joints, and the vestibular apparatus
    - **These sensory receptors serve the stretch reflex**
- Intracellular Receptors
  - Remember, steroid hormones can go directly into the cell w/o using an Extracellular receptor and cAMP, etc.

- Primary recognition of B-estradiol by its target cell, depends upon the binding of its hormone to a specific cytoplasmic receptor
- The principal mechanism by which glucocorticoids stimulate their target cells is by activating specific genes

➢ Adaptation **(to constants – They both have 2 Ts))**
- is a property of certain receptors through which they **become less responsive** or cease to respond to **stimuli of constant intensity**

➢ Accomodation **(to change)**
- the property of a nerve by which it adjusts to a **slowly increasing strength of stimulus**, so that its threshold of excitation is greater than it would be were the stimulus strength to have risen more rapidly

➢ Facilitation
- The enhancement or reinforcement of a nervous activity by the arrivals of signals from other neurons

➢ Another Q: The **generator potential** of a receptor is characterized by being **graded according to strength of the stimulus**

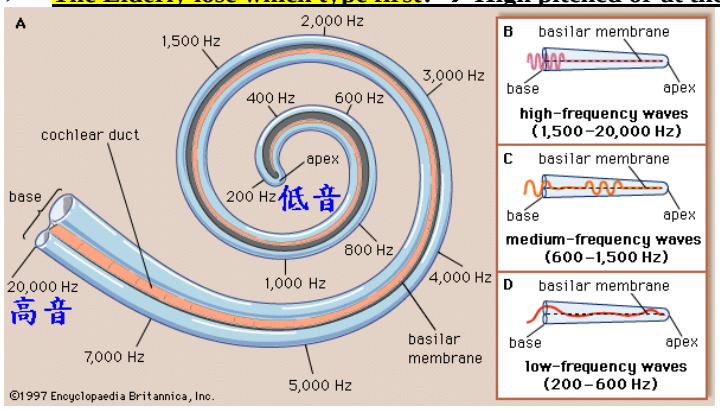
❖ **Special Sensory Organs**

➢ Retina:
- Innermost layer of the eye
- Receives visual stimuli and sends the info to the brain
- Photoreceptors called rods and cones compose the visual receptors of the retina and contain photopigments
  - Four different types of photopigments, each consisting of a protein called opsin to which a chromophore molecule called retinal is attached
  - Opsins differ from pigment to pigment and confer specific light-sensitive properties on each photopigment
  - Retinal (retinaldehyde) is produced by vitamin A
- Rods and Cones:
  - Rods:
    - ♦ Contain a photopigment called rhodopsin
    - ♦ Their response indicates **different degrees of brightness** – characterized by relative lack of color discrimination
    - ♦ They are numerous in the periphery of the retina
    - ♦ Visual purple is seen with rhodopsin in the retina
      - ➢ Visual purple = The pigment sensitive to red light in the retinal rods of the eyes, consisting of opsin and retinene
      - ➢ Usually formed in the retina
      - ➢ During dark adaptation (night vision) rhodopsin is synthesized in the rods of the retina
      - ➢ NOT part of accommodation for near vision
    - ♦ Rods are more abundant, have higher sensitivity, and lower acuity compared to cones
  - Cones:
    - ♦ Primarily responsible for color vision
    - ♦ Three different types of cones (red, green, blue)
      - ➢ Each one contains a different photopigment and is selectively sensitive to a particular wavelength of light
    - ♦ Concentrated in the center of the retina especially in the fovea
    - ♦ Principal photoreceptor during daylight or in brightly lit areas

➢ Intraocular structure:
- Sclera:
  - Tough white outer layer; maintains size and form of the eyeball
- Cornea:
  - Transparent dome on surface of the eye
  - Serves as a protective covering & helps focus light on the retina at the back of the eye
- Iris:
  - Circular colored area of the eye
  - Amount of pigment in the iris determines the color of the eye
  - The ciliary body is made up of three muscles and the iris
    - ♦ It controls the lens thickness
- Pupil:
  - Circular opening (black area) in the middle of the iris, through which light enters the eye
  - Pupil size is controlled by the papillary sphincter muscle, which opens and closes the iris
- Lens:
  - Situated directly behind the iris at the papillary opening, by changing its shape, the lens focuses light onto the retina
- Choroid:
  - Lines the inner aspect of the eyeball beneath the retina; very vascular

- The eyeball itself is divided into two segments, each filled with fluid
  - Anterior segment
    - Has two chambers (anterior and posterior)
    - Filled with aqueous humor (watery fluid)
  - Posterior segment
    - Filled with vitreous humor (thick, gelatinous material)
      - Made with Type II Cartilage
- Eyes:
  - Changes during accomodation for near vision:
    - Constriction of pupils
    - Convergence of eyeballs
    - Contraction of ciliary muscle
  - Problems with eyesight:
    - Myopia (nearsightedness) **(My opia, its what I have)**
      - The primary effect of myopia is related to eyeball length relative to refractive power of the lens
      - The eye is too long for the refractive power of the lens, and far objects are focused at a point in front of the retina
      - The eye can focus on very near objects
      - *Tx with concave lenses*
    - Hyperopia (farsightedness)
      - The eyeball is too short for the lens, and near objects are focused behind the retina
        - A slight detachment of the retina results in a decrease of length from the optical center, and the subject therefore exhibits farsightedness *(99% sure that farsightedness is the answer)*
        - So in a detached retina, you can't read!
      - Distant objects are focused correctly
      - *Tx with convex lenses*
    - Astigmatism
      - Occurs when the curvature of the lens is not uniform
      - *Tx with cylindric lenses*
    - Presbyopia
      - Inability of the eye to focus sharply on nearby objects
      - Results from the loss of elasticity of the lens with advancing age
      - *Tx with bifocals*
    - Miosis
      - The constriction of the pupil of the eye
      - Can be caused by a normal response to an increase in light, certain drugs or pathological conditions
    - Mydriasis
      - Prolonged abnormal dilation of the pupil of the eye induced by a drug or caused by a disease
- Parts of the ear:
  - External ear:
    - Auricle (pinna)
      - Directs sound waves
    - External auditory canal (meatus)
      - Contains hair and cerumen (brown earwax) serves as a resonator
  - Middle ear:
    - Air-filled cavity in the temporal bone
    - Auditory (eustachian) tube:
      - Equalizes pressure
      - Ear aches may develop as a result of blockage of the eustachian tube because pressure in the middle ear is not equalized with atmospheric pressure
    - Ossicles (malleus, incus, stapes)
      - Link together to transmit sounds to the oval window
  - Inner ear:
    - Formed by a bony labyrinth and a membranous labyrinth
    - Vestibule (saccule and utricle):
      - Associated with sense of balance
      - Responsible for static positioning (affected by gravity)
      - Responds to LINEAR acceleration or deceleration
    - Semicircular canals:

- Concerned with equilibrium, angular acceleration and deceleration
- Each one contains an enlarged region called the ampulla containing the receptor organ, the Crista ampullaris
  - The receptor contains hair cells whose processes are embedded in a gelatinous matrix
  - Rotary acceleration in any plane will cause a sense of rotation opposite to the direction of the endolymph displacement
- An angular (NOT LINEAR) acceleration or deceleration represents an adequate stimulus for semicircular canals

- Cochlea (contains two membranes, vestibular and basilar):
  - Portion of inner ear responsible for hearing
  - The spiral organ (organ of Corti)
    - Responsible for perception of sound
    - Contains receptors (called hair cells) for hearing
    - Basic functional unit of hearing – it transforms fluid vibration from sound waves (mechanical energy) into a nerve impulse (electrical energy)
  - Impulses for hearing are transmitted to the brain from receptors in the cochlea
  - Low pitch, low frequency (Bass) at the apex or middle of the snail
  - High pitch, High frequency at the big base of the snail
    - **The Elderly lose which type first? → High pitched or at the base**
  - 

It follows that there are five steps in the hearing process:

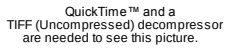
❖ air conduction through the external ear to the ear drum
❖ bone conduction through the middle ear (vibration and increase amplitude) to the inner ear
❖ water conduction to the Organ of Corti
❖ nerve conduction into the brain
❖ interpretation by the brain

The chain of ossicles connected to the ear drum—the incus, malleus, and stapes (middle ear)—carries the vibration to the oval window, increasing its amplitude 20 times on the way.

Otosclerosis is an excessive growth in the bones of the middle ear which interferes with the transmission of sound.

❖ **GI System**
  - Ptyalin
    - NZ in the saliva for digesting starches
  - The regulation of Gastric Secretion
    - Cephalic stage:
      - Eating, tasting, **smelling**, and thinking about food increases the rate of gastric secretion via activation of the PS nervous system, specifically the vagus
      - The cephalic phase of gastric secretion is a reflex mediated by the vagus nerve
      - What allows your stomach to become bigger?
        - **Receptive relaxation** is an increase in the stomach volume before the arrival of food
      - Vagotomies are sometimes used to control gastric ulcers
      - Vagus nerve also causes contraction of the gallbladder (not part of the cephalic stage)
    - Gastric stage:
      - **Stretch** associated with a volume of food filling the stomach also increases the rate of gastric secretions
      - This phase accounts for about 70% of the total gastric secretion
      - Involves both neural reflex pathways and the release of gastrin

- Gastrin:
  - Enteroendocrine cells (gastrin or G cells) of the pyloric glands of the stomach mucosa secrete it
  - Absorbed in the blood and carried to the **oxyntic glands (gastric glands) in the body of the stomach**
    - **There it stimulates the parietal cells to secrete HCL**
  - Relaxes the pyloric sphincter, activates the pyloric pump, and contracts the esophageal sphincter
    - **THINK opposite to the enterogastric reflex**



- Intestinal stage:
  - The delivery of acidic, high osmolarity food/stuff into the small intestine
  - Inhibits gastric secretion via the enterogastric reflex and hormonal mechanisms (secretin)

- Esophagus
  - Nitrous Oxide
    - Causes smooth muscle relaxation (lower esophageal sphincter)
- Gastric glands of stomach mucosa:
  - Stomach glands produce as much as 2–3 liters of secretions per day
  - The pH of gastric secretion is 1.0–3.5
    - Gastric juice usually has a $[H^+] > 1x10^{-3}$ M (among answer choices of bile, urine, saliva, & pancreatic juice)
  - The mucus produced by mucus-secreting cells is very alkaline and protects the stomach wall from being exposed to the highly acidic gastric secretion
    - G cell

- Secretes Gastrin
  - Stimulates secretions of Acid, IF, and Pepsinogen
  - Stimulates Gastric motility
  - Inhibited by secretin or stomach pH <1.5
  - Stomach emptying is enhanced by gastrin & the presence of food in the stomach
- **Mucous neck cells (pyloric glands):**
  - Secretes Mucus and some pepsinogen
    - Adheres to the stomach walls, lubricates the walls and protects the gastric mucosa from acidic secretions
- Chief (peptic or zymogenic) cells:
  - Secretes Pepsinogen
    - Formed inside chief cells in the inactive form (pepsinogen)
      - In the upper part (Fundus) of the stomach
    - Once pepsinogen is secreted & comes in contact with previously formed pepsin in the presence of HCl, it is converted to form active pepsin
    - Begins protein digestion
    - **The most important function of HCl (from parietal cell)is activation of pepsinogen**
      - Then that active pepsin, activates its other pepsinogen buddies
    - Does NOT secrete Bicarbonate
- **Parietal (oxyntic) cells:**
  - K+ and Cl- go out of the cell via a cotransporter
    - **Then K+ goes back down the gradient formed by that cotransporter via the H+/K+ ATPase and H+ goes out causing gastric acid**
  - Secretes HCl
    - Kills bacteria, breaks down food, activates pepsinogen to pepsin
    - Sterilizes chyme
    - **Stimulated by histamine, Ach, and gastrin**
    - **Inhibited by Prostaglandin (PGI2 and PGE2) and GIP**
    - NOT essential for digestion
  - Secretes Intrinsic factor
    - Vitamin B12 absorption in terminal ileum
    - So no parietal cells, you get pernicious anemia
  - **Secretion is increased by Ach, gastrin and histamine**
  - Peptic ulcers can result either from the oversecretion of acid and pepsin or a diminished ability of the mucosal barrier to protect against these secretions

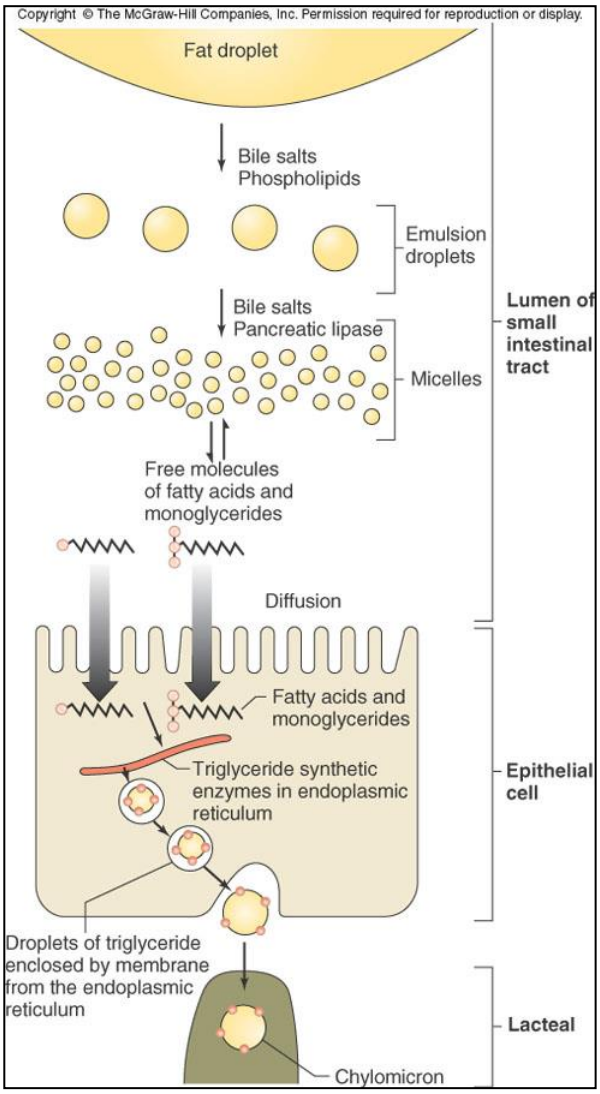
- Intestinal secretions
  - Mainly mucus, are secreted by goblet cells and enterocytes
  - The pH of the secretions in the small and large intestines is 7.5-8.0
  - Surface cells (duodenum)
    - Bicarbonate
      - Neutralizes acid
      - Stimulated by secretin (potentiated by vagal input) CCK
  - I cells (duodenum and jejunum)
    - Cholecystokinin (CCK)
      - Stimulates gallbladder, and pancreatic enzyme secretion
      - Inhibits Gastric emptying
      - Stimulated by FAs and AAs
      - Augmented flow from the gallbladder during feeding results in part from the release of CCK
      - Stimulates gall bladder contraction, releasing bile
        - Bile
          - pH ~7.8
          - Produced by the liver and stored in the gallbladder
          - Composed of bile salts, phospholipids, cholesterol, bilirubin, and water (97%)
          - Aids in the emulsification, digestion, and absorption of fats
  - S cells (duodenum)
    - Secretin
      - Nature's antacid
      - **Stimulates pancreatic Bicarb secretion**
      - Inhibits gastric acid secretion
      - Stimulated by FAs and AAs
  - D cells (pancreatic islets and GI mucosa)

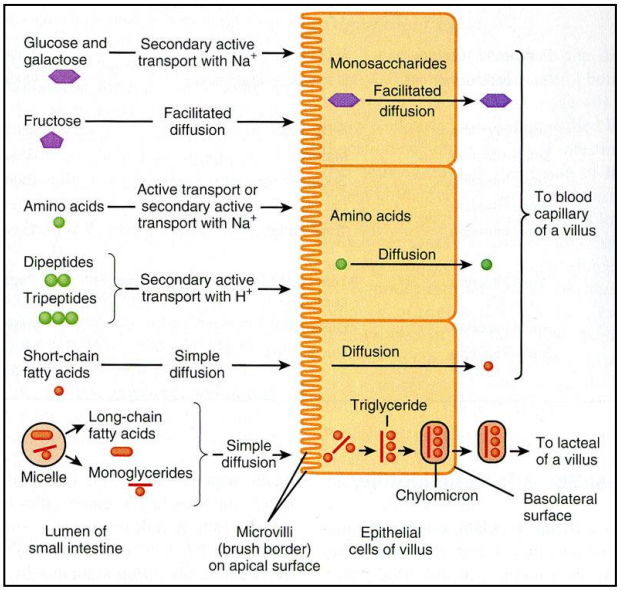
- Somatostatin
  - **Inhibits** Gastric acid and pepsinogen secretion, Pancreatic and intestine fluid secretion, Gallbladder contraction, and Release of both insulin and glucagons
  - **Stimulated by acid and inhibited by the vagus**
- Vasoactive Intestinal Peptide (VIP)
  - Secreted by smooth muscle and nerves of the intestines
  - Relaxes intestinal smooth muscle
  - Causes pancreatic bicarb secretion
  - Inhibits gastric H+ secretion

- Pancreatic secretions
  - From pancreatic acinar cells include enzymes involved in protein breakdown including:
    - Alpha-amylase – starch digestion, secreted in active form
    - Proteases – protein digestion, secreted as proenzymes
      - Trypsin – Converted from trypsinogen by enterokinase, then trypsin activates the other proenzymes
      - Chymotrypsin
      - Elastase
      - Carboxypolypeptidase
    - Lipase – Fat digestion
      - Bile salts aid in the action of pancreatic lipase
        - Activated by? → Acid, Typsin, Enterokinase , **bile salts**
    - Cholesterol esterase
    - Phospholipase A – Fat digestion
  - Pancreatic enzymes are secreted in an inactive form and are then activated in the small intestine
  - Pancreatic duct cells (I cells?) secrete a fluid that is high in bicarbonate ion concentration (pH of 8.0 – 8.3)
  - Pancreatic secretions stimulated by:
    - Ach – Major stimulus for zymogen release, poor stimulus of bicarb
    - CCK – Major stimulus for enzyme-rich fluid by pancreatic acinar cells
    - Secretin – Stimulates ductal cells to secrete bicarb-rich fluid
    - Somatostatin – Inhibits the release of gastrin and secretin
- Gastric empyting:
  - Foodstuff entering the duodenum, especially fats and acidic chyme, stimulates hormone release
    - Hormones released in duodenum:
      - Gastric inhibitory peptide (GIP)
        - Inhibits the pyloric pump
    - So, **fat** ingestion most markedly affects (inhibits) the rate of gastric emptying
- ParaSympathetic activation
  - Usually excitatory in the GI tract
  - Increases production of saliva
  - Increases H+ secretion
  - Increases pancreatic enzyme and Bicarb secretion
  - Stimulates enteric nervous system to create peristalsis and relax sphincters
- Sympathetic activation can have either excitatory or inhibitory effects
    - Increases the production of saliva (mucus)
    - Decreases splanchnic blood flow in flight or fight response
    - Decreases motility
    - Constricts sphincters
    - Stimulation of the sympathetic nervous supply to the gastrointestinal tract generally causes inhibition of motility
- Chyme
  - Semifluid contents of the stomach, consisting of partially digested food and gastric secretions
  - The volume and composition of chyme that enters the duodenum (beginning of the small intestine) exerts a major influence on gastric motility and the rate of gastric emptying
  - When a portion of the small intestine becomes distended with chyme, the stretch of the intestinal wall elicits localized rhythmic contractions, called ***segmentation***
    - Segmentation (aka rhythmic segmentation)
      - Occurs at a rate of 11 to 12 cycles/min in the terminal ileum
      - The contractions chop the chyme many times a minute
      - In this way they promote progressive mixing of the food with digestive secretions of the small intestine
      - Intensity can be influenced by mechanical, neural, and hormonal inputs

- For example, distension of the intestine by chyme and PS neural activity both increase the contractile force, while Symp neural activity decreases it.

- Two major types of contractions in the GI tract:
  - Peristalsis:
    - Contraction generates propulsive movements
    - Starts when food enters the stomach
  - Mixing contraction:
    - Serve to spread out the food and increase the surface area available for digestion and absorption
      - ***Smooth muscle control in the GI tract is under the control of the myenteric plexus of the enteric NS
- Entering the intestinal mucosa:
  - Fatty acid:
    - In the lumen of the small intestine, dietary TGs are emulsified by bile salts into smaller fat droplets (micelles) where they are enzymatically digested into free FAs and 2 monoglycerides
    - The free FAs and monoglycerides readily diffuse across the brush border **by simple diffusion**
      - Then are reconstituted in the **ER into TGs** and finally **transported by lymphatics**
  - Dipeptides and amino acids
    - The end-products of protein digestion
    - The final digestive stage occurs by brush border peptidases and absorption immediately follows
    - Absorption across the brush border occurs by multiple **secondary active transports utilizing either the Na^+ or H^+ gradients**
  - Disaccharides and small glucose polymers
    - Occurs at duodenum and proximal jejunum
    - Hydrolyzed at the brush border by lactase, sucrase, maltase and alpha-dextrinase
    - The resultant monosaccharides, glucose and galactose are then **absorbed by secondary active transporters driven by the Na^+ gradient – this is an example of a co-transporter**
      - The immediate energy source for glucose transport into intestinal endothelial cells is a Na^+ gradient across the luminal MB
    - **The Odd-ball → Fructose absorption is mediated by Facilitated diffusion (F for F)**
- The following secrete HCO_3^- into the GI tract:
  - Colon mucosa
  - Salivary glands
  - Stomach mucosa
  - (NOTE: Chief cells do not, b/c they produce gastrin, which will go to parietal cell to produce H+)





Liver

- Functions of liver:
  - Bile formation
  - Protein metabolism (deamination of aa, urea formation [not elimination], plasma protein formation, synthesis of aa)
    - **Another Q: Death from advanced liver disease caused by Hepatitis C is PRIMARILY due to inhibition of urea synthesis**
  - Steroid conjugation
  - Carbohydrate storage
  - Prothrombin synthesis and fibrinogen production
    - **Another Q: Thrombin itself is not found in blood plasma, only its precursor prothrombin**

        - Liver disease results in missing prothrombin and fibrinogen (not thrombin)
    - Detoxification
    - Gluconeogenesis
    - Formation of plasma proteins
    - Regulation of blood sugar level
        - NOT Secretion of digestive NZs
            - Bile is NOT an NZ, it is an emulsifying agent
        - NOT elimination of urea
- Gluconeogenesis:
    - Occurs mainly in the liver (90%), but the kidney is a minor contributor (10%)
        - During prolonged starving the kidney becomes the major glucose-producing organ
    - Is the synthesis of glucose from compounds that are not carbohydrates
        - **Glucose can be made from lactate, glycerol, pyruvate, and fructose (but not acetyl CoA, which comes from FAs)**
- Glucokinase
    - Found only in the liver and functions at a significant rate only after a meal
    - This enzyme uses ATP to catalyze the phosphorylation of glucose to glucose-6-phosphate during glycogen synthesis
        - Then the G-6-phosphate cannot diffuse back out of the cell membrane and can be used to make glycogen
    - ****Other tissues use hexokinase to do the same thing as glucokinase**
        - ONLY hexokinase is feedback inhibited by Glucose-6-Phosphate
- **Liver does not participate in the regulation of immediate blood glucose
- Functions of liver in protein metabolism:
    - 1. Deamination of amino acids:
        - Required before they can be used for energy or before they can be converted into CHO or fat
    - 2. Formation of urea for removal of ammonia from the body fluids:
        - **The liver is the organ pimarily responsible for the formation of urea**
        - Removes ammonia from body fluids – if the liver fails to do this, the result is a hepatic coma and death
        - Urea cycle
            - **O**rdinarily, **C**areless **C**rappers **A**re **A**lways **F**reaks **A**bout **U**rination
            - **Ornithine + Carbamoyl phosphate → Citrulline + Aspartate → Argininosuccinate→ (Fumarate), Arginine → Urea**

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

            - Occurs almost exclusively in the liver
            - It represents the fate of most of the ammonia that is channeled there
                - Ammonia is converted to urea in the liver for eventual excretion
            - The level of non-protein nitrogen in the blood is due primarily to the level of urea
                - Another Q: The major component of **non-protein nitrogen** in the **blood** is **urea**
                - Another Q: The main product of **protein nitrogen** metabolism in **urine** is **urea**
                - **The two nitrogen atoms that are incorporated into urea enter the cycle as ammonia and aspartate**
                    - **1 from ammonia, 1 from an AA (aspartate)**
                - **Urea** is produced by the hydrolysis of **arginine**, which is urea's direct precursor
                    - Another Q: **Arginase** directly catalyzes **urea formation** in a cell

        - Carbomyl Pi is formed from carbon dioxide and ammonia
    - The first two reactions (ammonia to carbamoyl P_i then added to Ornithine to form Citrulline) occur in the mitochondria, whereas the remaining cycle enzymes are located in the cytosol
        - **Ordinarily Careless Crappers**
    - **Nitrogen can also come from Carbomyl Pi**
    - Urea that is formed in the urea cycle is passed via the blood stream to the kidneys & is excreted into urine
    - Carbamoyl P_i is added to ornithine to become citrulline
        - Aspartate is added to citrulline to make argininosuccinate
            - Fumarate is released resulting in arginine
                - Arginine is hydrolyzed and yields urea and ornithine
- 3. Formation of plasma proteins:
    - Accounts for 90% of all plasma proteins
- 4. Ability to synthesize certain amino acids and other important chemical compounds from amino acids
    - The nonessential amino acids can all be synthesized in the liver
        - To do this for most aa, a keto acid having the same chemical composition (except at the keto oxygen) as that of the aa is first synthesized
        - Then the amino radical is transferred through transamination from an available aa to the keto acid to take the place of the keto oxygen

- Cholesterol

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-
    - Most abundant non-phospholipid component of the cell membrane
    - Least Polar
    - Fxns:
        - 1) Primarily used by mammalian cells as a component of the cell membrane
        - **2) Secondarily used as the immediate precursor of bile acid**
        - 3) Thirdly, used as precursor to various steroid hormones
    - Mainly synthesized in the liver from acetyl CoA
        - NADPH is necessary for the *de novo* synthesis of cholesterol **AND FA SYNTHESIS**
        - **NADPH is used in the reduction of cholesterol**
    - Key intermediates in biosynthesis of cholesterol are:
        - HMG CoA, mevaolonic acid, isopentyl pyrophosphate, and **squalene**
            - **NOT Cholic acids**
    - The major regulatory enzyme is HMG CoA reductase
    - Rate Limiting Enzyme of Cholesterol Synthesis → HMG CoA Reductase
        - "Statins" inhibit HMG-CoA reductase
    - Bile salts are formed from cholesterol (via cholic acid)
        - **Most endogenous cholesterol in the liver is converted into cholic acid**
    - Another Q: In certain endocrine tissues cholesterol is converted to steroid hormones:
        - Testosterone
        - Cortisol

- Progesterone
- Estradiol
  - The most potent naturally occurring human estrogen
- Estrogens – a class of steroids that contains 18 carbon and an aromatic ring

- Vitamin D is also formed from cholesterol by a series of reactions requiring the skin, liver and kidney
  - UV activation of precursors in the skin are required for vitamin D_3 synthesis
- Cholesterol absorption depends upon the presence of bile salts in the intestinal lumen
- Cholesterol is mostly esterified with FAs when circulating in blood plasma
- Circulating cholesterol is taken up into liver cells
  - Here it inhibits synthesis of additional cholesterol from acetyl CoA via allosteric inhibition of HMG CoA reductase
  - This provides intrinsic feedback control system to reduce excess cholesterol synthesis

➢ Glucose
- Liver releases glucose back into the circulating blood during exercise
- The skeletal muscle and the brain take up this extra glucose
- Liver has the major responsibility for maintaining blood glucose levels
  - Releases glucose into the blood during muscular activity and in the interval between meals
  - The released glucose is derived from two sources:
    - 1) Breakdown of stored glycogen
    - 2) Formation of new glucose by gluconeogenesis

➢ Fasting State vs. Fed State
- Fed State
  - Digestive System
    - Glucose → (*liver)* → Glu-6-P → Glycogen OR Glycolysis OR HMP Shunt
    - Amino Acids → (*liver)* → Proteins OR Glycolysis
    - Chylomicrons → (*liver)* → Fatty Acids → Glycolysis OR Fats → VLDLs
- Fasting State
    - Fatty Acids → (*liver)* → Acetyl CoA → Ketone Bodies
    - Amino Acids/Glycerol/Lactate → (*liver)* → TCA Cycle → Acetyl CoA → Ketone Bodies
    - (*liver)* Glycogen → G6P → Pyruvate → Acetyl CoA → Ketone Bodies
    - OR (*liver)* Glycogen → Glucose → (*out of the liver)* → Glucose
  - So, fasting for several hours leads to decreased liver glycogen
    - *NOTE: Here's a question that uses info from all over the place:*
      - ➢ Each of the following occurs during prolonged starvation:
        - Circulating T4 is converted to rT3 (reverse T3)
        - Ketoacidosis develops progressively
        - Insulin levels are depressed
        - (Primary fuel is not glycogen) it is FA to become ketone bodies
- Glucose is required particularly by tissues such as the brain and RBCs
  - RBCs oxidize glucose to pyruvate and lactate
  - Glucose is the major fuel for the brain
    - It oxidizes approximately 140 g/day to CO_2 and water, producing ATP
    - The brain contains no significant stores of glycogen, and is therefore completely dependent on the availability of blood glucose
- In skeletal muscle
  - Glucose is phosphorylated, then degraded by glycolysis to pyruvate, which is converted to acetyl-CoA and oxidized via the citric acid cycle
- Glucose is the major end-product of CHO ingestion

➢ Liver enzymes:
- Glutamate-pyruvate transmaminase (GPT): also **called alanine animotransferase (ALT)**
- Glutamate-oxaloacetate transmaminase (GOT): also **called asparatate aminotransferase (AST)**

❖ **Kidney**

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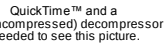
❖ ---

- Countercurrent mechanism: (picture)
  - The countercurrent theory is used to explain the functioning of the kidney
  - Essential for the concentration of urine
  - This is the mechanical system employed by a kidney dialysis machine (Counter current)
  - System in the renal medulla that facilitates concentration of the urine as it passes through the renal tubules
  - Responsible for secretion of hyperosmotic urine in response to elevated plasma osmolarity and requires that the penetration of the loop of Henle into the renal medulla for the development of the medullary osmotic gradient
    - The loops of Henle are responsible for the establishment of an osmotic gradient within the medulla of the kidney
  - Depends on the special anatomical arrangement and transport properties of the loops of Henle
- Countercurrent multiplier in the loops of Henle is dependent upon:
  - Active reabsorption of **sodium** ions by the thick **ascending** limb of the loop of Henle
    - Osmotic equilibrium between interstitial fluid and tubular fluid in the descending limb of the loop of Henle
    - Continued inflow of new sodium chloride from the proximal tubule into the loop of Henle
  - The sodium chloride reabsorbed from the ascending loop of Henle keeps adding to the newly arrived sodium chloride, thus multiplying its concentration in the medullary interstitium
  - Countercurrent exchange in the medullary BVs, called the *vasa recta*
    - The vasa recta do not create the medullary hyperosmolarity but do prevent it from being dissipated and can carry away the water which has been reabsorbed
- Nephron
  - The kidney's basic structural and functional unit
  - Parts:
    - Proximal convoluted tubule:
      - "Workhorse" of the nephrons
      - Requires the greatest amount of ATP
        - 80% of ATP is used for Na+ reabsorption
        - 67% occurs in the PCT
      - Water Permeable!!!, as solutes get pumped actively, water follows
      - Reabsorption of ALL glucose and AAs, most of the bicarbonate, water, and Na+, chloride, phosphate, calcium
      - **Secretes Ammonia which acts as buffer for secreted H+**
      - Approximately 2/3 of the glomerular filtrate is reabsorbed in the proximal convoluted tubule
        - This includes 100% of the filtered glucose and **amino acids**
      - Another Q: The osmotic pressure of the filtrate at the end of the proximal convoluted tubule is about the same as that of plasma
      - Another Q: Most fluid reabsorption by the kidney occurs here
    - Thin Descending limb of loop of Henle:
      - Reabsorption of solutes and water

- ♦ Impermeable to Na+

- Thick Ascending limb of loop of Henle (Thick and Thin)
  - ♦ **Has a thick swim suit on**
  - ♦ **Impermeable to Water**
  - ♦ Reabsorbtion Actively of Na^+, Cl-, and K+
  - ♦ Indirectly induces the reabsorption of Mg2+ and Ca2+
    - ➢ This, in the thick portion, is the basis for the countercurrent multiplier activity
    - ➢ Henle's loop is the segment of the nephron wherein the tubular fuid has the highest osmolarity & osmolality
    - ➢ Osmolarity of 1400 at the bottom
      - ▪ Don't get clowned – the Collecting duct is not part of the nephron
- Distal convoluted tubule:
  - ♦ **(controlled by aldosterone)**
  - ♦ **Secretion of H^+ and K^+**
    - ➢ **Proximal Secreted Ammonia**
  - ♦ Reabsorption Actively of Na+ and Cl-
  - ♦ Reabsorption of Ca2+ is under control of PTH
- Collecting duct
  - ♦ Where the distal ends of each distal convoluted tubule join
  - ♦ Reabsorbs Na+ in exchange for secreting K+ and H+ **(controlled by aldosterone)**
  - ♦ Secretes H+ and reabsorbs water (controlled by ADH = vasopressin = antidiuretic hormone =ADH = Pitressin
  - ♦ Osmolarity of medulla can reach 1200-1400mOsm



- ♦

- ♦
- Juxtaglomerular vs. Cortical Nephrons
  - Juxtaglomerular
    - Have their renal corpuscles close to the base of the medullary pyramid
    - Have Long loops of Henle and long thin segments that extend into the inner region of the pyramid
    - Most of the concentration of urine in the kidney is performed by juxtamedullary nephron, which are at a relatively deep position in the kidney[1].
  - Cortical
    - Have their renal corpuscles in the outer part of the cortex
    - Have Short Loops of Henle and the hairpin turn occurs in the distal thick segment
  - Intermediate
    - Inbetween the other two, duh!
  - Juxtamedular & cortical nephrons differ primarily in length of the thin segment of the loop of Henle
- Glomerular filtration
  - Filtration process as blood flows through the kidney
  - Some of the plasma (16-20%) is filtered out of the glomerular capillaries and into the glomerular capsules of the renal tubules as the glomerular filtrate
    - Formation of glomerular filtrate does not rely on diffusion (energy required from hydrostatic pressure of the blood)
    - Another Q: **Energy for filtrate formation is derived from the hydrostatic pressure of the blood**
  - Glomerular filtrate contains everything contained in plasma (urea, glucose, NaCl) **except plasma protein**
  - Glomerular filtrate contains the same concentration as plasma does of urea, glucose, amino acids, and plasma electrolytes
    - ♦ **NOT Steroid hormones**
    - Glucose & sodium chloride are filtered and subsequently reabsorbed
  - **The fact that increased concentration of colloids in plasma diminishes the formation of filtrate supports that the glomerulus acts like a simple physical microfilter**
  - Glomerular Filtration Barrier
    - Composed of:
      - ♦ 1. Fenestrated capillary endothelium (size barrier)
      - ♦ 2. Fused basement membrane with heparan sulfate (negative charge barrier)
        - The charge barrier is lost in nephritic syndrome, resulting in albuminuria, hypoproteinemia, generalized edema, and hyperlipidemia
      - ♦ 3. Epithelial layer consisting of podocyte foot processes
  - Inulin:
    - A starch that is given by mouth
      - ♦ NOT natural, that's the creatinine one
    - Is freely filtered from the glomerular capillaries into Bowman's capsule, but does not undergo tubular secretion or reabsorption
    - If the clearance of a substance which is freely filtered is < inulin, then there is a net reabsorption of the substance

- If the clearance of a substance which is freely filtered is > inulin, then there is a net secretion of the substance
- Measures Clearance Rate

- Glomerular filtration rate (GFR)
  - Can be calculated by the clearance of inulin from plasma
  - GFR may be measured by a substance that is filtered but not reabsorbed or secreted (not creatinine)
    - A substance that is actively secreted by the kidney is not useful in measuring GFR; it is useful is measuring:
      - Renal blood flow
      - Renal plasma flow
      - Filtration fraction
      - Tubular Maximum
      - Not GFR (if secreted or resorbed == No good for GFR, ONLY Filtered)
  - The rate at which a substance is cleared from plasma
  - Renal clearance equation
    - Cx = UxV/Px
      - Cx – Volume of plasma cleared
      - Ux – Urinary [ ] of x
      - V – Urine Volume
      - Px – Plasma [ ] of x
    - = (plasma volume completely cleared)/(unit time) = (urinary concentration of the substance * urine volume) / (plasma concentration of the substrate)
  - Assessment of blood urea nitrogen (BUN) and serum creatinine can also be used to estimate the GFR
    - Creatinine is freely filtered, is not resabsorbed, slightly secreted, and produced endogenously at a constant rate
    - Another Q: Creatinine is the natural metabolite measured clinically as a predictor of GFR
      - *(Don't mix this Q up with inulin)*

- **Clearance rate for a substrate that is completely removed in one pass through the kidney = renal plasma flow**
  - Simply put, the amount of the substance removed correlates to the amount of plasma that flows through the kidney
- Decrease in GFR is caused by:
  - Constriction of afferent arteriole:
    - Decreases the glomerular capillary hydrostatic pressure and decreases the renal blood flow (RBF)
    - RBF = Is the volume of blood delivered to the kidneys per unit time
  - Relaxation of efferent arterioles:
    - Decreases the glomerular capillary hydrostatic pressure
  - Increased plasma protein concentration of glomerular capillary blood:
    - Increases plasma oncotic pressure
  - Ureteral blockage (increased hydrostatic pressure in Bowman's capsule):
    - Blockage of urine transport through the ureters will increase hydrostatic pressure in Bowman's capsule
      - Capsule hydrostatic pressure is the major force causing glomerular filtration
  - Excessive constriction of the efferent arteriole will decrease RBF and GFR
    - **Another Q: A proportionate increase in resistance of afferent and efferent arterioles of the kidney would result in a decrease in RBF with no change in GFR**
- Increase in GFR is caused by:
  - Decreased plasma **oncotic** pressure (synonym with osmotic, less protein in blood)
  - Vasodilation of afferent arterioles
  - Decreased pressure in Bowman's capsule (no blockage of urine)
  - **Moderate** vasoconstriction of efferent arterioles
    - The most likely cause of an increase in **filtration fraction** is efferent arteriolar constriction
- PAH
  - Both filtered and secreted and is used to estimate renal plasma flow
    - (Filtration of PAH is also know as Effective Renal plasma flow (RPF))
  - **Secreted in proximal tubule**
  - Secondary active transport system
  - Mediated by a carrier system for organic acids
  - Competitively inhibited by probenecid
- Filtration Fraction
  - **= GFR/RPF or C_{inulin}/C_{PAH}**
  - The most likely cause of an increase in **filtration fraction** is efferent arteriolar constriction
  - NSAIDs
    - Prostaglandins dilate afferent arterioles (↑ RPF and ↑ GFR, so FF stays the same)
    - **So NSAIDs can cause renal failure because they inhibit the renal production of prostaglandins, which normally keep the afferents dilated to maintain GFR**

- ACE Inhibitors
  - **Angiotensin II constricts efferent afterioles (↓ RPF and ↑ GFR, so FF would increase)**
    - **End in –PRIL**
  - So if you inhibit ACE, no Angiotensin II and FF would be less)
- Free Water Clearance
  - $C_{H2O} = V - C_{osm}$
    - V = Urine flow rate
  - $C_{osm} = U_{osm}\ V/P_{osm}$
- Glucose Clearance
  - At a normal level, all glucose is reabsorbed in proximal tubule
  - At plasma glucose level of 200mg/dL, glucosuria begins (Threshold)
  - At plasma glucose level of 300mg/dL, transport mechanism is completed saturated (Tm)
    - Glucosuria can be caused by low insulin level, high blood sugar level, impaired tubular reabsorption, & high GFR
    - The best explanation why glucose does not appear in the urine is that glucose is freely filtered, but is removed by reabsorption in the proximal convoluted tubule
    - The normal clearance of glucose is 0 mg/min
    - Glucose transport from the lumen of the nephron depends on Na^+ transport (via a cotransporter)
    - The presence of glucose in the urine proves a person has exceeded his/her renal threshold for glucose
      - So a High renal threshold usually won't result in glucosuria
- Amino Acid Clearance
  - Resorption by at least 3 different carrier systems, with competitive inhibition within each group
  - Secondary active transport occurs in proximal tubule and is saturable
- Kidney normally excretes 1-2 L urine/day
- When tubular secretion and reabsorption processes are completed, the fluid remaining within the tubules is transported to other components of the urinary system to be excreted as urine
  - Urine consists of water and other materials that were filtered or secreted into the tubules but not reabsorbed
  - Although about 180 L per day of glomerular filtrate are produced, the kidneys only excrete 1-2 L
  - Approximately 99% of filtrate is returned to the vascular system, while 1% is excreted as urine
  - Water and substances the body needs are returned to the blood, whereas waste products and excess fluid and solutes remain in the tubules and are excreted form the body as urine
  - In response to elevated plasma osmolarity, a small volume of concentrated urine will be produced
    - If plasma osmolarity is lower than normal, a large volume of dilute urine will be excreted

➢ Excretion rate = filtration rate – reabsorption + secretion

➢ Reabsorption
- Movement of solutes from the tubular fluid into the interstitial fluid
- Occurs in the following:
  - Proximal tubule
  - Loop of Henle
  - Distal convoluted tubule
  - Collecting duct
- Processes include: 1° active transport, 2° active transport, facilitated diffusion, simple diffusion, and solvent drag
  - Transport can be either transcellular or paracellular

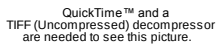
➢ ***The osmolarity of the renal fluid at the end of the proximal tubules equals that of plasma

➢ Secretion
- Movement of solutes from the interstitial fluid into the tubular fluid

➢ Urine
- Normal urine
  - Consists of Na+, Cl-, K+, calcium, magnesium, sulfates, phosphates, bicarbonate, uric acid, ammonium ions, creatine, and urobilinogen
    - The main route of calcium excretion from a normal human adult is FECES
  - Is clear, straw-colored, slightly acidic, and has the characteristic odor of urea
  - Normal specific gravity of urine is between 1.005 and 1.030
  - Formation is important in the regulation of acid-base balance, maintenance of ECF volume and BP, and in maintaining the normal osmolarity of ECF
- Diuresis:
  - Results from a decrease in the tubular reabsorption of water (often after ingesting a large quantitiy of water)
  - Another Q: An **osmotic diuresis** is observed during **diabetes mellitus**
- Causes of dilute urine:
  - Absence of ADH, diabetes insipidus

- Causes of concentrated urine:
  - Decreased plasma volume, cellular dehydration, diabetes mellitus, excess ADH
    - Think in DM, all of the glucose in the urine, so it still is concentrated even though you get osmotic diuresis to go with it
      - In cellular dehydration water moves from interstitial and Extracellular to inside the cells, now you have a decrease in plasma volume
        - This decrease produces action potentials to the **supraoptic hypophyseal tract** and into the neural lobe of the posterior pituitary resulting in the release of ADH
        - ADH of course gets water reabsorbed and leaves the urine more concentrated
  - ***Na+ has the greatest influence on water retention, even more than Cl- & K+
- The ability to concentrate urine is most closely related to the length of the loop of Henle

- Ammonia
  - Produced from the metabolism of a variety of compounds
  - Amino acids is the most important because most Western diets are high in protein and provide excess aa, which are deaminated to produce ammonia
  - **Sources of ammonia:**
    - From amino acids:
      - Many tissues, but particularly the liver, form ammonia from amino acids by the aminotransferase and glutamate dehydrogenase reactions
    - From glutamine:
      - The kidney (specifically, the tubular cells) **form ammonia from glutamine** by the action of renal glutaminase
      - Most of this ammonia is excreted into the urine as NH_4, which is an important mechanism for maintaining the body's acid-base balance
    - From amines:
      - Amines obtained from the diet and monoamines that serve as hormones or neurotransmitters give rise to ammonia by the action of amine oxidase
    - From purines and pyrimidines:
      - The catabolism of purines and pyrimidines, amino groups attached to the rings are released as ammonia
      - **Amino acids are the source of most of the nitrogen in purines**



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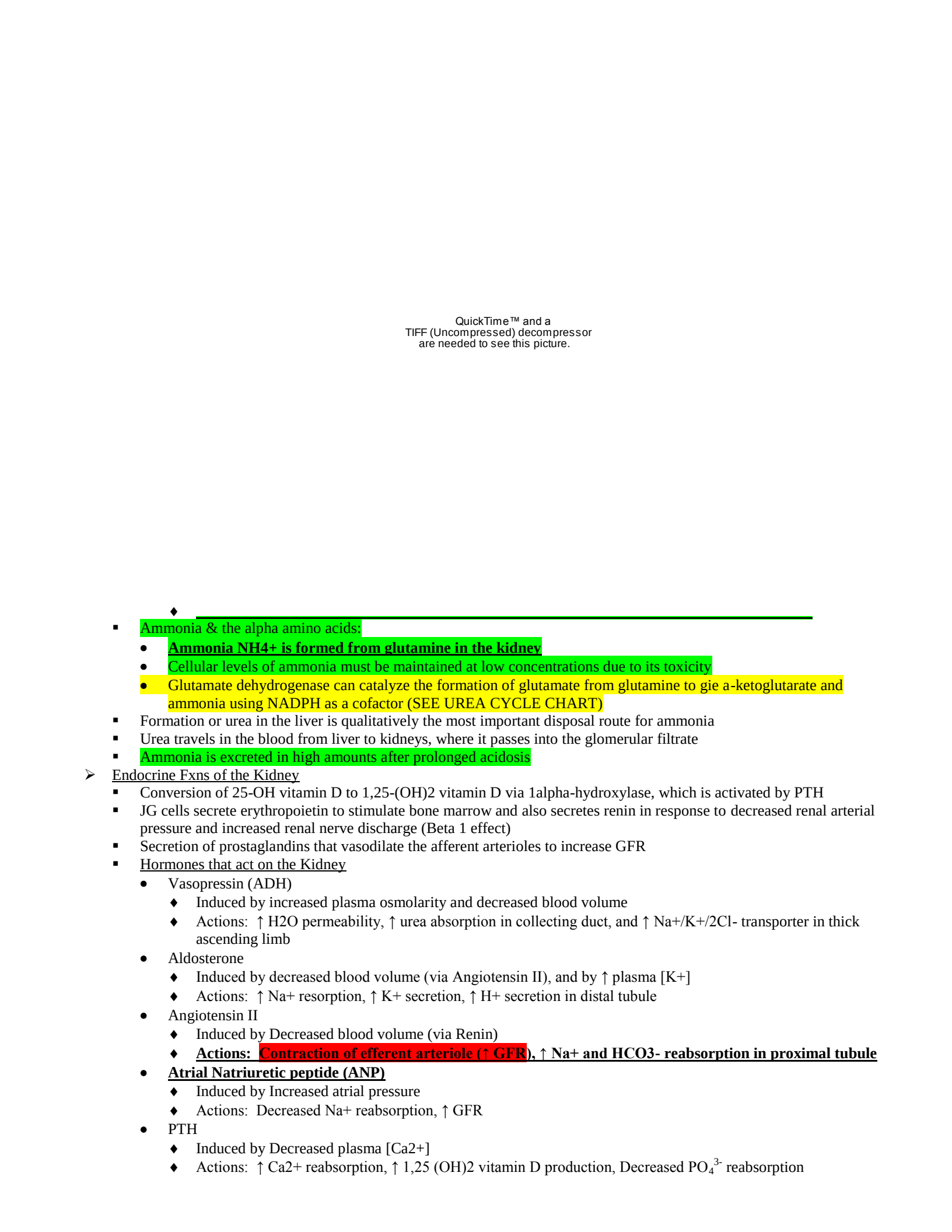


- ♦
- Ammonia & the alpha amino acids:
  - **Ammonia NH4+ is formed from glutamine in the kidney**
  - Cellular levels of ammonia must be maintained at low concentrations due to its toxicity
  - Glutamate dehydrogenase can catalyze the formation of glutamate from glutamine to gie a-ketoglutarate and ammonia using NADPH as a cofactor (SEE UREA CYCLE CHART)
- Formation or urea in the liver is qualitatively the most important disposal route for ammonia
- Urea travels in the blood from liver to kidneys, where it passes into the glomerular filtrate
- Ammonia is excreted in high amounts after prolonged acidosis

➢ Endocrine Fxns of the Kidney
- Conversion of 25-OH vitamin D to 1,25-(OH)2 vitamin D via 1alpha-hydroxylase, which is activated by PTH
- JG cells secrete erythropoietin to stimulate bone marrow and also secretes renin in response to decreased renal arterial pressure and increased renal nerve discharge (Beta 1 effect)
- Secretion of prostaglandins that vasodilate the afferent arterioles to increase GFR
- Hormones that act on the Kidney
  - Vasopressin (ADH)
    - ♦ Induced by increased plasma osmolarity and decreased blood volume
    - ♦ Actions: ↑ H2O permeability, ↑ urea absorption in collecting duct, and ↑ Na+/K+/2Cl- transporter in thick ascending limb
  - Aldosterone
    - ♦ Induced by decreased blood volume (via Angiotensin II), and by ↑ plasma [K+]
    - ♦ Actions: ↑ Na+ resorption, ↑ K+ secretion, ↑ H+ secretion in distal tubule
  - Angiotensin II
    - ♦ Induced by Decreased blood volume (via Renin)
    - ♦ **Actions: Contraction of efferent arteriole (↑ GFR), ↑ Na+ and HCO3- reabsorption in proximal tubule**
  - **Atrial Natriuretic peptide (ANP)**
    - ♦ Induced by Increased atrial pressure
    - ♦ Actions: Decreased Na+ reabsorption, ↑ GFR
  - PTH
    - ♦ Induced by Decreased plasma [Ca2+]
    - ♦ Actions: ↑ Ca2+ reabsorption, ↑ 1,25 (OH)2 vitamin D production, Decreased PO_4^{3-} reabsorption

- Acid/Base Regulation
  - Kidneys regulate acid-base balance by the secretion of hydrogen ions (H+) into the renal tubules and the reabsorption of bicarbonate ions (HCO_3^-).
    - **Measured by urine pH, ammonium excretion and phosphate excretion**
    - Secretion of ammonia is aid to the kidney in the elimination of H+ ions
  - Another Q: The kidney is the organ chiefly responsible for resistance to change in the blood pH
  - Hydrogen ions are secreted into the tubules by tubular cells
  - Secretion mechanism derives hydrogen ions from carbonic acid
  - Carbonic anhydrase
    - [$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO3^-$]
    - Present within tubular cells, and it catalyzes the formation of carbonic acid from carbon dioxide and water
    - Carbonic acid dissociates into hydrogen ion and bicarbonate
    - One of the fastest known enzymes and is found in great concentration in erythrocytes
    - Carbonic anhydrase in the kidney tubular cells is associated with reabsorption of bicarbonate ion
    - Although not required for CO_2 and water to form carbonic acid, it greatly increase the reaction in both respects
      - Absence of carbonic anhydrase drastically reduces blood CO_2 carrying capacity
  - Phosphate compounds (HPO) and ammonia (NH_3)
      - **The kidney can eliminate cations due to the high ratio of HPO42- to $H_2PO_4^-$**
        - **Eliminating Cations, i.e. H+, just like HCO3- to H2CO3**
    - **Mechanism for recovering from metabolic acidosis**
    - Act as buffers to tie up hydrogen ions in the tubular fluid
    - Ammonia is formed in the tubular cells by the deamination of certain aa, particularly glutamic acid
      - Ammonia interacts with the H+ and forms the ammonium ion to be removed from the body
      - **It acts in the elimination of H^+ in the kidney and allowing for the reabsorption of Na^+ into blood**
      - Secretion of ammonia aids in the elimination of hydrogen ion from the kidney
      - **Ammonia helps to reduce the Hydrogen Ion concentration in body fluids. This mechanism involves the reabsorption of Sodium into the blood**
    - **Phosphate and ammonium excretion measurements provide good information on how much acid is being eliminated by the kidneys – because phosphate and ammonium buffer the acid**
      - Phosphate compounds are excreted in combination with a cations such as Na^+
      - Ammonium ions are excreted in combination with anions such as Cl^-
      - Normal blood bicarbonate:carbonic acid ratio is 20:1. A patient with 10:1 ratio is in uncompensated acidosis
        - SO basically you have a 20:2 ratio, more carbonic acid, so H+ needs to go out!!!!
    - The most important secretory mechanism for conservation of Na+ by kidney is H+ secretion for the reabsorption of **Na^+ & HCO_3^- (1st Na+ is reabsorbed into epi cell from lumen via countertransport against H+, then the Na+ gets into the blood vessel via a cotransport with Bicarb)**

Reproductive System

- Male puberty:
  - During early childhood, a boy does not secrete gonadotropins, and thus has little circulating testosterone
  - During puberty, the penis and testis enlarge and the male reaches full adult sexual and reproductive capability
    - In males, growth and development of secondary sex organs are under direct control of testosterone
  - Puberty also marks the development of male secondary sexual characteristics
  - Secretion of gonadotropins from the pituitary gland, which usually occurs between the ages of 10 and 15, marks the onset of puberty
    - The normal delay in sexual development until puberty is attributed to lack of hypothalamic stimulation of gonadotropin release
  - Pituitary gonadotropins stimulate testes functioning as well as testosterone secretion
  - At puberty, an alteration in brain function leads to an increased production of gonadotropin-releasing hormone (Gn-RH) by the hypothalamus
  - GnRH stimulates the secretion of FSH and LH (gonadotropins) by the anterior pituitary gland
  - These gonadotropins stimulate the growth and function of the testes
    - (FSH & LH act on both ovaries & testes)
    - FSH
      - promotes the maturation of sustentacular cells (Sertoli cells)
      - **(FSH, S for Sertoli)**
        - which are involved in sperm development and maturation
        - produce ABP (Androgen Binding Protein) which ensures that testosterone is high in seminiferous tubules
        - produce Inhibin, which inhibits FSH (negative feedback)
    - LH

- stimulates the interstitial (Leydig cells) of the testes
- **(Leydig for LH)**
  - to produce testosterone – secondary sex characteristics

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

  -
- Anabolic Steroid Use
  - A person who used anabolic steroids, but who has recently stopped will experience
    - Low FSH, and LH levels
    - Low Testosterone levels
    - Decreased number of spermatids
      - NOT Sterility (Looked it up, it may take a few months, but gonads will get back to full production)
- Androgens
  - DHT> Testosterone> Androstenedione
    - Testosterone is converted to DHT **by 5alpha-reductase**
    - Testosterone and androstenedione are converted to estrogen in adipose tissue by the **NZ Aromatase**
  - Functions
    - Differenetiation of wolffian duct system into internal Gonadal structures
    - Secondary sexual characteristics and growth spurt during puberty
    - Required for normal spermatogenesis
    - Anabolic effects: increased muscle size, increased RBC production
    - Inhibits GnRH (negative feedback)
    - Fuses epiphyseal plates in bone
    - Increased Libido (Whoo-whee!)

- Female Puberty
  - Female reaches puberty 1 or 2 years earlier than males
  - Puberty is marked by the first episode of menstrual bleeding, which is called the menarch
  - An alteration in brain function leads to increased gonadotropins-releasing hormone (GnRH) secretion by the hypothalamus
  - GnRH stimulates the secretion of FSH and LH by the anterior pituitary gland, which ultimately leads to an increased production of estrogens (androgen hormone) by the ovaries
  - The events of puberty in the female (such as enlargement of the vagina, uterus, and uterine tubes; deposition of fat in the breasts and hips) are largely a result of increased production of estrogens by the ovaries
- Estrogen
  - Estradiol> Estrone> Estriol
    - **Estradiol from the Ovary**
    - **Estriol from the Placenta**
  - Functions:
    - Causes the development of female 2° sex characteristics (genitalia)
    - Causes the development of the breast
    - Maintains pregnancy
    - Growth of the follicle
    - Endometrial proliferation, myometrial excitability
    - Female Fat distribution

- Hepatic synthesis of transport proteins
- Feedback inhibition of FSH
- **LH Surge (Estrogen feedback on LH secretion switches to positive from negative just before LH surge)**

- Is effective at very low concentrations & generates a slowly developing long-term response in target tissues by binding to an intracellular receptor
- Contains 18 Carbons and an aromatic ring
  - Androgens do NOT (19 carbons, no ring)
  - Progesterones, Glucocorticoids, Mineralcorticoids (NO ring – 21 Cs)
- Estrogen Hormone Replacement Tx
  - Decreases risk of heart disease
  - Decreases hot flashes and postmenopausal bone loss
- Unopposed Estrogen Tx
  - Increases risk of endometrial cancer
    - Decreased risk when used with Progesterone

➢ Progesterone
- Funtions:
  - Stimulation of endometrial glandular secretions and spiral artery development
  - Maintenance of Pregnancy
    - Elevation of progesterone levels is indicative of pregnancy
  - Decreased myocardial excitability
  - Production of thick cervical mucous which inhibits sperm entry
  - Increased body temp
  - Inhibition of Gonadotropins (LH, FSH)
  - Uterine smooth muscle contraction
  - Promotes secretory changes in the endometrium during the latter half of monthly period, thus preparing endometrium for implantation of fertilized egg

➢ hCG (human chorionic gonadotropin)
- peptide hormone produced during pregnancy
- Synctiotrophoblast of placenta
- **Maintains the corpus luteum for the 1st trimester by acting like LH**
- **Its role is to prevent the disintegration of the corpus luteum of the ovary and thereby maintain progesterone production that is critical for a pregnancy in humans.**
- In 2nd and 3rd trimesters, **the placenta synthesizes its own estrogen and progesterone and the corpus luteum degenerates**
- Used to detect pregnancy because it appears in the urine 8 days after successful fertilization (blood and urine Testing)
- Elevated hCG in women with **hydatidiform moles** or **choriocarcinoma** (chorio- outer membrane of placenta)

➢ Precocious puberty
- A condition in which the changes associated with puberty begin at an **unexpectedly early age**
- Results from hyperactive adrenal cortex
- Is due to an excess of androgenic (in boys) & estrogenic (in girls) substance produced by the adrenal cortex
  - **NOTE: Androgens are produced in the testis & the adrenal cortex, Ovary,**
- These substances resemble the male and female sex hormones

➢ Menopause
- Cessation of estrogen production with age-linked decline in number of ovarian follicles
- Average age of onset is 51 (earlier in smokers)
- Therapy - Estrogen replacement
- **HAVOC –** Hot flashes, Atrophy of Vagina, Osteoporosis, Coronary heart disease

➢ Menstrual cycle:
- **Ovulation occurs 14 days before menses, regardless of cycle length**
- Average menstrual cycle usually occurs over 28 days, although the normal cycle may range from 22 to 34 days
  - Menstrual phase:
    - Aunt Flow begins the cycle
    - Cycle starts with menstruation (cycle day 1), which usually lasts 5 days
  - Proliferative (follicular) phase:
    - Lasts from cycle day 6 to day 14
    - **LH and FSH act on the ovarian follicle (mature ovarian cyst containing the ovum)**
      - **This leads to estrogen secretion from the follicle, which in turn stimulates buildup of the endometrium**
      - Development of ovarian follicles to the point of ovulation is stimulated primarily by FSH – **Follicle stimulating hormone**

- Late in this phase, estrogen levels peak, FSH secretion declines, and LH secretion increases, surging at mid-cycle (around day 14)
- **LH Surge (Estrogen feedback on LH secretion switches to positive from negative just before LH surge)**
- The LH surge leads to final maturation of follicle, rupture of follicle and ovulation
- Another Q: ovulation is believed to be caused by a shift in anterior pituitary gonadotropin secretion with LH predominating in the mixture
  - Without the LH, even though large quantities of FSH are available, the follicle will not progress to the stage of ovulation
  - FSH and LH are both **glycoproteins** and act in both the ovaries (in females) and the testis (in males)
    - FSH is a polypeptide
    - FSH exerts its action on germinal epithelium
- Then, estrogen production decreases, the follicle matures, and ovulation occurs

- Ovulation:
  - Day 15 – 14 days after Day 1 of menstruation, **BUT does VARY**
  - Occurs as a result of the estrogen-induced LH surge
  - The discharge of an mature ovum (oocyte) from the follicle (Graafian follicle) of the ovary
    - The ovum generally disintegrates or becomes nonviable if it is not fertilized within 4 days
  - Progestins
    - Being used as oral contraceptive substance due to their ability to suppress ovulation
    - Remember Progesterone is usually the maintainer of pregnancy, so body is fooled into thinking its prego
- Luteal (secretory) phase:
  - Lasts about 14 days
  - FSH and LH levels drop
    - **The corpus luteum begins to develop, and it synthesizes estrogen and progesterone**
      - hCG is promoting this in the 1st trimester
      - **The blood concentration of estradiol does NOT increase as corpus luteum develops**
        - This is why prego women are not horny in the 1st trimester, the corpus luteum is taking care of itself and there is no circulating estradiol to stimulate them to go find their man!!
        - But the 2nd Trimester is Great → The Madonna period
    - Ruptured mature follicle forms the corpus luteum, which secretes progesterone and estrogen
  - If fertilization does not occur, the corpus luteum degenerates (become nonviable)
    - As a result, estrogen and progesterone levels decrease until their levels are too low to keep the endometrium in a fully developed secretory state
    - The endometrial lining is shed as menstrual fluid during menstruation or menses
- Decreasing estrogen and progesterone levels stimulates the hypothalamus to produce GnRH, and the cycle beings again

- Two significant results of the female sexual cycle:
  - Only a single mature ovum is normally released from the ovaries each month so that only a single fetus can begin to grow at a time

Lipids

- Lipids:
  - Organic compounds that do not dissolve in water but do dissolve in alcohol and other organic solvents
  - Are not able to move in body fluids due to their hydrophobic nature so they are packaged in micellar structures called lipoproteins
  - Various lipoproteins are classified in terms of density
  - **Since lipids are much less dense than proteins there is an inverse relationship between lipid content and density (i.e., high lipid content means low density particle) – HDL good because little lipid content**
  - The major components of lipoproteins being transported are phospholipids and proteins which make up the micellar membrane (the protein component alone is called **apolipoprotein**)
  - The major lipids include **triacyglycerols or TGs** (the most common lipids) phospholipids, and steroids
  - Lipid is required in the average diet because it provides essential fatty acids
  - Another Q: Among cellular components, lipids are most characteristic of membranes
  - Another Q: Which of the following is least descriptive of lipids:
    - Hydrophilic (among answer choices of nonpolar, carbon-containing, and amphipathic)
  - **Lipids that are relatively polar, contain more Oxygen**
- Triglyceride: (TGs)
  - Provide more than half the energy requirements of some organs, particularly the liver, heart, and skeletal muscle
  - When hormones signal the need for metabolic energy, TGs stored in adipose tissue are brought out of storage and transported to those tissues (skeletal muscle, heart, renal cortex) in which FAs can be oxidized for energy production
  - TGs are *not* membrane constituents

- **TG is the principal lipid stored in adipose tissue**

- Phospholipids
  - Type of lipid that contains a phosphate group
  - Major lipid that makes up cell membrane
  - Would likely form a micelle when mixed with water & agitated
    - Like a phospholipid bilayer, but its only one layer, small circular
    - Another Q: Lipid micelles have spherical structures that are stabilized by hydrophobic interactions of lipid groups
    - The major driving force for formation of a liquid micelle is hydrophobic interaction between hydrocarbon tails
  - Three major types of Body Phospholipids:
    - **Lecithins: (aka phosphatidylcholine)**
      - Major component of cell membrane of RBCs, of myelin, of bile, and of surfactant (DPPC)
      - Phospholipid present in liver bile
      - They are water soluble emulsifiers
      - Are a group of phospholipids that upon **hydrolysis yields:**
        - **1) Two fatty acid molecules**
        - **2) One molecule each of glycerol, phosphoric acid, and choline**
      - **Lipotropic effect of lecithin upon fatty liver—also produced by choline**
        - Choline:
          - Lipotropic = **Lipotropic compounds are those which help catalyse the break down of FAT during metabolism in the body.**
          - Another Q: Choline is an important lipotropic substance
            - **Lipotropic substance one that promotes taking fat out of the liver**
          - Another Q: **Outer lamella of cell MB contains sphingomyelin & phosphatidylcholine** (not phosphatidylethanolamine)
          - Both choline and lecithin are lipotropic substances
          - A compound synthesized by the body and is found in most animal tissues
          - Is essential for the metabolism of TGs, particularly lipoprotein secretion, in the liver
          - A deficiency of choline in the diet can cause abnormalities in fat/lipid metabolism
          - Is a natural amine that is often classified with the B vitamins, although it is not a vitamin, and is a constituent of many biologically important molecules such as Ach and lecithin
          - It prevents the deposition of fats in the liver and facilitates the movement of fats into the cells
          - When converted to betaine, is also a source of transferable **methyl groups in metabolism**
          - A deficiency of choline in animals leads to fatty liver disease and eventually hepatic cirrhosis
            - **W/o choline you can't put fat in the other cells, because no choline no lecithin so no liprotropic effect**
          - Choline, choline phosphate and cytidine diphosphocholine are involved in the synthesis of phosphatidylcholine, a major phospholipids constituent of membranes and lipoproteins. It is synthesized *de novo* in liver cells
    - The cephalins:
      - A group of phospholipids having hemostatic properties and found especially in the nervous tissue of the brain and spinal cord
      - They resemble lecithin, except they **contain either 2-ethanolamine or L-serine in the place of choline**
    - The sphingomyelins:
      - Phospholipids that are found especially in nerve tissue and yield:
        - **Sphingosine, choline, a fatty acid, and phosphoric acid upon hydrolysis**
      - They are **membrane constituents**
    - Basic structure of phospholipids: glycerol + fatty acids + phosphate group + R group

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

- Types of Lipoproteins:
  - Lipid-binding proteins, responsible for the transport in the blood
  - Chylomicrons:
    - Least dense lipoprotein
    - **Most triglyceride and the least protein content**
    - **Transport primarily dietary triacylglycerols around the body and dietary cholesterol to the liver**
    - Secreted by intestinal epithelial cells
      - **Remember micelles emulsify in water to give phospholipids, (NOT TGs SEE PICTURE ABOVE)**
    - Another Q: triglyceride absorbed into the lymphatic system is transported to the liver as chylomicrons
    - They are the largest of the lipoproteins
    - Are plasma lipoprotein
    - Carry FAs obtained in the diet to the tissues in which they are consumed or stored as fuel
    - Remnants of chylomicrons, depleted of their tracylglycerols but still containing cholesterol, move through the bloodstream to the liver, where they are taken up, degraded in lysosomes, and their constituents recycled
  - VLDLs (very low-density lipoproteins):
    - More dense than chylomicrons
    - High content of triacylglycerides
    - Secreted by the liver
    - Transport endogenous (hepatic) triacylglycerols to various tissues (primarily muscle and adipose tissue)
  - LDLs (low-density lipoproteins):

- Large spherical particles made of a core of esterified cholesterol surrounded by a lipid bilayer containing protein
- Denser than VLDLs
- Less TG and more protein content
- High phospholipids content
- **Highest cholesterol content**
- Delivers hepatic cholesterol to peripheral tissues
- They are the primary plasma carriers of cholesterol for delivery to all tissues carrying cholesterol, cholesterol esters, and phospholipids from liver to body
- Another Q: LDLs are transported into the cells by way of receptor-mediated endocytosis
  - When cholesterol is needed, a cell will make a receptor for LDL and insert the receptor in the plasma membrane
    - Then LDL binds to the receptor and is engulfed (via endocytosis)
  - When the cell has enough cholesterol, gene regulation for the LDL receptor is down regulated
  - Which one adjusts the Cholesterol level in blood? → LDL

- HDLs (high-density lipoproteins):
  - Most dense lipoproteins
  - Has the lowest triglyceride and highest protein content
  - Transfers cholesterol as an acyl ester derivative **from other tissues back to the liver**
  - Mediates reverse cholesterol transport (from periphery to liver)
  - Secreted from both liver and intestine

- Familial Hypercholesterolemia
  - The key problem is a decrease in LDL receptors
  - Autosomal Dominant
    - **Comes with Xanthomas (Achilles heel)**

- Fats/TGs:
  - Contains three molecules of fatty acid combined with one molecule of glycerol
    - Neutral fats contain mixtures of one or more fatty acids esterified with glycerol
  - Is a long chain compound with an even number of carbon atoms and a terminal COOH group
  - Can be saturated, monounsaturated, or polyunsaturated
  - Classified by the number of double bonds between carbon atoms in their fatty acids molecules:
    - Ending in -ic
    - **Saturated fat:**
      - No double bonds between carbon atoms
      - Arachidic acid, behenic acid, butyric, capric, caproic, caprylic, lauric, myristic, palmitic, stearic
        - **Upon complete hydrogenation, oleic, linoleic and linolenic acids yield stearic acid**
    - **MonOunsaturated fat:**
      - One double bond between carbon atoms
      - Erucic, Oleic, palmitoleic
    - **Polyunsaturated fat:**
      - Multiple double bonds between carbon atoms
      - Arachidonic, linoleic, linolenic
      - Prostaglandins are made within cells from polyunsatured fats
    - ***Stearic→oleic→linoleic→linolenic→(arachidonic): a sequence that shows increasing number of double bonds
    - **Arachidonic acid has the most double bonds, among oleic, stearic, and palmitic**

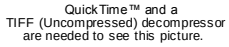
- Fatty acids:
  - **Essential FAs cannot be synthesized because we lack the lack the enzymes to place double bonds at certain positions (omega – 3 and omega – 6) and must therefore obtain them from the diet**
    - Essential FAs:
      - Arachidonic (20:4), linoleic (18:2), and linolenic (18:3)–Polyunsaturated fats
      - **Linoleic is a polyunsaturated fatty acid commonly found in animal cell MBs** (that's why we eat those animals)
  - All fatty acids are building blocks of phospholipids and glycolipids and are therefore needed for the synthesis of MBs
  - Cells derive energy from them through beta oxidation
  - The predominant source of ATP at moderate levels of activity (>20 min) are fatty acids

- Freeing stored fat/Free fatty acids:
  - Epinephrine and glucagons
    - **Increase glycogen and lipid breakdown**
    - **Activate adenylate cyclase**
      - Lies in the adipocyte plasma membrane
      - Raises the intracellular concentration of cAMP
      - Activated by Epi, Glucagon, and PTH, NOT Insulin

- A cAMP-dependent protein kinase, in turn, phosphorylates & thereby activates hormone-sensitive **triacylglycerol lipase**
  - Mobilization of fat stored in adipocytes involves activation of triglyceride lipase by a cAMP dependent protein kinase
    - **cAMP is broken down by cAMP phosphodiesterase**
      - Methyl xanthines such as caffeine & theophylline enhance lipolysis in adipose tissue by inhibiting cAMP phosphodiesterase

♦ **Triglyceride Lipase**
- This NZ initializes the **hydrolysis** of the ester linkages of TGs forming 3 free FAs and glycerol
- SIDE BAR → Fat, monoglycerides, and Proteins are broken down by **Hydrolysis**
  - The 3 FAs that are released bind to serum albumin and travel to the tissues where they dissociate from albumin and diffuse into the cells in which they will serve as fuel
  - Glycerol released by lipase action
    - **Is phospholyated by glycerol kinase, and the resulting glycerol-3-phosphate is oxidized to dihydroxyacetone phosphate**
    - This compound is then converted to glyceraldehyde-3-phosphate by the enzyme triose phosphate isomerase
      - **G3P is then oxidized via glycolysis to go on to make Pyruvate → Acetyl CoA → Kreb's**

- **Insulin causes activation of a phosphorylase which dephosphorylates the hormone-sensitive lipase and thereby diminishes lipolysis**



- ---

❖ Fatty acid degeneration occurs in the mitochondria and uses FADH+/NAD+ --- **Think FAD → Fatty Acid Degeneration**
- Degeneration occurs where its product (Acetyl CoA) will be used in Krebs!!

❖ Fatty acid synthesis occurs in the cytosol and uses NADPH, other different enzymes, and Malonyl CoA
- **Both require phosphopantothenic acid** *(the Q discussed the 2 previous lines)*
- Fatty Acid Catabolism
  - Involves beta oxidation

- Transported to the liver by employing **carnitine as a carrier substance, which is inhibited by cytoplasmic Malonyl-CoA**
- Once inside the mitochondria, the fatty acid is **transferred from the carnitine to a CoA and is oxidized (via beta oxidation) to acetyl CoA**
- Acetyl CoA molecules enter into the citric acid cycle (Kreb's cycle) to form carbon dioxide and reducing equivalents (NADH, $FADH_2$)
- The reducing equivalents are then reoxidized by electron transport system and the energy released by that process is used by the oxidative phosphorylation system to form ATP
- **18 carbon FA → 9 moles of acetyl CoA when broken down**
  - Ketone bodies:
    - Acetoacetate
      - **Synthesized by cleavage of B-hydroxy-B-methyglutaryl CoA**
      - Which of the following is a ketone body? **Acetoacetate** (not glycerol, glucagon, acetyl CoA, and phosphatidylcholine)
    - Beta-hydroxybutyrate
      - Sometimes referred to as D-Beta-hydroxybutyrate or 3-hydroxybutyrate
    - Acetone
      - Not utilized by the body as fuel
      - May normally leave the body via the lungs
      - Fruity smell of the breath
    - During conditions of low glucose availability (starvation or fasting, or a case of diabetes mellitus), adipose tissue breaks down its triacylglycerol stores into FAs and glycerol, which are released into the blood
      - Glycerol is converted into glucose, by first getting converted to Glyceraldehye 3 Phosphate, which is an intermediate in glycolysis, it makes Pyruvate, then because the brain needs energy, you get gluconeogenesis happening to send glucose out of the liver to the brain
      - When there is inadequate insulin, utilization of fat for energy in increased
    - Through the process of β-oxidation, the LIVER converts the FAs to acetyl CoA
    - Acetyl CoA is used by the liver mitochondria for the synthesis of the ketone bodies
      - The liver is the site for production of ketone bodies
      - Another Q: In relative insufiicient insulin, acetyl CoA is usually channeled into ketone-body formation
    - They are transported in the blood to peripheral tissues, where they can be reconverted to acetyl CoA and oxidized by the citric acid cycle (Kreb's cycle)
    - They are important sources of energy for the peripheral tissues
    - They are soluble in aqueous solution and therefore do not require carriers in blood
    - **Unlike fatty acids, ketone bodies can be oxidized by the brain**
      - Metabolized to 2 molecules of Acetyl-CoA by the brain
      - Under circumstances that cause acetyl-CoA accumulation (starvation or untreated diabetes, for example), thiolase catalyzes the condensation of two acetyl-CoA molecules to acetoacetyl-CoA, the parent of the three ketone bodies
    - High concentrations in the blood result in keto acidosis
  - Ketosis:
    - Condition characterized by an abnormally elevated concentration of ketone bodies in the body tissues and fluids
    - Occurs when fatty acids are incompletely metabolized, a complication of untreated diabetes mellitus, starvation, fasting and alcoholism
      - In severe diabetic acidosis, one would expect an increase in plasma keto acids
      - Another Q: Excessive ketone bodies in blood & urine are possible indications of diabetes mellitus
      - Another Q: Ketosis may be produced experimentally by fasting
    - Characterized by ketones in the urine (ketonuria), K+ loss in urine, and a fruity odor of acetone on the breath
      - Acetone is a compound that may leave the body by way of the lungs
    - A diabetic coma can be caused by the buildup of ketone bodies
      - It is commonly fatal, unless appropriate therapy is instituted promptly
    - **Glucose is the only effective substance in reversing ketosis in a non-diabetic patient**
    - Another Q: Excessive use of fat as energy source can lead to ketosis, acidosis and ketonuria (but not alkalosis)

- Fatty Acid Biosynthesis
  - WRITE OUT THE PROCESS
  - **Summary of fatty acid synthesis:** Acetyl CoA→malonyl CoA→malonyl-ACP→acetyl ACP→acetoacetyl ACP→butyryl ACP→fatty acid
  - Occurs in the cytosol, and gets there via a citrate shuttle
  - Active processes during FA biosynthesis: TCA cycle, pyruvate dehydrogenase, amino acid catabolism, glycolysis (not β-oxidation = catabolic process = break down of FA) – *these aren't necessarily a part of FA biosynthesis; the Q is going for us knowing about β-oxidation*

- Is not a simple reversal of β-oxidation used for the catabolism of fatty acids
- **Involves two carbon additions from acetyl CoA and an acyl protein (ACP)**
  - **Acetyl CoA** is the immediate **precursor** for **fatty acid** synthesis
- The important step
  - The first one in which acetyl CoA, ATP, and bicarbonate form malonyl-CoA
  - A key intermediate in the synthesis of FAs is malonyl-CoA, a 3-carbon intermediate, which is formed from acetyl-CoA, bicarbonate, and ATP
  - This is the committed step, the essential control point
    - Acetyl CoA is carboxylated by **Acetyl CoA carboxylase** to Malonyl-CoA
      - **Similar to the carboxylation of Pyruvate to start gluconeogenesis**
    - The pathway for synthesis of even-numbered fatty acids differs from that of the catabolism of fatty acids in that malonyl CoA is an intermediate in synthesis
    - Another Q: CO_2 is incorporated into acetyl coenzyme A (acety, forming malonyl coenzyme A (2 Carbon → 3 carbon)
    - Malonyl-CoA is formed in the metabolism from the carboxylation of acetyl-CoA by the enzyme acetyl-CoA carboxylase. (CO2+acetyl-CoA →Malonyl-CoA)
    - This irreversible reaction is the committing step in fatty acid synthesis and is the **principal regulator – Acetyl Co A carboxylase**
  - Kaplan
    - The diet is the primary source of FAs
    - The next source is from the biosynthesis
      - In many instances, the saturated straight chain 16 carbon acid palmitic acid is first synthesized and all other FAs are made by modification of palmitic acid
- Important points:
  - Glucose is first degraded to pyruvate by aerobic glycolysis in the cytoplasm
  - Pyruvate is then transported into the mitochondria, where pyruvate forms acetyl CoA (by pyruvate dehydrogenase) and oxaloacetate (by pyruvate carboxylase)
  - Acetyl CoA and oxaloacetate condense to form citrate
    - Then Oxaloacetate can either go up the Gluconeogenesis tract to PEP via PEPCKinase (the committed Step)
    - **OR** Oxaloacetate plays an important role in the body by reacting with acetyl CoA to form citrate in the first step of Kreb's
  - Citrate, in turn, can be transported out of the mitochondria to the cytoplasm (where fatty acid synthesis occurs), and **there it splits to generate cytoplasmic acetyl CoA for fatty acid synthesis**
  - **Citrate is a positive modulator** that allosterically regulates the enzyme catalyzing the **rate-controlling step in the *de novo* synthesis of fatty acids**
  - Another Q: The enzyme that catalyzes the 1st step in the fatty acid synthesis pathway is **acetyl CoA carboxylase**
    - It is an allosteric enzyme & is the pincipal regulator of the pathway
    - **So, for a little clarity, the 1st step of FA biosynthesis is the conversion of acetyl CoA to malonyl CoA**
      - **Citrate is a positive modulator of acetyl CoA carboxylase in this step**
      - **Acetyl CoA Carboxylase is the principal regulator of FA synthesis**
      - **Malonyl CoA inhibits carnitine actyl-transferase preventing fatty acid getting into mitochondria therefore stops B-oxidation (or break down of fatty acid)**
  - Coenzyme A (CoA)
    - A pantothenic acid containing coenzyme that is involved in both fatty acid synthesis and catabolism
    - *Coenzyme A participates in activation of carboxyl groups
    - *Acetyl CoA is a common intermediate of the metabolism of fatty acids, amino acids and CHOs

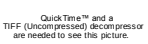
➢ Transporting FAs in the blood
- The body uses 3 mechs for transporting FAs in the blood
  - 1) FAs to albumin
  - 2) Chylomicrons (Cholesterol binds to fat and phospholipids to form chylomicrons)
  - 3) Ketone bodies (aceto-acetate and beta hydroxyl butyrate

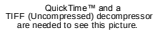
➢ Bile Salts:
- Are sodium salts composed of **cholic acid** (cholate & deoxycholate – most abundant) conjugated with **glycine** or **taurine** to form **glycocholate** and **taurocholate** respectively
- Sodium taurocholate/glycocholate are necessary for absorption of fatty acids. These are conjugated bile components
- Bile salts are amphipathic (hydrophilic and hydrophobic)
- Bile salts are synthesized in the liver and pass, via the bile duct, into the duodenum and then into the jejunum
- They aid in intestinal digestion and absorption of lipids by emulsifying and solubilizing them in micelles
- **Reabsorption of the bile salt micelles occurs in the ileum, from which a large proportion return via the blood to the liver**

- The bile ducts carry bile salts from the liver to the gallbladder, where they are stored; excreted (excess) cholesterol is dissolved in the bile salt micelles
- Overall 90% of bile salts involved in absorption of lipid from w/in the jejunum are recycled – in a process called enterohepatic circulation – they are reabsorbed into the portal circulation and reused
- Actions of bile salts:
  - Help in absorption of FAs, monoglycerides, cholesterol, and other lipids from the intestinal tract (form water-soluble complexes [micelles] with FAs and glycerides)
  - Aid in the absorption of ADEK Vitamins
    - NOTE on micelles:
      - The major driving force for forming a lipid micelle is hydrophobic interaction between hydrocarbon tails
  - Have a detergent action on the fat particles in the food, which decreases the surface tension of the particles and allows agitation in the intestinal tract to break the fat globules into minute sizes

Membrane

- Cytoplasmic membrane = cell membrane:
  - Function is to regulate the flow of material into and out of the cell
  - A selectively permeable barrier, meaning that the movement of molecules across the MB is selectively restricted
  - **Some small (<75Å),** uncharged, nonpolar molecules move across the membrane quite readily
  - Molecules and ions that are large, highly charged &/or polar move across the membrane via transport systems
  - Mammalian cell membranes **do NOT have endotoxin (but they do have LPS)**
- Passive Diffusion
  - Simple diffusion
    - Simple diffusion is movement down its concentration gradient
    - No transport or carrier system is needed
  - Facilitated diffusion (aka Mediated Diffusion)





  -
    - A form of passive diffusion that uses the assistance of transport or carrier proteins
    - Requires no energy & moves molecules down the concentration gradient
    - **Mediated diffusion of substances across cell membranes differs from simple diffusion in that mediated diffusion exhibits saturation kinetics**
      - Because the carrier can become saturated by the presence of large solute concentrations
    - Another Q: Facilitated diffusion differs from active transport in that facilitated diffusion requires a concentration gradient
    - **Another Q: What characterizes both active transport & facilitated diffusion? *Competitive inhibition***
    - Another Q: The process involving nonpenetrating solutes (e.g., proteins) best describes facilitated diffusion
      - *(The other answer options were osmosis, diffusion, & epithelial transport)*
- Active transport
  - Primary active transport – uses energy derived from ATP
    - EX: sodium-potassium pump
  - Secondary active transport – uses the gradient of one molecule to move another – no direct ATP coupling is used
    - EXs: sodium-calcium exchanger (counter-transport), glucose symporter (co-transport)
    - The rapid movement of a substance across a biologic membrane against a concentration gradient requires the participation of an energy-requiring active transport system
    - *****Another Q: the movement of Ca^{2+} across many cell MBs involves a Ca^{2+}/Na^{+} countertransport system**
    - Active transport systems generally involve specific binding molecules that are **protein** (not lipid, lipoprotein, CHO)
    - Another Q: Active transport is distinguished from facilitated diffusion by its requirement of metabolic energy

- Which of the following occur when active transport is involved in the movement of a solute across a biologic membrane?
  - Expenditure (spending) of metabolic energy
  - A gain in free energy by the system (Because basically you are creating a potential energy state)
  - A unidirectional movement of the solute
  - Movement of the solute against a concentration gradient

- Polar & hydrophilic
  - Molecules or groups that are soluble in water (e.g., ions, glucose, and urea)
  - Hydrophilic molecules require a carrier protein to cross the cell membrane
- Nonpolar, hydrophobic
  - Molecules or groups that are poorly soluble in water (e.g., O_2, CO_2, and alcohol)
    - **The cell MB is more permeable to O_2, CO_2, H_2O, ethanol & palmitic acid than to Na^+**
  - Hydrophobic molecules are transported across cell membranes by simple diffusion
  - Cholesterol
    - **Most abundant non-phospholipid component of the cell membrane**
    - **The least polar molecule** when listed with ethanol, palmitic acid, & glycocholic acid
    - Another Q: Lipids that are relatively **polar** contain more **oxygen**
- Amphipathic = amphiphilic
  - Both polar and nonpolar functional groups are essential for a substance to act an amphipathic molecule
  - An example of an amphiphilic molecule is phospholipid
- Is a fluid mosaic model of lipids and proteins
  - The plasma membrane is described best as a fluid mosaic composed primarily of phospholipids, cholesterol and glycoproteins
  - Another Q: The chief constituents of biologic membranes are lipids & proteins
  - **Another Q: The most abundant nonphospholipid component of the cell membrane is cholesterol**
  - The phospholipid forms the bilayer component
    - The hydrophilic head groups interact with water on both the extracellular & intracellular surfaces
    - The hydrophobic fatty acyl chains in the central portion of the membrane
  - Globular Proteins
    - Peripheral proteins are embedded at the periphery
    - Integral proteins
      - span from one side of the membrane to the other side & are associated with the hydrophobic phase of the bilayer
      - May move freely within the plane of the membrane
      - **Integral proteins are the reason for the selective permeability of biological membranes**
    - **Leucine & valine are found on the interior of globular proteins (LV is the center of the Globe)**
  - CHOs are attached to proteins and lipids on the exterior side of the cell membrane
  - The membrane mosaic is fluid because the interactions among lipids and between lipids & proteins are noncovalent, leaving individual lipid and protein molecules free to move laterally in the plane of the membrane
    - The primary force stabilizing the lipid-protein complex in cell membranes is the hydrophobic interaction
  - Bilayers arise through the operation of two opposing forces:
    - 1) attractive forces between hydrocarbon chains (van der Waals forces) caused by the hydrophobic effect forcing such chains together
    - 2) repulsive forces between the polar head groups
- Lipid classes commonly incorporated into the cell membrane:
  - **Phospholipids:**
    - **Sphinogomyelin**
    - **Phopsphatidylcholine**
  - Gangliosides—
    - **Glycolipids found on various cell surfaces; have N-acetylneuraminic acid residues in addition to sphingosine**
    - Named so because many cells in CNS ganglia have them
  - Cholesterol—primarily used as component in cell membrane
- Six common features of biological membranes:
  - 1. Sheetlike structure: only a few molecules thick (60-100 angstrom)
  - 2. Consists mainly of lipids and proteins (CHOs are attached to exterior)
  - 3. MB lipids – small molecules with hydrophobic and hydrophilic groups that form lipid bilayers in aqueous media
    - The hydrophobic center of the bilayer forms a barrier to the flow of polar molecules across the membrane
  - 4. The proteins function as transporters, enzymes, receptors, etc.
  - 5. Are noncovalent assemblies: the proteins and lipid molecules are held together by many noncovaelnt interactions
  - 6. Are asymmetric: inside and outside faces are usually different

- The plasma membrane has most of the CHOs (as glycoproteins and glycolipids) on the outer face while
- **The lipids phosphatidylethanolamine and phosphatidylserine are more concentrated on the cytoplasmic face**
- Two examples describing an asymmetric model of membrane assembly:
  - Some membrane proteins may have their N-terminal residues predominately on one side of the membrane
  - **The polar head groups of the phospholipids may be primarily oriented toward one side of the membrane**

➢ Proteins in cell membrane function as:
- Transporters – transport substances across the membrane
- Enzymes – catalyze biochemical reactions
- Receptors – bind hormones or growth factors
- Mediators – aid in triggering a sequence of events

❖ **pH**

➢ Buffer systems:
- Most commonly consist of a weak acid (the proton donor) and a salt or conjugate base of that acid (the proton acceptor)
- These systems minimize the pH changes brought about by a change in the acid or base content of the solution
- These buffer systems reduce the effect of an abrupt change in H+ ion concentration by:
  - 1) releasing H+ ions when pH rises
  - 2) accepting H+ ions when pH drops
- Major buffer systems include:
  - Sodium bicarbonate – carbonic acid buffer system:
    - The major buffer in extracellular fulid
    - Is very important in the oral cavity for acid neutralization in foods & those produced by oral bacteria
  - Phosphate buffer system:
    - The minor buffer in the extracellular fluid
  - Protein buffer system:
    - **Intracellular proteins absorb hydrogen ions generated by the body's metabolic processes**
    - Proteins contain many functional groups with diferring pK's, making them able to buffer over a wide pH range
    - **An increase in pK means a stronger ability to bind hydrogen ions (better base or proton acceptor)**
      - **pK → High pK means very low [H+] (1.0 x 10-14), so it will accept H+ faster**
    - Hemoglobin is a major intracellular buffer
- *** H_2CO_3, $NaHCO_3$, Na_2HPO_4, NaH_2PO_4 all function in buffer systems in blood

➢ Blood:
- Is slightly basic, between pH 7.35-7.44
- Acid-base balance is controlled precisely because even a minor deviation from the normal range can severely affect many organs
- The body uses three mechanisms to control the acid base balance:
  - 1. Excess acid is excreted by the kidneys as H+, NH_4+ or combined with phosphate
  - 2. The body uses pH buffers in the blood to guard against sudden changes in acidity
    - **The major blood buffers are bicarbonate, hemoglobin, and albumin**
    - **The most important buffer system in maintaining physiological pH of plasma is carbonic acid/bicarbonate**
  - 3. The excretion of CO_2: the blood carries carbon dioxide to the lungs where it is exhaled
    - Respiratory control centers in the brain regulate the amount of carbon dioxide that is exhaled by controlling the speed and depth of breathing
  - An abnormality in one or more of these pH control mechanisms can cause one of two major disturbances in acid base balance: acidosis or alkalosis
- From the Henderson-Hasselbach relationship we can see how plasma pH is determined by the plasma levels of carbon dioxide and bicarbonate. 6.1 is the pKa of the bicarbonate-carbon dioxide buffer system
  - pH = 6.1 + log [bicarbonate]/ (0.03 x partial pressure of carbon dioxide)

➢ Henderson-Hasselbach equation:
- $pH = pKa + \log[A^-]/[HA]$
- pH = pkA WHEN [HA] = [A-]
  - Or when the acid is Half Neutralized
- Describes the relationship between the pH, pK (the negative log of the dissociation constant) and the concentration of an acid and its conjugate base (aka, the 'salt' of the acid)
- EX: If adrug has a pK of 6.4, at pH = 7.4, the ratio of A^- to HA is 10
  - $7.4 = 6.4 + \log[A^-]/[HA] \rightarrow 1.0 = \log[A^-]/[HA] \rightarrow 10^{1.0} = [A^-]/[HA]$ = 10:1 ratio
- A useful way of restating the expression for the dissociation constant of an acid (K_a)
  - $K_a = [H^+][A^-]/[HA]$
  - **The larger the K_a, the stronger the acid, because most of the HA has been converted into H^+ and A^-.**

- Conversely, the smaller the K_a, the less acid has dissociated, and therefore the weaker the acid
- Shows that pH = pK when an acid is half neutralized
  - Because from our equation → pH = pK then 0 = log[A^-]/[HA] → 10^0 = ratio → 1 = ratio
- **The pH of a buffer system depends on the pK of the weak acid & the ratio of molar concentrations of salt and weak acid**
- At pH = pKa, there is maxiumum buffer capacity → i.e. half neutralized, and could then go either way
- Another Q: The optimum pH for an enzyme is the pH of the most rapid reaction rate

➢ This type of problem is solved by using the following equation: Kw = [H+][OH-]
- Kw is the ion product of water and always equal 10^{-14}
- [H+] is the hydrogen ion concentration (pH = -log[H^+])
- [OH-] is the hydroxide ion concentration (pOH = -log[OH^-]
- 14 = pH + pOH
  - Use the pH scale
  - 14 = pH + 4
  - pH = 10
- EX: The pH of a solution having a 10^{-5} M concentration of OH- ion is 9 (from 14 – 5 = 9)
- EX: The pH of a solution of 0.01 M HCl = 2
  - **pH = -log[0.01] → -pH = log[0.01] → $10^{(-pH)}$ = 0.01 → 10^{-2} = 0.01 → pH = 2**
  - **EX: If the pH = 5.7, the [H+] = $1x10^{-6}$**
- EX: Solution A has a pH = 7.0; Solution B has a pH = 6.0; volumes are equal; A has 1/10 as many H^+ ions than B
  - **This just recapitulates that pH is a fxn of log, or powers of 10!!!**

➢ Isoelectric point
- The pH at which number of positive charges equals the number of negative charges
  - The amino acid composition of a protein having an isoelectric pH of 10 has more basic than acidic amino acids
- The pH at which a solute has no net electric charge & thus does not move in an electric field (i.e., during electrophoresis)
  - It is designated **pI** for that solute
  - For example, at its isoelectric pH of 6.06, glycine will not move in an electric field
  - Another Q: Electrophoresis is a procedure that depends primarily on electrostatic net charge
  - **A protein in an electroPhoretic system, as the pH lowered below its isoelectric point → then protein would migrate to negative pole**
    - **This means you have more H+ and will move Negative**
- This information has practical importance – for a solution containing a mixture of amino acids, the different amino acids can be separated on the basis of the direction and relative rate of their migration when placed in an electric field at a known pH. The same applies to protein molecules and is frequenly used to separate proteins
  - Example: Glycine has a net negative charge at any pH above its **pI**, so it will move toward the positive electrode
    - **At any pH below its pI it has a net positive charge (b/c of H+) and moves towards the negative electrode**
    - The farther the pH of a glycine solution is from its isoelectric point (**pI**), the greater the net electric charge of the population of glycine molecules
- At physiologic pH, all amino acids have both a negatively charged carboxyl group (COO^-) and a positively charged amino group (NH_3^+) They are therefore dipolar ions **(zwitterions)**
  - In aqueous solution at pH 7, a peptide containing 1 amino group side chain & 2 carboxyl group side chains, the net charge would be (-1)

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

➢ pH Problems
- Metabolic acidosis:
  - Excessive blood acidity characterized by an inappropriately low level of bicarbonate in the blood
  - Major causes – chronic renal failure, diabetic ketoacidosis, lactic acidosis, poisons and diarrhea
    - Ketoacidosis can result from a sustained, severe CHO deficiency in the diet
  - Ammonia is the nitrogenous product that is excreted in high amounts after prolonged acidosis

- The kidney responds to metabolic acidosis by synthesizing NH3 to then pull out H+ and make NH4+ and excrete it

- Respiratory acidosis:
  - Excessive blood acidity caused by a buildup of CO_2 in the blood as a result of poor lung function or slow breathing
  - Major causes – hypoventilation, emphysema, chronic bronchitis, severe pneumonia, pulmonary edema, & asthma
  - In respiratory acidosis, CO_2 content increases and pH decreases
  - Signs/symptoms of elevated PCO_2:
    - Acute pain, anxiety, hyperventilation *(to attempt to compensate)*, dizziness, signs of loss of consciousness
  - Administration of a 90:10 nitrous oxide:oxygen mixture causes respiratory depression. Respiratory acidosis is likely to result (from the respiratory depression or *hypoventilation*). *Don't misunderstand this one.*
  - In respiratory acidosis, there would NOT be increased production of renal bicarbonate (KIDNEY (H2CO3)
    - Having all that CO2 would shift the equation back to $HCO_3^- + H^+$
      - There would be hypoxia, hypercapnia, and a response of tachycardia
- Metabolic alkalosis:
  - A condition in which the blood is alkaline because of an inappropriately high level of bicarbonate
  - Major causes – vomiting acidic gastric contents or as a result of ingestions of alkaline drugs
  - Renal compensation for chronic metabolic alkalosis involves a partial reabsorption of the filtered HCO3
    - Normally, over 99% of bicarb is reabsorbed to continue as a buffer, but in **alkalosis, there would be an excess of bicarb, so the kidney secretes more than usual into the urine to get the alkaline serum back down to normal**
- Respiratory alkalosis:
  - A condition in which the blood is alkaline due to rapid or prolonged deep breathing
    - **Results in a low blood CO_2 level, which causes H+ and HCO3 to shift to make CO1, hence reducing the H+**
  - **Alkalosis can cause hypocalcemia and tetany by promoting the binding of calcium to albumin, hence reducing the ionized Calcium in blood**
  - Major causes – hyperventilation (most common cause), pain, cirrhosis of liver, & low levels of oxygen in the blood **(high altitude)**
    - Hyperventilation causes some degree of temporary alkalosis
    - Another Q: **Hyperventilation often produces muscle spasms because the loss of CO_2 has caused alkalosis**
  - Much less common than respiratory acidosis
- High Altitude Respiratory Resopnse
  - Acute increase in ventilation
    - Increased pulmonary ventilation at high altitudes results directly from the effect of hypoxia on the carotid body
  - Chronic increase in ventilation
  - Increased erythropoietin → increased hamtocrit and hemoglobin
  - Increased 2,3-DPG (binds to Hb so that Hb releases more O2)
  - Cellular changes (increased mitochondria)
  - Increased renal excretion of bicarbonate (to compensate for respiratory alkalosis)
  - Chronic hypoxic pulmonary vasoconstriction results in right ventricular hypertrophy

➢ In water intoxication, most of the excess water will be found in the intracellular compartment (as opposed to extracellular, intravasacular compartments)

❖ **Hormones (GPA == Growth Hormone and Prolactione are Non-Tropic and Acidic)**

➢ Types of Hormones
- Steroid hormones:
  - Derivatives of cholesterol
    - **PET CAT → Pet for heavy Petting (Sex Hormones) and Cat for Catabolism Hormones**
    - **Progesterone, Estradiol, Testosterone, and Cortisol, Aldosterone, Thyroxine
      - NOT relaxin
  - Not water soluble and bind to intracellular receptors, forming complexes that activate or inactivate genes
  - Best characterized by binding to intracellular receptors
  - Adrenal Steroids
    - Cholesterol→Pregnenolone→Progesterone→11Doxycorticosterone→Corticosterone→**Aldosterone**
      - This is the Main chain, first NZ is Desmolase, which is controlled by ACTH and inhibited by ketoconazole
    - →Pregnenolone→17-Hydroxypgregnenolone→11-Deoxycortisol→**Cortisol**
    - →Progesterone→17a-Hydroxyprogesterone→Androstenedione→**Estrone**
      - →Androstenedione→**Estradiol**
      - →Androstenedione→**Testosterone**→DHT
    - Mineralocorticoids – Aldosterone (21 Cs)

        - Glucocorticoids – Cortisol (21 Cs)
        - Androgens – Testosterone (19 Cs)
        - Estrogens – Estrone/Estradiol (18 Cs)
    - AmINE hormones:
        - **Derived from tyrosINE**, an essential amino acid found in most proteins
        - They include **thyroid hormone (T3 and T4) and the catecholamines (epi and NE and dopamine)**

    - Polypeptide hormones:
        - Proteins with a defined, genetically coded structutre
        - Synthesized in precursor form (a pre-prohormone)
        - Usually transported unbound in plasma
        - Stored in secretory vesicles
        - Act by binding to a plasma MB receptor & generating second messengers
        - Another Q: Polypeptide hormones usually exert their effect by binding to receptors on the cell MB & altering the specific activity of certain enzymes
        - Another Q: Hormones that exert there effects through the activation of second messengers are usually water soluble peptide/protein hormones – *that's like a definition!!!*
        - They include:
            - Anterior pituitary hormones (GH, TSH, FSH, LH, & prolactin)
                - Thyroid hormones, glucocorticoids & gonadal steroids are similar in that each is released in response to signals from the hypothalamic-anterior pituitary complex
            - Posterior pituitary hormones (ADH & oxytocin)
            - Pancreatic hormones (insulin and glucagon)
            - PTH
            - Somatostatin
                - Inhibitory of GH, TSH, Insulin, Glucagon, and Gastrin
                - **Elaborated primarily by the median eminence of the hypothalamus and by the D for delta cells of pancreatic islets**
                - There is a positive N_2 balance following administration of GH (somatotropin)
    - A particular hormone does not necessarily affect all cells; only its target cells
        - Target cells of a hormone possess receptors to which molecules of a hormone can attach
        - These receptors can be located either on the plasma membrane or within the cell itself
- Second messenger:
    - A molecule found inside a cell which responds to the presence of a hormone outside the cell
    - cGMP and cAMP are second messengers that carry signals from the cell surface to proteins within the cell
        - cAMP is the intracellular, "second" messenger for many peptide and polypeptide hormones
        - Another Q: cAMP (adenosine-3', 5'-monophosphate) is directly invovled in the action of hormones on target cells
        - **Another Q: cAMP increases the rate of glycogenolysis by promoting the phosphorylated form of glycogen phosphorylase (**It breaks up glycogen into glucose subunits.alpha 1→4)
    - Frequently they act to stimulate protein kinase
    - They are rapidly broken down in cells (to terminate response) by enzymes called phosphodiesterases
    - Some hormones that use cAMP as a second messenger are:
        - Glucagon
        - Epinephrine
        - ACTH
        - Parathyroid hormone
        - TSH
        - FSH
        - FL
    - Glucagon, epinephrine, & PTH induce activation of cAMP (insulin does not)
        - **This increases the rate of glycolysis & gluconeogenesis**
    - cAMP is formed from ATP in a reaction catalyzed by adenylate cyclase
        - Adenylate cyclase is an integral protein of the plasma membrane
        - Many hormones act by way of stimulation of the MB-bound adenylate cyclase
- Signal Molecule Precursors
    - ATP → cAMP via adenylate cyclase
    - GTP → cGMP via guanylate cyclase
    - Glutamate → GABA via glutamate decarboxylase (requires Vitamin B6)
    - Choline → Ach via choline acetyltransferase (ChAT)
    - Arachidonate → Prostaglandins, thromboxanes, Leukotrienes via cyclooxygenase/lipoxygenase

- Fructose-6-Phosphate → Fructose 1,6-bisphosphate via phosphofructokinase (PFK), the rate limiting NZ of glycolysis
- 1,3-BPG → 2,3-BPG via bisphosphoglycerate mutase

➢ Hypothalamus:
- Located on the floor of the forebrain
- ADH and oxytocin are synthesized in certain hypothalamic nuclei (supraoptic --ADH and paraventricular -- Oxytocin) of the brain, which contain the cell bodies of neurosecretory cells
- Hormones are then transported along the axons of the neurosecretory cells to the pars nervosa (posterior pituitary)
- Neural inputs to the brain influence their release
- Secretions of the anterior pituitary are controlled by hormones called hypothalamic releasing and inhibitory factors, which are secreted within the hypothalamus itself
  - These tropic hormone releasing factors conduct to the anterior pituitary through minute BVs called the hypothalamic-hypophyseal portal system
  - The function of hypophyseal portal vessels is to carry hypothalamic releasing factors to the adenohypophysis
- Center of the brain regulating body temperature – **Anterior Hypothalamus (A/C)**
- Center of the brain for ANS regulation
- Factors include:
  - Gonadotropin releasing hormone (GnRH) – stimulates release of both FSH and LH
  - Thyrotropin releasing hormone (TRH) – stimulates release of TSH
  - Corticotrophin releasing hormone (CRH) – stimulates release of ACTH
    - Stimulated by: low plasma cortisol, hypoglycemia, pyrogen, and stress
    - Suppressed by: high plasma glucocorticoids
  - Growth hormone releasing hormone (GH RH) – stimulates release of GH
  - **Dopamine (DA) – inhibits release of prolactin**
  - **Somatostatin – inhibits release of GH**

➢ Pituitary (Hypophysis)
- Has direct hormonal control over the mammary glands (among many things)
- Posterior Pituitary = pars nervosa = neurohypophysis
  - The neurohypophysis produces vasopressin & oxytocin, which both affect contraction of smooth muscle
  - Antidiuretic hormone (ADH) = vasopressin
    - Produced in the Hypothalamus (specifically in the supraoptic nuclei)
    - Vasopressin is a peptide that is stored and released into the bloodstream by the posterior pituitatry
    - End organ resistance to ADH is called nephrogenic diabetes insipidus
      - Kidneys fault for not absorbing the water
      - ➢ This results in the inability to concentrate urine, polyuria, and increased serum osmolarity (resulting from the loss of free water in the urine)
        - Urine Osmolarity of less than 200 mOsm/L
    - Decreases the urine volume by increasing the reabsorption of water by the renal tubules (increases the permeability of the collecting ducts and distal convoluted tubules to water)
      - ➢ ADH receptors are located on the membranes of these collecting ducts and distal tubules
    - Released in response to:
      - ➢ Increased plasma concentration of Na+
        - Most important variable regulating ADH is plasma osmolarity
        - Most sensitive hormone to plasma osmolarity
      - ➢ Decreased blood volume
      - ➢ Hypotension
    - Ethanol and caffeine decrease ADH release, while nicotine increases its release
    - Sweating causes an increase in ADH, while drinking large amounts of water causes a decrease in blood ADH
    - Hyposecretion of ADH results in diabetes insipidus (polyuria, polydipsia and polyphagia)
      - ➢ **Diabetes insipidus** would also result from the **hypoactivity of the posterior pituitary**
    - Infusion of vasopressin results in a decrease in osmolality
  - Oxytocin
    - Causes muscle of the uterus and milk ducts in the breast to contract
      - ➢ What causes contraction of the uterus → oxytocin
    - Released from the posterior pituitary in **response to dilation of the cervix and to suckling**
    - Stimulates smooth muscle cells of myoepithelium of mammary gland alveoli
      - ➢ Oxytocin is responsible for causing contractions of the uterine smooth muscle during labor
    - ADH and oxytocin are stored and released form the pars nervosa, but neither hormone is produced there
      - ➢ **Produced by the paraventricular nuclei in the hypothalamus**
- Anterior Pituitary (FLAT PEG) = pars distalis = adenohyposphysis

- **Complete destruction of anterior pituitary would result in Addison's disease (No ACTH No cortisol), myxedema(hypothyroidism), & hypogonadism**
- FSH (Follicle Stimulating Hormone)
  - Stimulates graafian follicle development and induces secretion of estrogens
  - Polypeptide
  - Exerts its action on the germinal epithelium
- LH (Luteinizing Hormone)
  - Stimulates ovulation and the development of the corpus luteum
    - FSH and LH work together to cause ovulation & the formation of the corpus luteum
    - GnRH (produced by the hypothalamus) stimulates release of both FSH and LH
- Adrenocorticotropic hormone (ACTH)
  - **Called the stress hormone**
  - Controlled by the hypothalamus
    - When body is stressed, corticotropin-releasing hormone (CRH) produced by the hypothalamus travels through a portal system to the anterior lobe of the pituitary, where it induces the production and secretion of ACTH by the **basophils of the pars distalis**
    - **Paras disalis: The major secretory portion of the anterior lobe of the adenohypophysis. Also known as pars distalis**
  - ACTH stimulates the adrenal cortex to synthesize cortisol
    - **Cortisol influences CHO, lipid, & protein metabolism**
  - The mineralcorticoid aldosterone and the glucocorticoids are collectively called corticosteroids
  - Aldosterone secretion from the adrenal cortex is induced by elevated plasma K^+ & angiotensin II, **not by ACTH**
    - IV injections of KCl would increase the secretion of aldosterone
  - Aldosterone – primary effect is on the kidney tubules, where it stimulates Na+ retention and K+ excretion
    - Results in high Na & low K in plasma
    - Another Q: Aldosterone causes increased renal tubular reabsorption of sodium
    - Another Q: Reabsorption of sodium chloride is controlled in the kidney tubules by an adrenal cortical hormone (aldosterone)
    - Another Q: Aldosterone is normally associated with partial regulation of sodium balance
    - Another Q: Aldosterone increases K^+ secretion into the urine
  - The following statements describe aldosterone:
    - It is a mineralocorticoid
    - It increases Na^+ uptake from the kidneys
    - Its production is stimulated by angiotensin II
    - NOTE: it is not produced in the zona fasciculata of the adrenal cortex (it's made in the zona glomerulosa)
- Thyroid Stimulating hormone (TSH)
  - Aka thyrotropin
  - Secreted by basophils of the pars distalis of the anterior pituitary gland
  - Controls the rate of secretion of thyroid hormones (thyroxine and triiodothyronine)
  - Thyroxine in turn controls the rates of many metabolic processes and the metabolic rate
  - Exposure to cold increases the rate of TSH secretion
    - Thyroid secretion is stimulated by prolonged exposure to a cold environment
  - **Stress can inhibit TSH secretion**, most likely by way of neural influences that inhibit the secretion of TRH from the hypothalamus
  - TSH is stimulated by TRH. There are several negative feedback loops which regulate:
    - High levels of circulating thyroid hormone decreases the secretion of both TRH and TSH
    - Elevated levels of TSH decreases secretion of TRH
  - Disease:
    - Hypersecretion of TSH results in Grave's disease (and Plummer's)
    - Hyposecretion of TSH results in Cretinism (in young people) and Myxedema (in adults)

▪ **NOTE ACTH and TSH are pituitary tropic hormones

- Prolactin (aka lactogenic or luteotropic hormone)
  - Produced by eosinophils (remember PeG –e is for Eosins) of the pars distalis of the anterior pituitary gland
  - Stimulates milk production by the mammary glands (during pregnancy for breast development and after delivery of the child for lactation)
  - Basically, **Prolactin increases dopamine synthesis, then Dopamine inhibits Prolactin secretion**
  - Hypothalamus synthesizes a **prolactin inhibitory factor (dopamine)**
    - Under normal conditions, large amounts of dopamine are continually transmitted to the anterior pituitary gland so that the normal rate of prolactin secretion is slight

        - This is why prolactin is said to be under predominant inhibitory control by the hypothalamus
        - This is also why blocking the hypothalamic-hypophyseal venous portal system increases the release of prolactin
    - During pregnancy and lactation, the formation of dopamine itself is suppressed, thereby allowing the anterior pituitary gland to secrete an elevated amount of prolactin
- Most anterior pituitary hormones are enhanced by the neurosecretory releasing factors transmitted from the hypothalamus, but not prolactin
- Blocking the hypothalamic-hypophyseal venous portal system increases the secretion of prolactin
    - But, it does not increase the secretion of ACTH, TSH, and oxytocin
        - Not oxytocin, because it is a hormone of the posterior pituitary
        - Not ACTH & TSH, since release is *stimulated* by CRH & TRH, respectively – from the hypothalamus
        - Prolactin secretion increases, because release is *inhibited* by dopamine – from the hypothalamus
- In females, Prolactin inhibits GnRH synthesis and release, which inhibits ovulation (Breast feeding CAN be birth control)

- Growth Hormone (aka Somatotropin)
    - From the anterior pituitary alpha cells:
    - Does not function through a target gland but instead exerts effect on all or almost all tissues
    - GH causes the liver (and to a much lesser extent other tissues) to **form several small proteins called somatomedins (also called insulin-like growth factors)** that in turn have the potent effect of increasing all aspects of bone growth
        - Insulin-like growth factor 1 **(IGF-1)** is secreted by the **liver**; IGF-1 secretion is **stimulated by ↑GH** in blood
    - Basic metabolic effects:
        - Increased rate of protein synthesis in all cells of the body
        - **Decreased rate of carbohydrate utilization throughout the body == because you use more Fat (lose baby fat)**
        - Increased mobilization of fats and the use of fat for energy
        - Causes cells to shift from using carbohydrates to using fat for energy → **Think you lose your baby Fat**
    - Secretion is increased by: sleep, stress, starvation, exercise, hypoglycemia, hormones related to puberty
    - Secretion is decreased by: somatostatin, somatomedins, obesity, hyperglycemia, and pregnancy
    - The rate of GH secretion increases and decreases within minutes
        - Most of the time it is in relation to the person's state of nutrition or stress
    - GH is released in a pulsatile fashion
    - Acidophile Hormone of Hypophysis?? → GH
    - **GH is also released in response to a decline in plasma glucose** concentration and an elevated plasma level of certain amino acids, particularly arginine
    - Growth hormone undersecretion produces pituitary dwarfism in children
        - Oversecretion of GH causes gigantism in children or in adults, acromegaly
    - Hypersecretion of GH causes hyperglycemia
        - **This is because GH stops usage of CHOs and makes you use FAs for energy**
    - Nitrogen Balance
        - Positive Nitrogen Balance
            - **Means that nitrogen intake exceeds nitrogen output**
            - Patients taking GH are likely to exhibit a positive nitrogen balance
            - A positive nitrogen balance is likely to take place following administration of GH
            - Growth, Protein Synthesis because the ammonia is incorporated into the alpha amino groups of amino acids and therefore less nitrogen will be secreted
        - Negative Nitrogen Balance (BAD for wasting or NOT growing)
            - Means the nitrogen output exceeds nitgrogen intake
            - A negative nitrogen balance is most likely to occur during old age
            - Negative nitrogen balance may be caused by a dietary lack of essential amino acids
                - ***Not during fetal growth or adolescence for obvious reasons***
                - ***Not during convalescence, which is a period of recovery from injury, surgery, etc***
        - Nitrogen can be used as a measurement of protein level in meat
    - **An example of synergism is GH & thyroxine on skeletal growth**

- Ovaries (From F for FSH and L for LH)
    - Produce ova, the female sex hormones (progesterone and estrogen) and follicles
    - The corpus luteum
        - Is a yellowish mass of cells that forms from an ovarian follicle after the release of a mature egge
        - If the mature egg is not fertilized and pregnancy does not occur, the corpus luteum retrogresses to a mass of scar tissue (corpus albicans) which eventually disappears

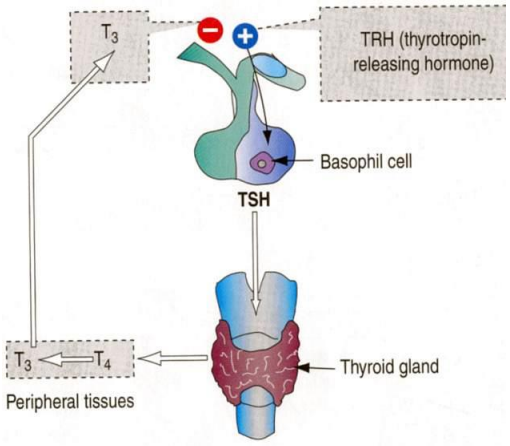
- If the mature egg is fertilized and pregnancy does occur, the corpus luteum does not degenerate but persists for several months. Human chorionic gonadotropins HCG which is produced by the placenta stimulates the corpus luteum to produce estradial and progesterone
- Granulosa cells in the corpus luteum produce progesterone and estrogen
  - **It produces more progesterone than estrogen**

- Ovulation
  - Oral contraceptives prevent ovulation:
    - Most contraceptives are combined pills which contain synthetic estrogen-like (ethynl estradiol, mestranol) and progesterone-like (norethindrone, norgestrel) substances
    - Progestins
      - Being used as oral contraceptive substance due to their ability to suppress ovulation
    - It stops LH, but does NOT decrease FSH secretion
      - Preventing the rise in LH prevents ovulation
    - Primary recognition of B-estradiol by its target cell depends upon the binding of the hormone to a specific cytoplasmic receptor
    - Exact mechanism is thought to be as follows:
      - In presence of either estrogen or progesterone, the hypothalamus fails to secrete the normal surge of LH releasing factor
      - This inhibits the release of LH from basophils of the anterior pituitary gland
      - Subsequent ovulation does not occur
      - Ovulation occurs as a result of the estrogen-induced LH surge
      - Unlike other steroid hormones, all estrogens have an aromatic A ring

- Adrenal Medulla (From A for ACTH)
  - Specialized ganglion of Symp NS
  - Preganglionic fibers synapse directly on chromaffin cells in the adrenal medulla
    - These cells secrete epi (80%) and NE (20%) into the circulation
  - Both of these hormones are direct-acting adrenergic agonists and are biosynthesized from tyrosine
    - Tyrosine is a metabolic precursor for epinephrine
    - Epinephrine is most closely related structurally to Tyrosine
  - NE and its methylated derivative epi act as regulators of CHO and lipid metabolism
    - NE & epi increase degradation of triacylglycerol & glycogen, AND increase heart output (specifically, epi) & BP
  - These effects are part of a coordinated response to prepare the individual for emergencies – "fight or fright" reactions
    - Increase in response to fright, exercise, cold, low levels of blood glucose
  - The adrenal medulla is supplied by cholinergic preG Symp neurons that release Ach
    - In terms of origin & function, the adrenal medulla is comparable to a postganglionic sympathetic nerve
  - In response to this, the adrenal medulla releases mainly epi (and some NE) into the bloodstream, which carries the secretions to the effector organs
  - The pathway of Origin (NE and Epi)
    - Tyrosine → L-Dopa → Dopamine → NE → Epi
      - Dopamine is synthesized in 2 steps from which of the following compounds (Tyrosine)
    - Epinephrine (adrenalin):
      - The release of epinephrine is controlled mainly by nerve impulses
      - Stimulates glycogenolysis and gluconeogenesis (except in the liver), which tend to raise blood glucose levels
        - When injected, epinephrine causes an increase in blood sugar
        - Another Q: Sympathetic stimulation affects CHO metabolism because epinephrine increases liver glycogenolysis
      - Also stimulates lipolysis in adipose tissue (breakdown of TGs into glycerol and fatty acids)
      - Increases rate, force, and amplitude of heart beat
        - Administration of local anesthetic w/ epinephrine will most likely produce an increased heart rate
      - **Constricts BVs in skin, mucous membranes, and kidneys**
      - **Sympathitic stimulation dilates bronchioles in the lungs & relaxes bronchiolar smooth muscle**
        - Another Q: Increased parasympathetic activity causes bronchiolar smooth muscle contraction
      - Another Q: Epi activates muscles glycogen phosphorylase
        - Tags glycogen to be degraded
    - Norepinephrine (noradrenalin):
      - Increases heart rate and the force of contraction of heart muscle
      - Promotes lipolysis in adipose tissue
      - Constricts blood vessels in almost all areas of the body, thus increasing total peripheral resistance
      - Has the LEAST effect on Calicum Metabolism
      - NE can be released in two ways:

        - 1. By the adrenal medulla into the bloodstream
            - The effects are more widespread when NE is released into the bloodstream by the adrenal medulla as opposed to directly onto an organ by the postganglionic sympathetic neuron
        - 2. Directly onto an organ by a postganglionic sympathetic (adrenergic) neuron which stores NE
- Cortisol (hydrocortisone)
    - Has direct inhibitory effect on hypothalamus and anterior pituitary gland
    - Is a glucocorticoid
        - The principal mechanism by which glucocorticoids stimulate their target cells is by activating specific genes
    - Release of cortisol is controlled primarily by ACTH, which is secreted by basophils in the pars distalis of the anterior pituitary
        - Release of ACTH is influenced by corticotrophin-releasing hormone (CRH) from the hypothalamus
        - Cortisol exerts an inhibitory influence on both ACTH and CRH by way of negative feedback
    - Main glucocorticoid produced and secreted by the cells of the zona fasciculata in the adrenal cortex
    - Fxns:
        - **Allows glucagon and epi to work more effectively at their target tissues, but antagonizes the action of insulin**
        - Increases hepatic glycogen content, gluconeogenesis, protein breakdown, & adipose tissue breakdown
        - Anti-inflamatory properties
        - Impairs cell-mediated immunity
        - Influences behavior (decreasing stress)
        - Stimulates leukocytosis
        - Inhibits synthesis of nucleic acids (except liver)
        - Affects immune system, bone, **calcium absorption from the GI tract**, and the CNS
    - Effects:
        - ↑ blood glucose (by stimulating gluconeogenesis and inhibiting glucose uptake)
            - Cortisol stimulates synthesis in the liver of pyruvate carboxylase (NZ of gluconeogenesis)
        - ↑ amino acids (by stimulating protein breakdown)
        - ↑ fatty acids (by stimulating lipolysis)
        - Decreases glucose utilization from the cells
    - A patient taking cortisol for a long period of time may experience atrophy of the adrenal cortex due to inhibition of ACTH production
    - 15-30 mg released daily in diurnal rhythm, mostly in morning, same is true for ACTH
    - **90% is bound to transcortin (corticosteroid binding globulin = CBG)**
    - **Cushing's syndrome**
        - Metabolic disorder resulting from the chronic and excessive production of cortisol
        - The most common cause of this syndrome is a pituitary tumor that causes an increased secretion of ACTH
        - Characterized by **hypertension, hyperglycemia, hypokalemia (due to aldostrone secretion) , increased androgen levels, and increased protein catabolism (All the things a pheochromoctyoma does)**
            - NOT increased protein anabolism
- Thyroid (From T for TSH)
    - Thyroglobulin:
        - TSH from the pituitary gland stimulates synthesis and the release of thyroid hormones
        - Thyrotropin releasing hormone (TRH) from the hypothalamus promotes TSH secretion
        - Glycoprotein prohormone (10% carbohydrate)
        - Contains iodine which is attached to tyrosine molecule
        - The follicle cells of the thyroid gland synthesize thyroglobulin and secrete it into the colloid-containing regions of the follicle
            - Here the thyroglobulin undergoes iodination and coupling processes that produce the thyroid hormones
            - Thyroglobulin molecules containing these hormones are then stored in colloid-containing regions of the follicle
                - So if your body needs iodine, then it breaks down thyroglobulin and releases iodinated T3 and T4
            - When the thyroid is actively secreting, these thyroglobulin molecules are then taken back into the follicle cells and broken down into the two hormones (T4/T3)
        - An iodine deficiency will increase the secretion of thyroglobulin (not T3, T4, or TSH)
    - Thyroid hormones:

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.



- Thyroglobulin (stored)
  - Hydrolysis of thyroglobulin liberates a number of iodinated compounds, only 2 are considered thyroid hormones
    - T3 (Triiodothyronine)
    - T4 (Thyroxin) in the blood and will get converted to T3 in the tissue.
    - Tyrosin + I ➔ Thyroxin
- **T3 (triiodothyronine) has several times the biologic activity of T4 (thyroxine)**
  - T4:T3 = 20:1
  - **T4 could be said to act primarily as a pro-hormone for T3; T4 is converted to T3 primarily in the kidney and liver, also can be converted to rT3, which is produced during illness, malnutrition or induced by some drugs**
  - 0.03% of T4 is free and 0.3% of T3 is free, the rest are bound to **thyroxine binding globulin (TBG)**
  - **4 Bs of T3**
    - Brain Maturation
    - Bone Growth
    - Beta-adrenergic effects
    - BMR increased (Basal Metabolism Rate)
- Thyroid secretes two iodine containing amine hormones that have a structural differences of one iodine atom
  - The majority of T4 is converted peripherally by target cells to T3 which is a more potent hormone
    - **This is done by the enzymatic removal of one iodine atom**
    - Iodine is important in the biochemical synthesis of thyroxin (T4)
- Thyroid hormones are lipophilic hormones which exert their effects via transcriptional processes
- Thyroid hormones are synthesized from Tyrosine
- Fxns:
  - Important for normal growth and development (especially for brain)
  - Affect many metabolic processes and the metabolic rate
    - **Basal Metabolism Rate is an increase in H2O, related to surface area???**
    - **Increased BMR is done via increasing Na+/K+ ATPase activity = increased O2 consumption, increased body temp**
  - Increase glycogenolysis, gluconeogenesis, and lipolysis, protein degradation **(SAME AS CORTISOL)**
    - This is why removal of the anterior pituitary (TSH) would result in a drop of blood glucose level
  - Regulate metabolism by speeding up cellular respiration
  - Beta-adrenergic effects
    - CV: increased CO, HR, SV, contractility, and RR
  - Stimulate bone maturation as a result of ossification and fusion of the growth plates

- Calcitonin:
  - Synthesized and secreted by the parafollicular cells **(C cells)** of they thyroid gland that are located in the interstitium
  - Its secretion is stimulated by a increase in serum calcium
    - The immediate effects of **calcitonin** secretion are **decreased serum levels** of both **calcium and phosphate**
    - Most significant immediate result of lowered serum calcium is hyperirritability of nerves and muscles
  - It acts on bone cells to suppress bone resorption and enhance bone formation
  - Along with parathyroid hormone 1,25 DHC, it is a regulator of calcium metabolism
  - Is a linear polypeptide consisting of 32 amino acids
  - Is not required in adult humans
  - Although it is important during bone development, the major regulator of plasma calcium level in the adult is PTH

- Parathyroid hormone (PTH)
  - **Phosphate Trashing Hormone (Decreases Serum Phosphate, but increases Urinary Phosphate)**
  - Secreted by **Chief Cells** in the parathyroid glands in response to decreased plasma calcium levels
    - NOT in response to Hypothalamus-Pituitary Complex
  - Plasma calcium level is the major controller of PTH, NOT Hormonal
    - Another Q: Bone resorption seen in elderly patients with low dietary calcium is enhanced by PTH (not insulin, estrogen, aldosterone, or TSH)
  - The principal controller of calcium and phosphate metabolism and is involved in the remodeling of bone
  - The most prominent function of bone is a calcium reservoir
  - Increases the plasma calcium concentration and decreases the plasma phosphate concentration
    - In a parathyroidectomized animal, plasma calcium is low and plasma phosphate is high
  - PTH modes of action:
    - The major target tissues of the calcium regulating hormones are: bone, intestine, kidney
    - Stimulates **BOTH osteoclasts and osteoblasts**
      - Bone cells (osteoclasts) increase bone resorption, leading to release of calcium & phosphate into blood plasma
      - Accelerates removal of calcium and phosphate from skeleton, but NOT from teeth
      - Q: Theories of the effect of PTH on bone:
        - PTH influences the rate of bone resorption
        - The action on bone is related to its action on phosphate excretion
        - The effect of parathyroid extract is to influence osteoclastic activity
        - PTH does NOT cause a decrease in new bone formation
    - Increases Kidney reabsorption of Calcium in DCT
      - Acts on the kidney to decrease calcium excretion and increase phosphate excretion in the urine
      - Also stimulates **1-alpha-hydroxylase in the kidneys → Activates Vitamin D**
    - Causes an increase in 1,25 hydroxycholecalciferol formation, which then causes an increase in Calcium absorption from the intestine
      - Increases the absorption of calcium in the GI tract
  - Diseases associated with PTH
    - Hyperparathyroidism (von Recklinghausen's disease)
      - Causes extensive bone decalcification
        - A patient w/ hyperparathyroidism is predisposed to an increased likelihood of bone fracture
      - Is marked by extremely high blood calcium levels and low blood phosphate levels
        - BOTH PTH and Calcitonin lead to Low serum phosphate levels
        - This leads to muscular weaknesses
        - The low serum phosphate level in hyperparathyroidism is caused by increased renal loss of phosphate
      - Renal **calcium excretion** is **increased** in hyperparathyroidism
        - *Seems a little counterintuitive, but websites confirm – it must be due to the excess of PTH, since normal PTH levels would decrease calcium excretion*
        - *This is the "stones" part of "moans, groans, stones, bones & psychiatric moans" symptoms*
    - Hypoparathyroidsim
      - (tetany) (hyperirritability of neuromuscular areas)
      - Causes decreased bone resorption, decreased renal calcium reabsorption, increased renal phosphate reabsorption, and decreased production of the active form of vitamin D (1,25 dihydroxycholecalciferol)
      - Together these effects **decrease** serum **calcium** & **increase** serum **phosphate**
      - Marked reduction in serum calcium will result in increased muscular irritability
      - ***Another Q: the movement of Ca^{2+} across many cell MBs involves a Ca^{2+}/Na^{+} countertransport system**
      - Another Q: Complete **removal** of the parathyroid glands leads to **tetany**
  - Hormonal Calcium Metabolism
    - Androgen, Estrogen, Thyroid Hormone, and Parathyroid Hormone all have effects
      - Norepinephrine is the LEAST involved
- Pancreas
  - Secretions are stimulated by blood levels of certain molecules
    - A piece of pancreas transplanted under the skin (re-establishmed circulation) would secrete after ingestion of food
      - A piece of parotid gland would not secrete
  - Insulin:
    - Proinsulin is converted to insulin (a segment of proinsulin's polypeptide chain is removed)
    - Secreted by beta cells in the islets of Langerhans of the pancreas in response to a rise in the blood glucose level
      - Insulin is secreted more in the absorptive state than the post-absorptive state

- Fxns:
  - It causes glycogenesis in the liver
  - Insulin lowers the blood glucose level by stimulating and facilitating the uptake of glucose and the utilization of glucose as an energy source by many cells
    - A principal action of insulin is to enhance cell permeability to glucose
  - It also promotes the synthesis of glycogen, triglycerides, and proteins
  - **INSERT GLUT List**
  - **GLUT 1 receptors are found on RBCs, Brain, Renal Cortex**
  - **GLUT 2 receptors are found in Beta cells**
  - **GLUT 4 receptors are found in muscle and fat**
  - Has NO effect on glucose uptake by the brain
  - Inhibits lipolysis (it enhances triglyceride synthesis)
  - Stimulates protein synthesis (inhibits protein breakdown)
  - Increases entry of glucose into muscles & adipose tissue
    - **Brain uptakes Glucose Independent of Insulin**
  - Enhances cell permeability to glucose
  - Another Q: Insulin increases the rate of **anabolic** (biosynthetic) reactions
  - Another Q: Insulin conserves protein, carbohydrate, & fat stores in the body
  - Another Q: Insulin increases the activity of phosphofructokinase
    - Basically, tells to cell to get storing the energy and also pushes the glucose down the chain faster
    - **Remember the Factory, and the Truck that showed up analogy**
- Secretion inhibited by:
  - Decrease in blood glucose
  - Secretion of somatostatin
  - Secretion of either epi or NE
  - **BUT NOT by secretion of glucagons - I guess insulin is KING**
- Insulin released by beta cells is promoted by:
  - Rise in blood glucose: this is the major factor governing insulin release
  - Elevated level of amino acids (especially arginine, lysine, and leucine) in the blood plasma
  - **Glucagons, GH, and cortisol – because all of the following blood glucose levels**
  - PS stimulation
- Removal of the anterior pituitary gland increases the sensitivity to insulin
  - **(To pick up what little glucose there is!!) – Because w/o Anterior Pituitary, Blood glucose goes down**
  - Another Q: **The blood glucose level in diabetes mellitus is decreased by removal of the anterior pituitary gland**
  - *I think this might be due to the absence of T4, GH, and ACTH, which would normally elevate blood glucose, hence activating Insulin*

- Insulin vs. Glucagon
  - **Insulin (If your house is insulated, you can take stuff off, i.e. Phosphates)**
    - Dephosphorylates stuff
    - Turns Glycogen Synthase (A) ON, but Phosphorylase (B) OFF
  - Glucagon
    - Phosphorylates stuff
    - Turns Glycogen Synthase (B) OFF, but Phosphorylase (A) ON
  - **The A Form is ON FORM**
  - Glucagon:
    - Secreted by the alpha cells in the Islets of Langerhans of the pancreas in response to ↓ blood glucose level
    - Fxns:
      - Most important function = ability to cause glycogenolysis in the liver (which, in turn, ↑ plasma glucose)
        - Cyclic AMP – ↑ rate of glycogenolysis by promoting formation of phosphorylated form of Glycogen phosphorylase
        - **cAMP → PKA → P form of glycogen phosphorylase → glycogen-P → glycogenolysis**
          - The phosphorylation of phosphorylase b to phosphorylase a operates in liver cells to regulate breakdown of glycogen
      - Glucagon is found in standard medical emergency kits because it promotes glycogenolysis in hypoglycemic pts
      - Does not stimulate glycogen degradation in muscle → Because it can't leave the cell anyway (No G-6-P)
    - Frequently called the hyperglycemic factor
      - Hyperglycemic affect of glucagon is mediated primarily through the liver glycogenolysis
    - Glucagon released by Alpha cells is promoted by the following:

- A fall in blood glucose level (hypoglycemia): this is the major regulator of glucagon
  - NOTE on hypoglycemia: clinical manifestations of hypoglycemia include:
    - Dizziness, confusion, convulsion, coma (not hyperventilation)
  - Same Pt has a seizure
    - Most likely due to Hypoglycemia
- Sympathetic stimulation
- Epinephrine and norepinephrine secretion
- Elevated level of amino acids (especially arginine) in the blood plasma
- Cholecystokinin secretion

- Factors that decrease glucagon secretion
  - Rise in the blood glucose level
  - Insulin
  - Somatostatin
  - Free FAs
  - Ketoacids

- Kidneys
  - Aldosterone:
    - Exhibits main effect on the distal convoluted tubule and the collecting duct to increase Na^+ permeability
    - Stimulates Na^+ retention and K^+ excretion
      - This restores extracellular fluid volume and blood volume to normal
    - Is the principle mineralcorticoid
    - Secreted by cells located in the zona glomerulosa of the adrenal cortex
      - Secretion is induced by 1) plasma K^+ levels and 2) the renin-angiotensin system
      - Decreased [Na^+] causes JG cells of the kidneys secrete renin
        - (Reduced renal blood flow causes hypertension by the release of renin)
          - Your kidney thinks BP is down, so it kicks out renin to preserve Na+, which preserves fluid, which raises BP
  - Renin-Angiotensin System
    - Renin is released by the kidneys upon sensing decreasing BP
      - Renin cleaves angiotensinogen to angiotensin I **(in the blood)**
        - ACE cleaves Angiotensin I to angiotensin II primarily in the **lung capillaries**
          - Angiotensin II
            - Stimulates the adrenal cortex to release aldosterone
            - Potent vasoconstrictor
            - Release of ADH from posterior pituitary
            - Stimulates Hypothalamus (increase thirst)
          - ****ANP (Atrial Natriuretic Peptide) released from the atria may serve as a "check"**
    - Addison's disease
      - Caused by the hyposecretion of aldosterone and cortisol
- GI Hormones:
- NEED TO STUDY
  - Gastrin
    - Stimulates gastric acid secretion (HCl) by parietal cells coupled with the release of pepsinogen by chief cells
    - Released caused by:
      - Presence of peptides and amino acids in gastric lumen
      - Distension of stomach
    - Synthesized and stored in the cells of the antrum and duodenum (Antrum is the distal end of the stomach)
    - Secretion of gastric acid inhibits gastrin secretion – an example of feedback regulation
      - Also inhibited by secretin
  - Enterogastrone:
    - **Includes secretin, cholecystokinin, and gastric inhibitory peptide, GIP**
    - Are released by the small intestine in response to the acidity of the duodenal chyme and the presence of amino acids and free fatty acids
    - The hormones enter the blood and are carried to the stomach, where they depress the pyloric pump (pumping action of the stomach), thus inhibiting gastric motility, which slows down gastric emptying
    - The enterogastric reflex
      - Initiated when the duodenum fills with chyme, also inhibits the pyloric pump, thereby inhibiting gastric motility and emptying and secretions
      - The rate of gastric slow waves is unchanged but gastric emptying is reduced

- The enterogastric reflex produces a decrease in gastric motility
- Fats have the largest control over the release of the gastrones and the subsequent rate of gastric emptying
  - Fat in the small intestine inhibits gastric emptying through activity of enterogastrone
- Cholecystokinin:
  - Produced in the **small intestine in response to the presence of certain amino acids and free fatty acids**
  - Functions:
    - Stimulates the release of pancreatic enzymes (trypsin, chymotrypsin, and carboxypeptidase)
    - Stimulates the contraction & emptying of the gallbladder
    - Delays gastric emptying following fat ingestion
      - *NOTE: although secretin also inhibits gastric emptying, the Q was asking about it in relation to fat intake*
- Secretin:
  - Secreted in the duodenum, and is an enteroendocrine cell
  - Is released when the gastric contents (especially, H^+) are delivered to the duodenum
  - In turn secretin stimulates pancreatic duct cells to secrete a fluid high in bicarbonate (HCO_3^-), which neutralizes the H^+ in the duodenum
  - Functions of secretin:
    - Inhibits stomach motility and gastric acid secretion
    - Stimulates the pancreatic duct cells to secrete a fluid which contains a lot of bicarbonate ion but is low in enzyme
    - Stimulates the secretion of bile from the gallbladder
    - Secretin functions in digestion of **proteins** by increasing flow of pancreatic juice (which contains trypsin, chymotrypsin, carboxypeptidase)
- Gastric inhibitory peptide:
  - Like secretin, is secreted from the mucosal cells in the duodenum
  - Functions:
    - Inhibits gastric acid secretion (HCl) and motility and potentiates the release of insulin from the beta cells in response to elevated blood glucose concentrations
  - Release stimulated by presence of fat & glucose in small intestine

➢ Enterokinase (enteropeptidase)
- This hormone causes the release of pancreatic zymogens (e.g., trysinogen, chymotrypsinogen, proelastase, and procarboxypeptidase A & B) and the contraction of the gallbladder to deliver bile to the duodenum when chyme comes into contact with the mucosa
- **Enterokinase is found in the succus entericus (**upper intestinal mucosa**)but NOT found in the pancreatic juice**
- Converts trypsinogen to trypsin
- Pancreatic proteases are secreted in inactive forms (zymogens) that are activated in the small intestine:

Site of Synthesis	Zymogen	Active NZ
Stomach	Pepsinogen	Pepsin
Pancreas	Chymotrypsinogen	Chymotrypsin
Pancreas	Trypsinogen	Trypsin
Pancreas	Procarboxypeptidase A	Carboxypeptidase A
Pancreas	Procarboxypeptidase B	Carboxypeptidase B
Pancreas	Proelastase	Elastase

- Pepsinogen:
  - Secreted by the chief cells of the body (or Fundus -- BOTH) of the stomach (Pepsinogen)
  - Activated by pepsin and low stomach pH
    - The most important fxn of Hydrochloric acid in the stomach is activation of pepsinogen
  - **Pepsinogen is not found in pancreatic juice** (but lipase, amylase, trypsinogen, and chymotrypsinogen are)
- Trypsinogen:
  - **Activated to trypsin by enterokinase**
- Trypsin: THINK TRYPs the SWITCH
  - Cleaves peptide bonds in which the carboxyl group is contributed by **lysine and arginine (basic amino acids)**
  - **Converts trypsinogen, chymotrysinogen, proelastase, and procarboxypeptidase A and B to their active form**
  - **Serine** is an important aa in the active site of both **chymotrypsin** & **trypsin**
- Chymotrypsin:
  - Hydrolyzes peptide bonds on the alpha carboxyl side of aa residues with **large polar side chains, like Tyrosine, Tryptophan, Phenylalanine, Methionine, and Leucine**
    - **Phenylalanine, Tyrosine, Tryptophan are AROMATIC**
  - **Serine** is an important aa in the active site of both **chymotrypsin** & **trypsin**

- Elastase
  - Cleaves at the carboxyl end of aa residues with **small, uncharged side chains such as alanine, glycine or serine**
- Carboxypeptidase A
  - Has little activity on aspartate, glutamate, arginine, lysine, or proline
- Carboxypeptidase B
  - Cleaves basic amino acids: lysine and arginine

❖ **Sub**

➢ **Eicosanoids: prostaglandins and the related compounds of thromboxanes and leukotrienes**

- Prostaglandins:
  - 20-carbon FAs that contain a five carbon ring
  - Chemical messengers present in every body tissue
    - Differ from true hormones in that they are formed in almost all tissues rather than in specialized glands
  - Act as primarily as local messengers that exert their effects in the tissues that synthesize them
  - Have a very short half-life
  - Synthesis can be inhibited by a number of unrelated compounds including **aspirin, indomethacin, ibuprofen, phenybutazone, which are all NSAIDs**
  - Major Classes
    - PGA, PGB, PGE, and PGF
  - Seem to modulate the action of hormones rather than act as hormones
  - They enhance inflammatory effects, whereas aspirin diminishes them
- Arachidonic acid:
  - A polyunsaturated fatty acid
  - The major compound from which prostaglandins, prostacyclins, thromboxanes, and leukotrienes are derived
    - Prostaglandins are made within cells from polyunsaturated fatty acids
    - **Linoleic & arachidonic acids serve as precursors to prostaglandins**
    - Upon complete hydrogenation, oleic, linoleic, linolenic acids yield steric acid
  - It is part of phospholipids in the plasma membranes of cells
  - When a cell is stimulated by a neurotransmitter or hormone, a plasma membrane enzyme called **phospholipase A** is activated, and this enzyme splits **arachidonic acid from the phospholipids**
    - Cortisol inhibits phospholipase A activity which results in the formation of arachidonic acid from MB lipids
- Different metabolic pathways utilize different enzymes that convert arachidonic acid into:
  - Cyclooxygenase: prostaglandins, prostacyclins, and thromboxanes
  - Lipooxygenase: Leukotrienes

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

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➢ **Prostacyclin (PGI2) (Platelet Gathering Inhibitor)**

- Acts to prevent platelet formation and clumping
- Also a potent vasodilator
- Physiologic Anticoagulant (secreted from endothelium) ➔ Anticoagulant
- **Contrast to Thromboxane A2 – which is secreted by platelets ➔Coagulant**

➢ Heparin:

- Is a heteropolysaccharide that serves as a **powerful anticoagulant that prevents the formation of active thrombin**
- Another Q: Heparin administration results in symptoms similar to vitamin K deficiency – increased bleeding time due to lack of thrombin formation
- Unlike other glycosaminoglycans that are extracellular compounds, heparin is an intracellular component of mast cells

        - These mast cells line arteries, especially the liver, lungs, and skin
            - Mast cells are abundant in the tissue surrounding lung capillaries & to a lesser extent in liver capillaries
        - Small quantities are produced by basophils – functionally almost identical with mast cells
    - Used in treatment of certain types of lung, blood vessel, and heart disorders, and during or after certain types of surgeries (open heart or bypass surgeries)
    - Concentration in the blood is normally slight, so that only under limited physiological conditions does it have significant anticoagulant effects
    - **HEPARIN Think Hugh Heffarin with his PERFECT 10 girls → stops 10 from doing its thing**
    - **Administration of heparin will result in an increase in bleeding time due to the activation of antithrombin, a major protease inhibitor, which rapidly inhibits thrombin.**
    - It is used in treating pts who have suffered a coronary thrombosis
    - Heparin can also enhance the removal of lipoproteins from the blood by binding apolipoprotein E (protein found on some liposomes) and by activation lipoprotein lipase
- Histamine:
    - Causes:
        - Vasodilation (particularly the arterioles by the **decarboxylation of histidine)**
            - Decarboxylation of the aa histidine results in formation of a vasodilator (histamine)
        - Secretion of HCL – H2
        - Bronchoconstriction
        - Decreased blood pressure
        - Increased vascular permeability (particularly in the capillaries and venules)
    - Found in tissues, mast cells, basophils (and is in highest concentration in the lungs)
    - Secreted by mast cells as a result of allergic reactions or trauma
    - When tissue is injured, histamine is liberated by the damaged tissue into the surrounding fluids
        - This increases the local blood flow as wells as capillary & venule permeability, allowing large quantities of fluid protein to leak into the tissue – characteristic "wheal"
    - Powerful pharmacologic action from two receptors:
        - **H1 receptors**:
            - Mediate the typical allergic and anaphylactic responses to histamine – bronchoconstriction, vasodilation, and increased capillary permeability
        - **H2 receptors:**
            - Mediate other responses **to histamine, such as the increased secretion of gastric acid and pepsin**
- **Serotonin: (aka 5HT)**
    - Synthesized from the aa **tryptophan (also secretes another tonin – melatonin and Niacin NAD)**
    - Released from platelets upon damage to the blood vessel walls
    - Acts as a potent vasoconstrictor and increases vascular peripheral resistance
    - **In gastric mucous membranes it is secreted by the enteroendocrine cells and causes the smooth muscle to contract (TONIN)**
    - **In brain it acts as a neurotransmitter**
        - Lysergic acid diethylamide interferes with the action of serotonin in the brain

Disorders

- Diabetes mellitus:
    - The most common pancreatic endocrine disorder
    - A metabolic disease involving mostly carbohydrates (glucose) and lipids
    - In uncontrolled DM,
        - Infection
        - Delayed Wound Healing
            - Type I DM pt scheduled for extractions, dentist should be most concerned about Increased potential for infection
    - Caused by:
        - (Type I)
            - An absolute deficiency of insulin
            - Defective or absent beta cells in the pancreas
        - (Type II)
            - Resistance to insulin's actions in the peripheral tissue
            - Results from loss of the insulin receptor fxn in the target tissue
            - 80-90% of diagnosed cases
            - Polygenetic etiology
            - Middle aged, obese

        - Insulin is present at elevated or near normal levels
    - Cardinal symptoms include: polydipsia, polyuria, polyphagia, weight loss, loss of strength
        - In untreated diabetes mellitus, polyuria is related to the osmotic effect of glucosuria
        - Another Q: Glucosuria with hyperglycemia usually occurs in diabetes mellitus

Characteristics	**Type 1**	**Type 2**
Level of insulin secretion	None or almost none	May be normal or exceed normal
Typical age of onset	Childhood	Adulthood
Percentage of diabetes cases	10 – 20%	80 – 90%
Basic defect	Destruction of B cells	Reduced sensitivity of insulin's target cells
Associated with obesity	No	Usually
Speed of development of symptoms	Rapid	Slow
Development of ketosis	Common if untreated	Rare
Treatment	Insulin injections, dietary mgmt	Dietary control, weight reduction, occasionally oral hypoglycemic drugs

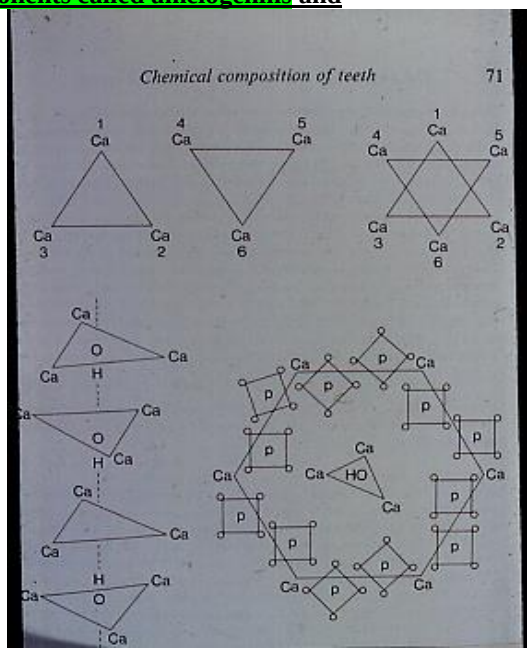
- Diabetes insipidus:
    - A disorder in which insufficient levels of antidiuretic hormone (ADH) cause excessive thirst (polydipsia) and excessive production of very dilute urine (polyuria)
    - Results from hypoactivity of the posterior pituitary gland or destruction of the supraoptic nuclei of the hypothalamus
    - ADH deficiency results in failure of tubular water reabsorption (kidney) and the consequent passage of a large amount of dilute urine and great thirst
    - Body fluid volumes remain close to normal so long as the pt drinks enough water to make up for increased H_2O clearance
- Nephrogenic diabetes insipidus:
    - Congenital and familial form of diabetes insipidus due to failure of the renal tubules to reabsorb water
    - Excessive production of ADH but the tubules fail to respond
- Shock:
    - Inadequate perfusion of tissue
    - Symptoms:
        - Tiredness, sleepiness, and confusion
        - Skin becomes cold and sweaty and often bluish and pale
        - Pulse is weak and rapid
        - Blood pressure drops as well
    - Stages of shock:
        - **Compensated:**
            - Compensatory mechanisms
                - Activation of the sympathetic nervous system, increased cardiac output, and increased total peripheral resistance in order to maintain perfusion to vital organs
                - If blood has been lost & the pt is in shock, the following are likely to occur:
                    - Decrease in GFR
                    - Decrease in urine formation
        - **Progressive:**
            - Decreased heart perfusion leads to cardiac depression and decreased cardiac output
        - **Irreversible:**
            - Depletion of high energy phosphate reserves
            - Death occurs even if treatment can restore blood flow
    - Major categories of shock:
        - Hypovolemic:
            - Produced by a reduction in blood volume
            - Results **from** severe hemorrhage, dehydration, vomiting, diarrhea, and fluid loss from burns
            - Results **in** a decrease in GFR and a decrease in urine formation
            - A patient is dehydrated due to severe vomiting; a symptom he/she might present with is an increased pulse rate
        - Cardiogenic:
            - Circulatory collapse resulting from pump failure of the left ventricle
            - Most often caused by massive myocardial infarction
        - Septic:
            - Due to severe infection
            - Causes include endotoxin from G- bacteria
        - Neurogenic:

        - From severe injury or trauma to the CNS
    - Anaphylactic:
        - Occurs with severe allergic reaction
        - Heparin
- Jaundice:
    - Yellow discoloration of the skin and white of eyes caused by abnormally high levels of the bile pigment, bilirubin, in the bloodstream
        - Bilirubin
            - Heme is scavenged from the RBC (after their 120 day life span) and the Fe2+ is reused
                - Actively taken up by hepatocytes
            - **Heme→ Biliverdin→ Bilirubin**
            - Sparingly water soluble, toxic to CNS, and transported by albumin
            - Bilirubin is the product of heme degradation
            - Another Q: RBC destruction is measured by the bilirubin (bile pigments) excreted from the liver each day
            - Another Q: The amount of bile pigment secreted by the liver is deteremined by the amount of hemoglobin destruction
        - Heme portion of the hemoglobin, the part of the red blood cells that carries oxygen is broken down into bilirubin
            - Bilirubin is carried to the liver as unconjugated and bound to albumin
            - **UNconjugated is INdirect and INsoluble**
                - Free bilirubin-albumin complex
            - Converted to the diglucuronide derivative **(conjugated bilirubin) in the liver**
                - Conjugated is Direct
                - Conjugated version is **water-soluble**
                - Conjugated is then ready to be excreted via bile
                - Then…
                    - excreted into intestines as a component of bile
                    - OR excreted by the kidneys as urobilirubin
            - Bacterial conversion to urobilinogen in the colon (precursor for urobilirubin???)
            - Some excretion as **stercobilin** in feces
                - But most is recycled via enterhepatic circulation of urobilinogen
    - If the excretion from the liver is hindered, **excess conjugated bilirubin** passes into the bloodstream, resulting in jaundice
    - Very common – the leading manifestation of liver disease
    - Can occur at any age and in either sex
    - Symptom of many disorders – liver disease, gallstones, pancreatic cancer, and acute biliary obstruction
    - Normal plasma concentration of bilirubin averages 0.5 mg per 100 ml of plasma
        - In jaundice it can rise to as high as 40 mg per 100 ml
    - Causes of jaundice:
        - Increased destruction of red blood cells with rapid release of bilirubin into the blood
        - Obstruction of bile ducts or damage to liver cells causes inability of bilirubin to be excreted into the GI tract
- Phenylketonuria (PKU):
    - An abnormal presence of phenylketone and other metabolites of phenylalanine in the urine
    - **PKU** is caused by the absence of or a deficiency of **phenylalanine hydroxylase**, the enzyme responsible for the conversion of the amino acid phenylalanine into tyrosine
    - Metabolic defect in phenylketonuria results in failure to hydroxylate phenylalanine adequately
    - Tyrosine lessens the need for Phenylalanine
        - Tyrosine becomes essential
        - Phenylalanine is the amino acid that can be converted to Tyrosine most easily in the human body
    - Accumulation of phenylalanine is toxic to brain tissue
        - It will impair normal development of the brain causing severe retardation
        - **Signs: mental retardation, musty smell, fair skin, excema – NO melanin**
- **Alkaptonuria (aka homogentisuria): Think AKU**
    - Due to the failure to catabolize tyrosine beyond the intermediate, homogentisic acid, which is excreted in the urine and **makes it appear black**
        - **THINK you make melanin from tyrosine, so of course its intermediate is dark colored**
        - **Homogentisic acid accumulates in the urine**
        - **Homogentisic acid is an intermediate product of metabolism of phenylanaline to tyrosine.**
    - Results from a deficiency of a dioxygenase (homogenetisate)
    - Usually, the condition does not result in any serious ill effects
- Cystinuria:
    - A hereditary disorder characterized by excessive urinary excretion of cystine and other amino acids

- **COLA – Cysteine, Ornithine, Lysine, and Arginine**
  - Caused by a defect in the renal tubules that impairs the reabsorption of these amino acids
  - Excess cysteine in urine can lead to kidney stones
- Albinism:
  - Due to the failure to convert **tyrosine** to **melanin**, as a result of a deficiency of the enzyme, **tyrosinase**
    - **Tyrosine** is a precursor of the pigments of the **skin, hair & nails**
  - Albinos do not have problems with epinephrine synthesis, despite melanin and epinephrine having DOPA as a common intermediate, because of different enzymes used in malanocyte for DOPA synthesis

Teeth/Mouth

- Enamel:
  - Highly mineralized structure containing approximately 95% inorganic matter
  - Hydroxyapatite (HA) crystals
    - Made up of calcium & phosphate
    - Are the largest mineral constituent (90-95%) of enamel
    - Have a multi-ionic structure
    - Solubility is pH-dependent (as pH ↓, solubility ↑)
    - Tends to bind polar substances
    - **Substitution of carbonate into HA increases the solubility (instead of phosphate) – around the Ring**
    - **Fluorapatite forms during hard tissue formation by a substitution of OH ions by F ions – in the center of the Ring**
    - The distribution of carbonate within dentin and enamel follows the same surface to DEJ pattern as NONE of the above??? (Not Lead, Calcium, Fluoride, or Strontium) – **maybe the same as phosphate as it substitutes in HA**
  - Ameloblasts produce an **enamel matrix (organic matrix) with protein components called amelogenins and enamelins**
  - **Amelogenin forms the collagen Rods by which are then calcified by Ca, PO4 and OH minus**
    - AMELOGENIN disappears – makes the rods, but then disappears when collagen and water decrease
    - **Enamelins stay behind as an interrod structure and are the MOST abundant**
    - This organic matrix makes up about 1-2% of enamel and water makes up about 4%
    - Protein content of enamel from mature teeth is approximately 0.1-1%
    - The tooth becomes more resistant to acid-producing bacteria because fluorapatite has lower solubility product constant than hydroxyapatite
      - Fluorapatite is less soluble than hydroxyapatite in solutions with low pH
  - What LEAST contributes to Fluoride's anti-caries effectiveness??????
    - **Substitutes for PO4, because it doesn't**
  - Enamel is harder than bone
    - The main reason for this is that enamel hydroxyapatite **crystals are larger and more firmly packed**
    - These tightly packed masses of hydroxyapatite crystal are called enamel prisms and they are structural units of enamel
    - These crystals in enamel are four times larger than those in bone, dentin, and cementum



- Dentin
  - **Dentin is not metabolically inert – it is in dynamic equilibrium with blood and metabolites**
  - Another Q: Collagen is the major protein produced by odontoblasts & is contained in the organic matrix of dentin
  - Another Q: **Phosphophoryn is the noncollagenous protein component that best characterizes dentin matrix**
- Cementum
  - Collagen is the major protein component of cementum
- Enamel Hypoplasia
  - A defect in the formation of enamel matrix
  - The enamel of primary and permanent teeth appear pitted, yellow to brown and have open contacts
  - Radiographically the enamel is either absent or very thin over tips of cusps and IP areas
  - Can be caused by nutritional deficiencies, hereditary
    - Vitamin A and C deficiency may cause it as well as inadequate intake of calcium, fluorosis, congenital syphilis, high fever, rickets, injury or trauma to the mouth
    - Vitamins A and D are primarily responsible for **enamel tooth formation**

        - A vitamin A, D deficency in a developing tooth most likely affects enamel → Enamel Hypoplasia (more than dentin, pulp, & cementum)
    - Hypoplasia results only if the assault occurs during the time the teeth are developing
    - So, a prolonged vitamin A or D deficiency, Rickets, or inadequate intake of calcium can produce enamel hypoplasia
        - The Least important in producing enamel hypoplasia is Fluoride intake of less than 0.2ppm in the water
    - Another Q: Vitamins A, C, & D, K are all involved in tooth development & calcification; Vitamin B_1 is not
    - Another Q: The lack of Vitamins A & D during tooth formation induces enamel hypoplasia
- Enamel Hypocalcification
    - A defect in the mineralization of the formed enamel matrix
- Pulp
    - Proprioceptors are not found in pulp
    - The hemodnamics of flow in the tooth pulp are most likely analagous to those in the cranium
- Caries activity is directly proportional to:
    - Consistency of fermentable carbohydrates ingested
    - Frequency of ingesting fermentable carbohydrates (most important factor)
    - Oral retention of fermentable carbohydrates ingested
- Caries development:
    - The first event in the development of caries is the deposit of plaque on the teeth
        - Plaque arises primarily as a result of bacterial enzymatic reaction using sucrose & saliva (fermentable CHOs)
    - SUCROSE is the most important factor for caries
    - Large numbers of bacteria **(mainly *S. mutans* and Lactobacilli)** inhabit plaque and are readily available to cause caries
    - However, these bacteria depend to great extend on CHOs (sucrose) for their food
        - When carbohydrates are available, their metabolic systems are strongly activated and they also multiply
            - As a result of the metabolic activity they release acids, particularly lactic acid, and proteolytic enzymes
- **When the acidity level (pH level) of the mouth drops below 5.5, demineralization of the teeth can occur**
    - Carbonated Beverages
        - **Carbonic acid, H2CO3, is a weak acid, but when ingested in large quantities can slowly decalcify teeth due to low pH (They also contain Phosphoric acid which has the same effect)**
        - Drinking large quantities of carbonated cola type beverages could lead to enamel decalcification due to low pH
    - Another Q: Tooth erosion in bulimic (bulimia) patients is due to solubility of hydroxyapatite in acid
- Extracellular dextrans
    - **An extracellular polysaccharide synthesized by cariogenic streptococci (not** a mucopolysacch) in the presence of sucrose
    - The structural component of plaque
    - Are formed from sucrose by bacterial enzymes (glycosyl trasferase GTF) which are located on the cell surface of certain lactic acid bacteria (e.g., *S. mutans* and *Lactobacilli*)
        - Another Q: Sucrose most directly contributes to the addition of polysaccharides to dental plaque
        - Sucrose → forms dextran → using S. Mutans which has glycosyl transferase enzyme
    - Dextrans are essential for the cariogenicity of these bacteria
- Acquired Pellicle
    - **Essentially absent of microorganisms**
    - Brownish structureless film that accumulates on the surfaces of the teeth
    - Brownish color from tannin
    - Forms the interface between tooth structure and dental plaque and calculus
    - **Calcium phosphate is NOT in the pellicle**
    - **The acquired pellicle is primarily composed of salivary glycoproteins**
    - **Most similar to organic composition of plaque????**
- Saliva:
    - pH of saliva is between 6.0 and 7.0
        - Saliva is able to neutralize acids mainly due to its bicarbonate content
        - Another Q: The principal buffer system in stimulated parotid saliva is carbonic acid/carbonate
    - Approximately 2/3 of the ~1 L/day produced by an average adult comes from the **submandibular glands**
        - ~1/4 comes from the parotid glands & the remainder is produced by the sublingual & buccal glands
    - Occurs Most inbetween Meals
    - Saliva production drops at night
    - Composition of saliva:
        - 97% to 99.5% water, contains electrolytes (Na^+, K^+, Cl^-, and HCO_3^- ions; not F^-)
            - **Some chemicals, like Potassium, Iodine, and Mercury are excreted in part by the saliva**
            - High K^+ and HCO_3^- concentration (at least in the mucous portion)
            - Low Na^+ and Cl^- concentration

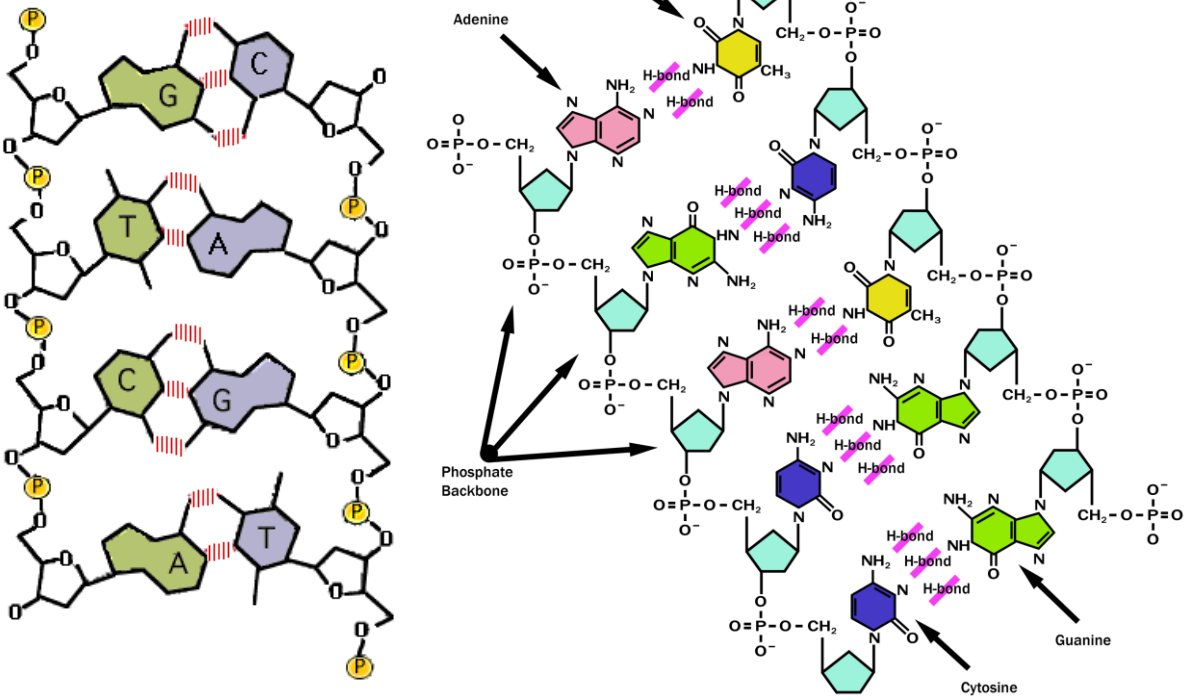
        - **Hypotonic due to the fact that the salivary ductal cells reabsorb Na^+ and Cl^- in exchange for K^+ and HCO_3^-**
    - **Also contains proline-rich proteins which have antimicrobial properties**
- Saliva supplies calcium and phospate for remineralization
- Control of salivary secretion:
    - Both PS & Symp stimulations cause secretion
        - **PS has the greatest effect**
    - Vagal stimulation increases saliva production, so a vagotomy inhibits saliva production – xerostomia
    - Atropine also prevents saliva secretion (normally stimulated by chorda tympani)
        - *Sidenote*: The chorda tympani nerve contains ONLY preganglionic parasympathetic secretory fibers
            - *This isn't all it contains – see Anatomy section for notes on its taste fibers, etc*
        - It prevents the action of Ach on the secreting cells (anticholinergic – competitve inhibitor of Ach)
- Salivary Secretions:
    - Mucous secretion:
        - Contains mucins, which are proteins w/ polysaccharides attached to them – lubricates mouth and food
            - Mucins are glycoproteins
        - Sublingual & buccal glands – produce mucous secretions
    - Serous secretion:
        - Contains salivary amylase (ptyalin)
            - This enzyme splits starch into alpha dextrin, maltotriase, and maltose (see below)
            - So, α-amylase ptyalin is secreted by the parotid glands
            - NOT produced from a zymogen
            - NOTE: The digestive action of salivary amylase continues for some time after swallowing, because the amylase inside the bolus is protected from the inactivating action of gastric HCl
        - A number of proteins (proline-rich proteins, statherin, etc.) play important roles in maintaining the enamel surface and preventing calculus formation
        - Parotid glands – produce serous secretions
            - **Parotid saliva is believed to be hyposmolar because reabsorption of water by striated duct cells is less than reabsorption of sodium**
    - Submandibular produce both mucous & serous secretions
- Functions of Saliva:
    - 1) Lubrication – for the mastication and swallowing of food
    - 2) Protection – prevents dehydration of the oral mucosa
    - 3) Oral hygiene – antimicrobial properties and washes away food particles
        - Salivary lysozymes have bactericidal activity
    - 4) Digestion – starch digestion by alpha amylase (ptyalin) [not required]
        - Amylases:
            - Digest starches by hydrolysis
            - Types:
                - Alpha amylase:
                    - Converts starch to oligosaccharides
                    - Salivary amylase (ptyalin) and pancreatic amylase are this type
                    - They both hydrolyze 1,4 glycosidic bonds in starch yielding alpha-dextrin, maltotrios, and maltose
                    - Malatase, alpha dextrinase, and sucrose in the intestinal brush border then hydrolyze the oligosaccharides to glucose
                    - Salivary amylase is inactivated by acidic environment of the stomach
                - Beta amylase:
                    - Converts starch to maltose and dextrin
                - Glucamylase:
                    - Converts starch to glucose
            - Monosaccharides are absorbed in the small intestines
        - Disaccharides
            - Maltose
                - Glucose + Glucose
                - Must be digested into an absorbable form that can be ingested by the enterocytes
            - Sucrose
                - Glucose + Fructose
                - Degraded by sucrase
            - Lactose
                - Glucose + Galactose

- ♦ **Isomaltase cleaves a glucose-linked 1,6 to another glucose as is found at branch points in starch/glycogen**
- The belief that the secretion of saliva is an active process is supported by the observation that secretion continues even when the pressure within the salivary duct is **higher** than the blood pressure
- Xylitol increases salivation

❖ **DNA/RNA**

➢ DNA double helix:
- The two antiparallel polynucleotide chains of double helical DNA are not identical in base sequence or composition
  - Instead they are complementary to each other
  - Because strands are complementary, separated strands are able to reassociate
- Wherever adenine appears in one chain, thymine is found in the other
- Watson and Crick deduced this specificity of base pairing because of **stearic and hydrogen bonding factors**
- In their structure the two chains or strands of the helix are antiparallel – one strand runs 5' – 3' & the other runs 3' – 5'
- The DNA double helix is held together by two sets of forces:
  - **1) hydrogen bonding between complementary base pairs**
  - **2) base stacking interactions**
- The two chains of dsDNA are so arranged that hydrophobic aromatic nitrogen bases are held close to each other
- The helix structure results in a major and minor groove being formed along the DNA molecule
  - The major groove is the binding region for many proteins which control the transcriptional activity of the DNA

➢ DNA backbone: picture



- It is constant throughout the molecule
- **Monomeric units of nucleic acids are linked by phosphodiester bonds**
  - The 3' hydroxyl group of one nucleotide bonds to the 5' hydroxyl group of the next nucleotide by a phosphodiester linkage
  - The covalent backbones of a nucleic acid consists of alternating phosphate & pentose residues, w/ a purine or a pyrimidine base is attached to each pentose
- **Phosphodiester bond connects the pentose hydroxyl groups of DNA and RNA are always 3' to 5'**
  - Bond formed from the esterification of 2 or 3 hydroxyl groups of phosphoric acid to adjoining nucleotide residues
  - Two free hydroxyl groups are present on the 3'C and 5'C
- Is hydrophilic and highly polar
- The hydroxyl groups of the sugar residues form hydrogen bonds with water
- The ribose phosphate portion of purine & pyrimidine nucleotides comes from 5'phosphoribosyl-1-pyrophosphate (PRPP)
  - PRPP is synthesized from ATP and ribose-5-phosphate, which is primarily formed by the pentose phosphate pathway
  - So, ribose phosphate needed for nucleic acid synthesis can be derived from the pentose phosphate pathway

➢ What happens when DNA is denatured? *(from 2 Qs)*

- UV light absorption increases
- Complementary strands become random coils
- Base stacking becomes disrupted
- Hydrogen bonds are broken
- Peptide bonds are broken
- Loss of native conformation, 2° & 3° structure
- Loss of biological activity
  - ***Total G-C or A-T content does not change**

➢ Nucleic acids
- Store and transmit information to synthesize the polypeptides and proteins present in the body's cells
- Nucleic acids are complex molecules composed of structures known as nitrogenous bases (purines and pyrimidines), five carbon sugars (pentoses) and phosphates groups (which contain phosphorous and oxygen)
- The backbone of nucleic acids is made up of alternating phosphate and pentose units, with a purine and pyrimidine attached to each

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

-
- **Nucleotide = a single base (G,C,A,T) + sugar +phosphate unit**
  - The nucleotide is the basic unit of DNA
  - NOTE: catabolism of nucleotides yields no energy production in the form of ATP (unlike lipid, protein & CHO)
  - Another Q: An example of a nucleotide is thymidylate (dTMP); urate, uracil, ribose, adenosine are not nucleotides
- **NucleoSide(WITHOUT PHOSPHATE SIDE) = a single base sugar phosphate unit w/o a phosphate group**
- These individual nucleotides are linked together to form a polynucleotide chain (the link or bond is between a phosphate group of one nucleotide and the sugar of the next)
- If the polynucleotide chain contains the sugar ribose, the chain is called a ribonucleic acid (RNA); if it contains the sugar deoxyribose, the chain is called deoxyribonucleic acid (DNA)
  - 2-deoxyribose is always found in DNA
- Hydrolysis of nucleic acids yields
  - Ribose, adenine, deoxyribose, phosphoric acid, NOT acetic acid

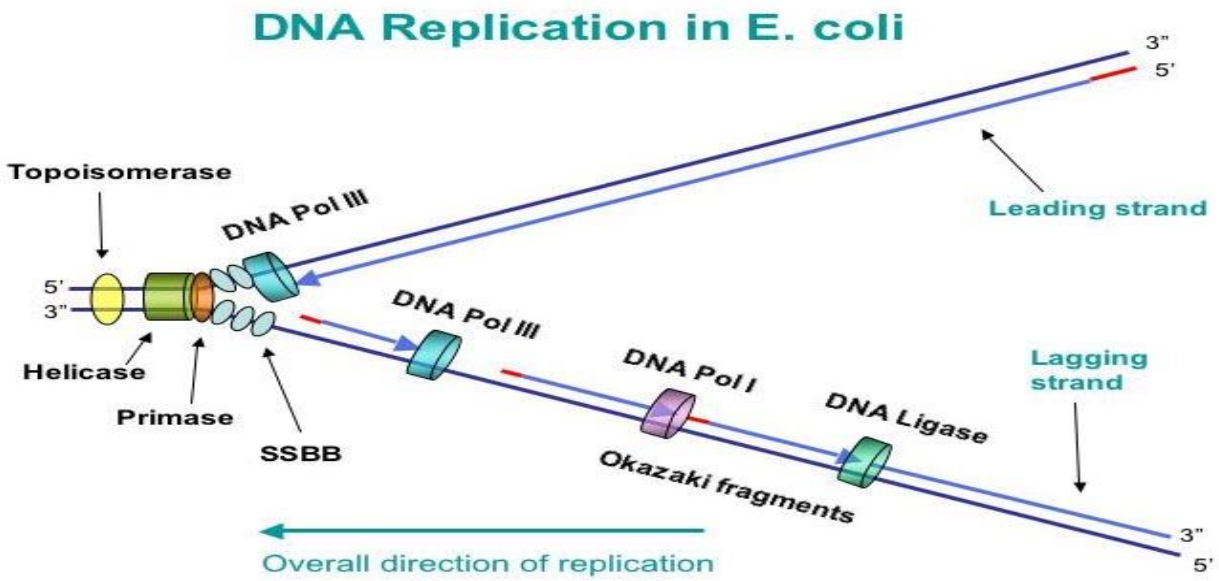
➢ Bases
- PURINES (PURe **A**s **G**old)
  - Have 2 rings
    - Guanine has a ketone
  - Adenine (A) and guanine (G)
    - The C-G bond results from 3 H-bonds
    - The A-T bond results from 2 H-bonds
  - Purine bases consumed in the human diet in the form of DNA or RNA are mostly excreted in the form of **uric acid**
    - Another Q: The end product of the catabolism of purine is uric acid
    - Another Q: **Xanthine oxidase** catalyzes this formation of uric acid from purine bases (**NOT hydrolysis**)
      - Xanthine oxidase is involved in the last step of purine degradation changing xanthine to uric acid
      - It is inhibited by allopurinol
  - Hypoxanthine and xanthine are also purine bases
    - Nucleoside derivatives of these bases will contain either ribose or 2 deoxyribose linked to the purine ring through a beta N-glycosidic bond at N9
    - **The link between Ribose (Sugar) and Purine (Base) is via a glycosidic bond**
      - In the final rxn of the de novo synthesis of purine ribonucleotide, inosine monophosphate (IMP) is formed
        - **IMP is converted to adenosine phosphates and guanosine phosphates**

- **Purine ribonucleoside phosphates are all synthesized *de novo* from the common intermediate inosine phosphate**
- PYRIMIDINES (**CUT** the PY)
  - Have 1 ring
    - Thymine has a Methyl
  - In DNA, pyrimidine bases are thymine (T) and cytosine (C)
  - In RNA, pyrimidine bases are uracil (U) and cytosine (C)
    - Uracil is the pyrimidine base that is present in RNA, but not in DNA
- Three H bonds are formed between G and C, but only two form between A and T
  - The melting temperature of the double helix is a function of the base composition
    - Higher GC content having a higher melting temperature and an increased stability of the double helix
- If the molar % of A in a native DNA specimen is 22%, then the molar content of G is…28% (do the math)
- Bacteria found in hot springs, high G-C content for high Bpoint, from 3 bonds
- The weaker bonding between A and T is used in transcription to aid in the release of the newly formed RNA from the DNA template
  - Remember U substitutes T in RNA—they both bind to A
- The use of tetrahydrofolic acid (TFA) by several of the enzymes in purine and pyrimidine synthesis have made TFA metabolism a prime target for a number of antimetabolites such **as methotrexate, used in cancer chemotherapy**
    - **Methotrexate works in the S phase**
  - **Tetrahydrofolic acid is a coenzyme required in the general reaction for the transfer one-carbon fragments**
- **Another Q: DNA damage by ultraviolet light is due to induction of dimerization by way of covalent bonds between adjacent thymine groups**
  - **Just Like SAM???**
  - The pyrimidine dimers then interfere with replication and transcription

➢ Replication:
- The process of completely duplicating the DNA within a cell
- The process is semi-conservative
  - Each new double helix will consist of one old and one newly synthesized strand
- The primary enzyme in this process is DNA polymerase
  - **The polymerase that initiates the primary synthetic reaction is polymerase 3**
    - But first needs primer to initiate synthesis
  - Reads a single strand of DNA from 3' to 5' while forming the new, complementary, continuous strand from 5' to 3'
  - As the DNA polymerase complex moves along the DNA molecule, the original complementary stand (lagging strand) is also duplicated
    - DNA polymerase moves along the lagging strand from 5' to 3' and thus cannot form a continuous copy of the lagging strand
    - Instead, it forms ~1000-5000base long multiple segments (Okazaki fragments)
      - The fragments are joined together by DNA ligase to form a continuous strand
      - DNA Ligase
        - Involved in DNA Replication, Repair, and Recombination **(The 3 Rs)**
          - **NOT transcription**
        - Immediately following the production of Okazaki fragments, the gap between fragments becomes connected through the action of DNA-ligase
        - Another Q: DNA ligase seals single stranded nicks in DNA
  - DNA polymerase can only add nucleotides to a pre-existing piece of nucleic acid (primer)
- During replication the primer is provided by RNA polymerase (which has no primer requirement)
  - The short 10-base segments created by RNA polymerase are removed, once the DNA has been added to it, by an **exonuclease** and the gap in the sequence is filled in by a DNA polymerase
  - **RNA polymerase**
    - is an enzyme that synthesizes polynucleotide sequences from nucleotides and **does not require a primer chain (opposite to DNA polymerase)**
    - No proofreading fxn
    - But can initiate chains
      - **RNA polymerase II opens DNA at promoter sites (A/T rich upstream sites, i.e. TATA and CAAT)**

➢ DNA Repair
- First a special **glycosylase** recognizes the error
  - Endonuclease cuts internal phophodiester bonds
- Exonuclease removes jacked-up pieces
  - Cuts at the end of the chain
- DNA polymerase fills the gaps

- DNA Ligase seals



- FROM PIC, read it 3'- 5' and **Make 5' FIRST**
- The Genetic Code
  - Degenerate nature of the genetic code:
    - Implies that many amino acids are designated by more than one codon
      - Unambigous = only one codon for that amino acid **(Tryptophan, Selenocystein, and Methionine)**
        - The other 18 amino acids are coded by 2+ codons
  - Codons (sometimes referred to as a triplet)
    - A sequence of three adjacent nucleotides (AUG, for example) in a nucleic acid that codes for a specific aa
      - How many nucleotides are required to code for a protein with 150 amino acids? *Ans: 450*
    - Codons that specify the same amino acid are called synonyms
    - Multiple codons for an amino acid usually differ in the third base (at the 3' end)
    - Several of the Codons Serve Special Functions:
      - Initiation codon (AUG or rare GUG):
        - Signals the beginning of polypeptide chains and codes for methionine (all proteins begin with methionine)
        - Starts the in**AUG**ural Methionine **(In prokaryotes its f-met)**
      - Termination codon (UAA, UAG, and UGA):
        - Signals the end of polypeptide chain sythnesis
        - These codons are also referred to as STOP codons or Nonsense codons
      - **Selenocysteine is the 21st genetically coded aa**
        - The **codon UGA** occurring in the correct contex, leads to the incorporation of this serine derived aa
    - Anticodon
      - A specific sequence of three nucleotides in transfer RNA complementary to a codon for an amino acid in a messenger RNA
        - The aa inserted in a polypeptide chain during protein synthesis is determined by a complementary relationship between mRNA & tRNA
    - The two RNAs are paired antiparallel:
      - **DNA Polymerase reads from 3' to 5' on the DNA, and makes 5' to 3' mRNA to match**
        - **Then, tRNA matches the 5' to 3' mRNA by its anticodon which is a 3' to 5', BUT anticodons are ALSO read 3' to 5'**
          - **The first base of the codon pairs with the third base of the anticodon (both are read in the 5' to 3' direction)**
      - EX: If the codon on mRNA is CGU, then the corresponding anticodon on tRNA is ACG
        - *Don't get clowned by simply lining up the codon & anticodon and giving that as your answer*
        - *It's really **5'CGU3'** and **5'ACG3'***
        - *So, you could just match up **5'CGU3'** and **3'GCA5'**, then switch it up to **5'ACG3'** for your answer, got it?*
- Transcription
  - Process in which DNA serves as a template for the assembly of molecules of RNA (all three types)
  - Cellular process of making RNA from DNA
  - This process involves the **enzyme RNA polymerase**
  - *From way out in right field*: **Rifampin** is effective in treating active TB because it targets transcription

- Translation **(L for last step)**
  - Is the process by which genetic information flows from RNA to protein
  - Involves 4 steps
    - Activation
      - Involves joining the correct amino acid to the correct tRNA (AUG)
    - Initiation
      - Small subunit of ribosome binds to the 5' end of the mRNA
      - Uses the help of Initition factors
      - The first step in the utilization of amino acids for protein synthesis requires aminoacyl-tRNA synthetase
    - Elongation
      - Next AA in line will form complex with Elongation fractor and GTP
      - In prokaryotic protein synthesis, the **elongation factor G** serves to translocate the growing peptide chain and to move the ribosome along the mRNA
      - At the end of each elongation cycle, the growing polypeptide is found as peptidyl-tRNA bound to the P site
    - Termination
      - When A site faces nonsense codons (UAA, UAG, UGA), no tRNA can recognize it, but releasing factor will recognize it and release the newly synthesized protein
- Types of RNA:
  - Messenger RNA **(mRNA or RNA polymerase II):**
    - **M for Massive**
    - Single-stranded; made in the nucleus; made as a complement to one strand of DNA; template for protein synthesis
    - Molecules carrying information (genetic code) from DNA in the nucleus to ribosomes in the cytoplasm, where polypeptides and proteins are synthesized (translation→mRNA is the template for protein synthesis)
    - Random Q: Addition of synthetic polyuridylic acid to a cell-free system capable of protein synthesis results in greatly enhanced incorporation of phenylalanine into peptide linkages. In this system, **polyuridylic acid** is performing a function normally performed by **mRNA**.
      - A landmark experiment was formed where polyuridylic was dumped into a cell-free, but protein synthesizing system. It resulted in the production of polyphenylalanine, and **lead us to the breaking of the genetic code**, so here the polyuridylic acid served as the mRNA that brought in the instructions for translation
    - Splicing
      - Small lariot shaped intermediate is formed
        - Then a **SnRNP** (small nuclear ribonucleoprotein particle splices out the intron)
        - Intron vs Exon
          - **Exons stay in the mRNA to EXIT the nucleus**
        - Another Q: During nuclear processing of hnRNA to mRNA the portion of the molecule that is removed is the **intron**
    - Processing
      - Occurs in the nucleus
        - **Capping on the 5' end (7 methyl G)**
          - What is the reason for the GGG repetition in prokaryotes →
            - Protects the mRNA from degradation outside the nucleus
            - For the ribosome movement, translation process
        - Polyadenylation on 3' end (300 As)
      - **Pre-processed transcript is called hnRNA heterogenous RNA, where post is called mRNA**
  - Transfer RNA **(tRNA or RNA polymerase III):**
    - **T for Tiny**
    - **Made in the nucleolus**
    - Molecules carry the amino acids to ribosomes, where the amino acids are linked together in the order specified by mRNA to form particular polypeptides and proteins
    - **Clover shaped, with the amino acid covalently bound to 3' end**
    - Amino acyl-tRNA synthetase
      - is a group of ligases (enzymes) that ensures that the correct amino acid is attached to the tRNA with the correct anticodon to be used during protein synthesis
      - Uses ATP for its monitoring "energy"
        - **SO, ATP is used for Activation tRNA**
        - **BUT, GTP is used to bind tRNA to ribosome**
    - tRNA activates and selects specific amino acids for protein synthesis
    - Individual enzymes are highly specific for one amino acid
      - No error checking occurs during the translation process on the ribosome
  - Ribosomal RNA **(rRNA or RNA polymerase I):**

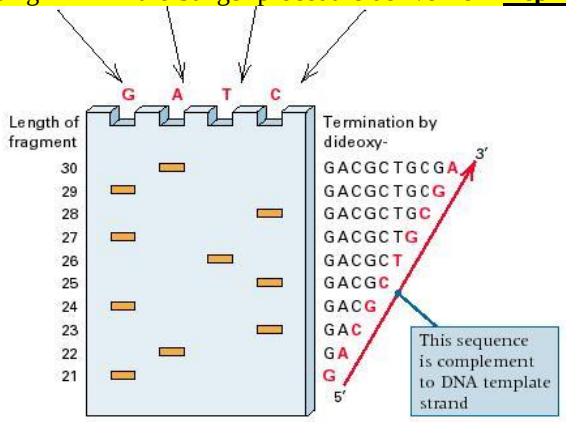
- **R for Rampant (OUT OF CONTROL)**
- **Made in the Nucleolus**
- Molecules are the major component of ribosomes, which are the physical and chemical structures on which protein molecules are actually assembled
- **rRNA is the most abundant of the three types of RNA (rRNA > tRNA > mRNA in abundance)**
  - mRNA is the largest (Massive mRNA, Rampant rRNA, and Tiny tRNA)

- Ribosomes:
  - Small structures found floating free in the cytoplasm (polyribosomes) that contain rRNA and protein
  - Translation (aka protein synthesis)
    - At a ribosome, amino acids are linked together in the order specified by mRNA to form a polypeptide or protein
    - **Have E, P, and A sites for Translation**
      - Come in on A site, shift to P site to be added to, and then bumped out on the E site
  - Ribosomes have enzymatic activity
    - They catalyze the formation of peptide bonds, which link amino acids to one another
  - Rough ER
    - **Carboxy-terminal of protein attaches to the RER????**
    - Some are attached to the cytosolic suface of the endoplasmic reticulum membrane
    - Proteins formed by ribosomes attached to the RER are destined for secretion from the cell, incorporation into the plasma membrane, or formation of lysosomes
    - Since all protein synthesis begins on free ribosomes, attachment of a ribosome to the ER requires the presence of a specific sequence at the amino end of the growing protein chain to signal the attachment of the ribosome to the ER
  - 70s ribosomes are the sites of protein synthesis (translation) in bacterial cells and chloroplasts
  - 80s ribosomes are the sites of protein synthesis (translation) in eukaryotic cells
  - **Most protein synthesis occurs on polyribosomes**
- Hydrolysis of DNA will yield:
  - Phosphoric acid
  - Deoxyribose (sugar)
  - Nitrogenous bases (A,G,T,C)
- Hydrolysis of RNA – yields the same stuff (but U instead of T and ribose instead of deoxyribose)
  - Ribose and uracil are the only differences between the products of RNA and DNA hydrolysis
- Another Q: Hydrolysis of nucleic acids produces pentoses, phosphates, amino acids, purine bases, pyrimidine bases
- Replication forks are sites at which DNA synthesis (replication) is occurring
- **Helicases** unwind the helix
- **Topoisomerases** act to decrease the degree of supercoiling of the helix, aiding in unwinding the DNA at the replication forks
  - DNA gyrase, a topoisomerse found in prokaryotes, in addition to reducing the supercoiling prior to replication induces a negative supercoil following replication
- **Primase**
- Reverse transcriptase:
  - Certain RNA viruses contain within the viral particle a unique RNA-directed DNA polymerase which is called reverse transcriptase
    - Building DNA from RNA
  - On infection, the single stranded RNA viral genome and the enzyme enter the host, and the reverse transcriptase catalyzes the synthesis of a DNA strand complementary to the viral RNA or mRNA (different question)
  - This enzyme is found naturally in certain viruses called retroviruses
    - These viruses in which the genetic information is carried on an RNA molecule
    - When one of these viruses infects a host cell, it uses this enzyme to make a complementary DNA (cDNA) copy of its genetic information which is then incorporated into the host DNA
    - cDNA Library
      - A collection of DNA sequences generated from mRNA sequences
      - This type of library contains only protein-coding DNA (genes) and does not include any non-coding DNA
      - *NOTE: The distinguishing feature of a cDNA library is the presence of multiple copies of RNA transcriptase
      - *NOTE: Reverse transcriptase is used *in vitro* to make cDNA from mRNA
    - The human immunodeficiency virus (HIV) the causative agent in AIDS, is a retrovirus
      - The **drug AZT (a thymidine analog) is a competitive inhibitor of the HIV reverse transcriptase**
      - NOT **Flurouracil – antineoplastic drug used in carcinoma pts to interfere with DNA and RNA**
      - **NOT Methotrexate – Antineoplastic drug that interferes with DNA synthesis, repair, and cellular respiration**
        - **Inhibits dihydrofolate reductase, inhibiting formation of THF, which inhibits thymidine synthesis, which inhibits DNA synthesis, etc.**
        - **Methotrexate works in S phase**

        - The wild-type reverse transcriptase seems to have a higher affinity for AZT and other base analogs
        - Reverse transcriptase is one of the enzymes used in genetic engineering, where it can be used to obtain a copy of a particular gene from the relevant mRNA
    - NOTE on viruses: **Certain viruses isolated in crystalline form have been found to be nucleoproteins**
        - *This didn't fit anywhere else in the document*
- Mutations
    - Nonsense
        - Worst
        - Results in termination of protein, usually mutation to a stop codon
    - Missense
        - Changed AA, but similar in strucure
    - Silent
        - Same AA, but codon was changed
        - **Usually in 3rd position of codon**
    - Frame shift
        - Results in entire misreading down-stream
        - Usually results in truncated protein
- Transition vs Transconversion
    - Transition = purine for purine
    - **Transconversion = purine for pyrimidine or vice versa**
- Genetic recombination experiments:
    - Depend heavily upon the action of **DNA ligase and restriction endonucleases**
        - *NOTE: Restriction enzymes are best described as site-specific endonucleases
    - Nuclease
        - Used to cleave both the DNA to be clones and a plasmid DNA
        - **The specificity of the nuclease is such that when mixed, the DNA to be cloned and the plasmid DNA will anneal (base pair) and can then be joined together by a DNA ligase**
    - The first organism used for DNA cloning was *E. Coli* and it is still the most common host cell
    - Bacterial cloning vectors – plasmids, bacteriophages, and cosmids
        - **Plasmid vectors suitable for cloning have 2 genes conferring resistance to different antibiotics (it's true!)**
    - Commercial products of recombinant DNA technology include:
        - Human insulin (for diabetes)
        - Anticoagulants (tissue plasminogen factor)
        - Erythropoietin for anemia
        - Human growth factor (for dwarfism)
    - Some other enzymes that are used in recombinant DNA technology include:
        - DNA polymerase I (not RNA polymerase) – fills in gaps in duplexes by step-wise addition of nucleotides to 3'end
        - Reverse transcriptase – makes a DNA copy of an RNA molecule
        - Exonuclease – removes nucleotides from 3' ends of a DNA strand
    - **DNA ligase, DNA polymerase I, restriction nucleases, reverse transcriptase are involved in gene cloning**
        - **RNA polymerase is not – Huh???**
    - Restriction Nucleases (Site specific Endonucleases)
        - Find specific sites to cut open in the DNA
        - **Usually work in dimers and create palindromic 5' to 3' segements**
        - Used for the Introduction of recombinant DNA into a bacterial cell
        - *NOTE: Restriction enzymes are best described as site-specific endonucleases
- Southern Blotting (**S for Same)**
    - The type of blotting used to identify DNA restriction fragments is Southern blotting
    - DNA-DNA Hybridization
- Northern Blotting
    - DNA-RNA hybridization (northe**RN)**
    - Which is used for mRNA
- Western Blotting **(Think Western society with their protein bars/shakes, etc.)**
    - Antibody-**Protein** Hybridization
- Southwestern Blotting
    - DNA-protein interaction
- ELISA (Enzyme linked immunosorbant assay)
    - Basically test the blood with an antigen, it it links with an antibody, it luminsces a bright color
        - HIV test
- PCR (Polymerase chain Reaction)

- **Used to synthesize many copies of desired DNA**
- Steps
  - Heat DNA to denature it
  - Then cool it with added premade primers
  - Then a heat stable DNA polymerase copies
    - Then repeat
- The polymerase chain reaction is most useful for amplifying a specific DNA sequence

➢ Sanger Methods
- You throw a bunch of **dideoxynucleotides, that lack OH at the 2' and 3' position**, and they are used to terminate DNA synthesis at specific bases
- Four separate reactions are carried out, when the dideoxynucleotide is incorporated, DNA synthesis stops, so each of the 4 reactions would yield a series of products extending from the primer to the DNA terminating dideoxynucleotide
- Products are then separated by electrophoresis and analyzed by autoradiography to determine the DNA sequence
  - Basic principles for sequencing DNA in the Sanger procedure derive from **Replication**



❖ **Proteins/Amino Acids**

➢ Proteins
- A polypeptide chain of ~100 or more amino acids linked by peptide bonds
- 10+ amino acids linked in a chain by peptide bonds form a polypeptide
- Proteins function as hormones, catalysts, structural elements, & oxygen carriers
  - NOT carriers of genetic information
- Proteins are able to buffer physiologic solutions over a wide range of pH because they contain many functional groups with varying pKs
- Deficiency in proteins may be indicative of: lack of vigor and stamina, weakness, mental depression, poor resistance to infection, impaired wound healing, slow recovery from disease
  - Primary structure
    - Amino acid sequence (linked together by covalent peptide bonds)
    - From N-amino terminal to carboxy terminal of the protein chain
      - **Always linked from N to C**
    - The primary structure of proteins is best described as the polymer formed by amide linkages between alpha-carboxyl group and alpha-amino groups
    - The Amide bond links amino acid residues to form proteins
  - Secondary structure
    - Refers to the spatial arrangement of a portion of a polypeptide chain determined by the amino acids present
    - The most common types of secondary structures are:
      - Alpha helix (coiled conformation of a peptide chain)
      - Beta pleated sheets (an extended, zigzag arrangement of a polypeptide chain)
      - Beta bends (reverse turns)
    - Secondary protein structures are stabilized by **hydrogen bonds**
  - Tertiary structure
    - Stabilized by **hydrophobic interactions,** (Non-Covalent) then hydrogen bonds
    - Refers to the **irregular folding** of a polypeptide chain
    - The overall 3D conformation of the polypeptide (globular, fibrous, and pleated sheet)
    - **Proline** contributes to the tertiary structure of a protein by **causing a bend** when it occurs in the primary sequence
    - **Cysteine** can stabilize the tertiary structure by **forming a covalent bond** in its side chain
  - Quaternary structure
    - Refers to the spatial arrangement of subunits in a protein consisting of >1 polpeptide chain

- Two EXs of proteins with quaternary structures are 1) hemoglobin and 2) Ab molecules found in blood
    - This is the level of protein structure in which 2+ individual polypeptides interact to form a noncovalent complex
- Protein Bonds
    - Noncovalent
        - Ionic, Hydrogen, and Hydrophobic
    - Covalent
        - Peptide (Amide)
    - X-ray diffraction
        - Requires a protein in crystalline form
        - Beam of x-rays is diffracted by the electrons around each of the atomic nuclei in the crystal and with an intensity proportional to the number of electrons around the nucleus
        - Another Q: The best method for determining the 3D structure of a protein is by x-ray diffraction
    - Electrophoresis
        - Used to separate various proteins based on **protein size and charge**
        - **Procedure that depends primarily on electrostatic net charge**
    - Ultracentrifugation
        - Separates and characterizes proteins **based on molecular weight and size**
- Peptide bond:
    - A specific type of amide bond
        - Because a **peptide bond is a form of an amide bond, amide bonds link amino acid residues to form proteins**
    - Covalently joins the alpha-carboxyl group of one aa and the alpha-amino group of another aa
        - Formation of peptide bond results from the **removal of a molecule of water** between the carboxyl group of one amino acid and the amino group of a second amino acid
    - Extremely stable and cleavage generally involves the action of proteolytic enzymes
    - Characteristics of peptide bonds:
        - No freedom of rotation around the bond
        - Has partial double-bond character – means it is shorter than a single bond and is therefore rigid & planar
        - Bonds involving the alpha carbon can rotate freely
        - Is generally a trans bond (instead of a cis bond)
        - Is uncharged but polar
        - Proline, due to formation of a tertiary amine, restricts the range of rotation of the α-carbon in the peptide bond
- Disulfide bond:
    - Another type of covalent bond that occurs in many proteins
    - Formed from the sulfhyrdyl group (SH) of each of two cysteine residues, to produce a cystine residue
        - (A residue is a single aa unit within a polypeptide chain)
    - It is widely thought that these strong, covalent bonds help stabilize the structure of proteins and prevent them from becoming denatured in the extracellular environment
    - EXs – insulin & immunoglobulins
    - Cysteine is the aa that can stabilize the 3° structure of some proteins via a covalent bond involving its side chain

➢ Protein Denaturation
- Denaturation usually destroys hydrogen, hydrophobic, & electrostatic bonds (but not covalent bonds)
- Characterized by
    - Loss of native conformation, secondary and tertiary structures
    - Loss of biological activity
    - Breakage of H bonds

➢ Amino Acids (AAs) – I need pictures/diagrams
- Have a central or alpha carbon to which is attached a H atom, a COOH carboxyl group, an NH2 amino group, and a 4th group, R—which determines the AAs identity
    - Except Glycine, which has 2 H groups (in other words, R = H for glycine)
- Used for Energy
    - **First the AA loses its amino group and is converted to alpha-keto acids that can enter Kreb's cycle**
        - **An alpha-keto acid is similar to an AA, except that is has O_2 rather than an amino group bonded to its alpha carbon**
        - When proteins are broken down for energy, most of the energy is derived from the oxidation of the alpha-keto acids (Pyruvate, Oxaloacetate, and alpha-ketoglutarate)
- Negative nitrogen balance (nitrogen output exceeds intake) may be caused by a dietary lack of essential AAs
    - Another Q: Total urinary nitrogen excretion is least when an individual is on a diet containing adequate fat & CHO but no protein
- Higher temperatures facilitates the increase intake of salts

- Metabolism of carbohydrates serve as a principal source of carbon for nonessential AAs
- All are stereoisomers (aka optical isomers or enantiomers) EXCEPT Glycine
  - All have a chiral center (4 different groups attached to a central carbon)
  - Non-superimposable mirror images of each other
  - **Glyceraldehyde**
    - The reference compound for naming all other compounds is the smallest sugar w/ an asymmetric carbon
    - (An asymetric carbon is characterized by having 4 different groups attached to it)
    - **In other words, the arrangement of sugars into D- and L- configurations is based upon their resemblance to D- and L-glyceraldehyde**
    - Established by x-ray diffraction analysis
    - **All AAs are "L" designated compared to glyceraldehydes (except for some "D" in ABX and bacteria cell walls)**
      - **(aLL for L)**
- Grouped by their "R" Group (5)
  - Nonpolar, aliphatic R groups:
    - alanine, valine, leucine, isoleucine, glycine and proline
  - Aromatic (generally nonpolar):
    - phenylalanine, tyrosine, and tryptophan
      - Forming tyrosine from phenylalanine only requires hydroxylation of the benzene ring at carbon 3
        - That is why it is most easily converted in the human body
  - Polar, unchared R groups:
    - serine, threonine, cysteine, methionine, asparagines, and glutamine
      - **(the polarity of cysteine and methionine is contributed by their sulfur atom**, and that of asparagines and glutamine by their amide group)
  - Negative charged:
    - **aspartate and glutamate (Aspartic ACID and Glutamic ACID)**
  - Positively charged: **(Think HAL plays the Bass)**
    - lysine, arginine, and histidine
      - **Arg and Lys have an extra NH3** and are found in large amounts in **Histones**, which bind to negatively charged DNA
      - **Arg is the most basic AA
- Essential vs. Nonessential
  - Essential AAs (9):
    - **PriVaTe TIM HArgLL**
    - **Phenylalanine, Valine, Tryptophan, Threonine, Isoleucine, Methionine, Histidine, Arginine, Lysine, Leucine**
      - **Arginine and Histidine are required during periods of growth
      - Methionine is a thio-ether
      - One question lists groups of 3 AAs & asks which group contains only essential AAs
      - Phenylalanine
        - Is an essential AA needed for optimal growth in infants and for nitrogen equilibrium in adults
      - Tryptophan
        - **Forms 5 HT (serotonin), melatonin, niacin, and the nicotinamide moiety of NAD and NADP**
      - NOTE: proteins obtained from corn are "poor" in nutritional values for man because they are low in lysine & low in tryptophan – *both are essential AAs, get the drift?*
  - Nonessential AAS (11):
    - **Glutamate, glutamine, proline, serine, glycine, aspartate, asparagines, alanine, cysteine, & tyrosine**
    - Ten of the nonessential amino acids contain carbon skeletons that can be derived from glucose
    - Are synthesized in mammals and generally are those with simple pathways
    - They are not needed in the diet
    - Can be synthesized from:
      - The corresponding alpha keto acid
      - An alpha amino acid (as the NH_3 donor)
      - A specific transaminase enzyme
        - And the coenzyme pyridoxal phosphate (vitamin B6) can help synthesize Nonesential AAS.
      - These AAs include alanine, aspartate, and glutamate
    - The other nonessential AAs are synthesized by amidation (glutamine and asparagine)
    - **Glutamate, glutamine, proline, arginine, serine, glycine, aspartate, asparagines, alanine, cysteine, & tyrosine**

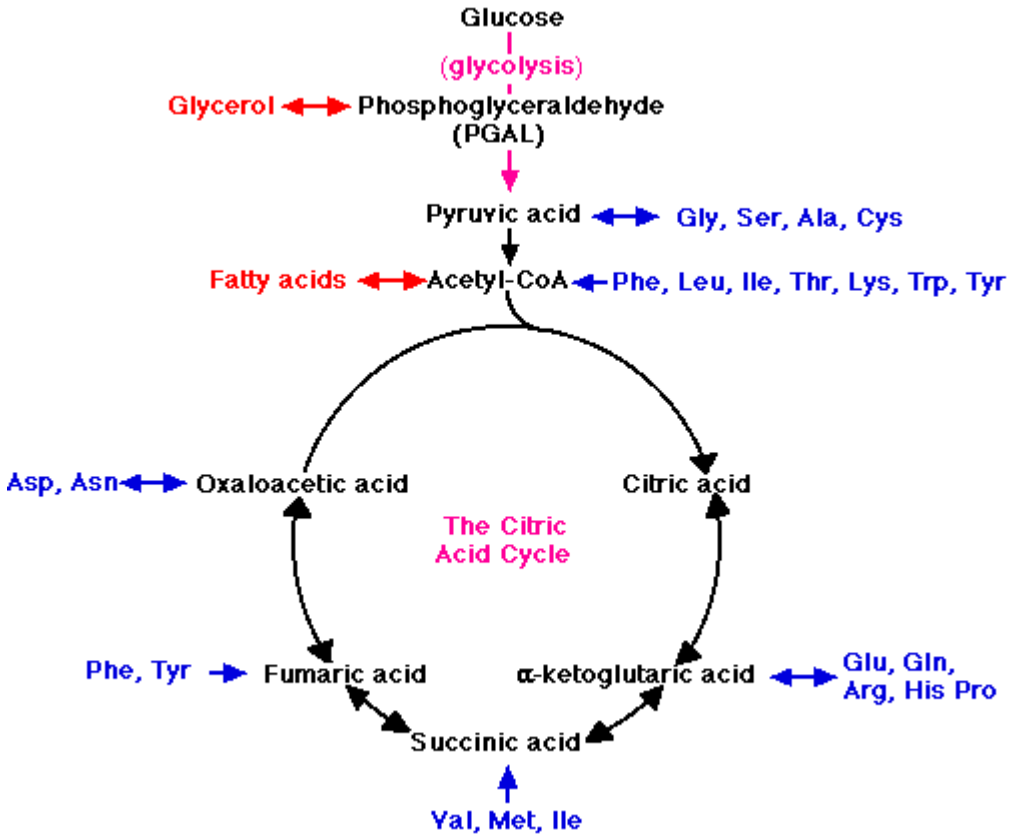
- **Cysteine and tyrosine become essential when their precursors, methionine and phenylalanine, are restricted**
  - In a phenylketonuric person, tyrosine is an essential aa
- Cysteine and methionine have sulfur containing side chains
- Cysteine
  - Although its carbon skeleton can be formed from carbohydrates, requires the essential amino acid **methionine** to supply the sulfhydryl group
- Tyrosine
  - Is synthesized by hydroxylation of the essential amino acid phenylalanine
    - Presence of tyrosine lessens the need for phenylalanine
    - Another Q: Phenylalanine can most easily be converted to tyrosine in the human body
  - Synthesizes dopamine, the thyroid hormones (triiodothyronine and thyroxine), melanin, norepinephrine and epinephrine
  - Dopamine is synthesized in two steps from tyrosine
- **Alanine**
  - **can be synthesized by transamination directly from pyruvic acid, using glutamic acid as an amino group donor**
- Glycine
  - Glycine is the immediate precursor for **creatine, purines & porphyrins**
- Serine
  - **Has a hydroxyl group that often participates in NZ reactions**

- Classified as ketogenic, glucogenic, or both according to the nature of their metabolic end-products:
  - Ketogenic:
    - Amino acids whose catabolism yields either acetoacetate or one of its precursors, acetyl CoA or acetoacetyl CoA
      - **EXs – leucine and lysine**
  - Glucogenic and ketogenic:
    - Amino acids whose catabolism yields both ketogenic and glucogenic end-products
      - EXs – tyrosine, isoleucine, phenylalanine, and tryptophan
  - Glucogenic:
    - **Amino acids whose catabolism yields pyruvate or one of the intermediates of the citric acid cycle (alpha ketoglutarate, oxaloacetate, fumarate, and succinyl CoA)**
      - EXs – the remaining amino acids
- **Synthesis of Amino Acids:**
  - Alpha ketoglutarate gives rise to **glutamate (think "a" comes first 'ate' before 'ine')**
    - **A-ketoglutarate + alanine → *glutamate* + pyruvate**
    - which in turn is the precursor of **glutamine, proline,** and **arginine**
  - 3 phosphoglycerate gives rise to **serine**
    - which, in turn, is the precursor of **glycine** and **cysteine**
  - Oxaloacteate gives rise to **aspartate**
    - which in turn is the precursor of **asparagines, methionine, threonine** and **lysine**
      - Threonine along with pyruvate is the precursor of isoleucine
  - Pyruvate gives rise to **alanine, valine, leucine,** and **isoleucine**
    - *Isoleucine can be formed by either pyruvate or threonine
  - Phosphoenolpyruvate and erythrose 4 phosphate produces shikimate
    - which is converted to Chorismate
      - Chorismate gives rise to **tryptophan, tyrosine and phenylalanine**
        - Tyrosine is synthesized from phenylalanine in humans
  - Ribose 5 phosphate gives rise to **histidine**
- Catabolism of Amino Acids????
  - **The first step in the catabolism of most AAs involved the removal of the alpha amino group**
  - Once removed, this nitrogen can be incorporated into other compounds or excreted
  - The enzymes that catalyze these reactions are known as transaminases or aminotransferases

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

-
  - **Transamination:**
    - Involve the transfer of amino group from one AA to an alpha keto acid
      - **Glutamate and alpha ketoglutarate** are often involved in these reaction, serving as one of the amino acid/alpha keto acid pairs
      - ALL transaminases require the coenzyme pyridoxal phosphate (PLP) = vitamin B6
    - **Transamination of the alpha amino to a keto acid is the 1st step in the catabolism of many amino acids**
  - Pyridoxal phosphate (PLP) – derived from vitamin B6 & serves as the cofactor for these reactions (required in all transaminase reactions)
    - Vitamin B6 (**pyridoxal phosphate**) acts as a coenzyme in **transamination** reactions
    - PLP functions as the intermediate carrier of amino groups at the active site of aminotransferases
    - It undergoes reversible transformations between its aldehyde form, pyridoxal phosphate (PLP) which can accept an amino group, and its aminated form, pyridoxamine phosphate (PMP) which can donate its AA to an alpha keto acid
  - **Glutamate Dehydrogenase: (Top of the Urea Cycle Chart)**
    - **Catalyzes the oxidative deamination of glutamate to form alpha ketoglutarate, using either NAD+ or NADP+ as an electron acceptor**
    - The reversible reaction has major function in both the synthesis and degradation of glutamic acid and via transaminases, other AAs as well
    - **These reactions (oxidative deamination) occur primarily in the liver and kidney and provide alpha keto acids (for energy) and ammonia (source of nitrogen in urea synthesis)**
  - Histidine is deaminated by histidase to form ammonium ion (NH_4^+) and urocanate
  - Serine and threonine are deaminated by serine dehydratase
    - **Serine is converted to pyruvate**
    - Threonine to alpha ketobutyrate; NH_4^+ is released
  - Glutaminase deaminates glutamine to glutamate and NH_4^+
  - Asparaginase deaminates asparagines to aspartate and NH_4^+
    - **In synthesis, you add the amine group to the acid ('-ate') to make it an ('ine')**
    - **In catabolism, its backwards, you pull off amino group from the ('ine') and get the acid for (ketone body) energy and ammonia goes to the urea cycle**

- Amino Acid Derivatives
  - **Phenylalanine**→Tyrosine→
    - Thyroxine
    - Dopa→Dopamine→
      - Melanin
      - NE→Epi
  - **Tryptophan**→
    - **Nicin→NAD+/NADP+**
    - **Serotonin (5-HT)**
    - Melatonin
  - **Histidine→**
    - Histamine
  - **Glycine→**
    - **Porphyrin→Heme**
  - **Arginine→**
    - **Creatine**
    - **Urea**



- Collagen
  - General facts:
    - **Collagen is 35% glycine**, 21% proline, & 11% alanine (hydroxyproline & hyroxylysine are also present – see below)
      - The unique aa composition of collagen is reflected in the high content of **glycine, proline, & hydroxyproline**
        - **Hydroxyproline** can be used as an estimatation of the amount of collagen present in a tissue of meat
        - Collagen is Unique because of its Hydroxyproline
    - Mature collagen lacks aromatic & sulfur-containing amino acids
    - The amino acid composition of mammalian collagen (Type 1) is characterized by the presence of
      - glycine (nearly 1/3 the total # of aa residues)
      - hydroxyproline & hydroxylysine
      - no sulfur-containing amino acids
  - The basic structural unit of collagen is tropocollagen
    - Tropocollagen is the longest known protein and is formed from procollagen, which is secreted by fibroblasts into the Extracellular space
  - The Process
    - Procollagen peptidases cleave terminal regions of procollagen, which transforms it into tropocollagen which then aggregates to form collagen fibrils
    - The fibrillar structure is reinforced by the formation of covalent lysine-hydroxylysine cross-linking between tropocollagen molecules
    - Tropocollagen is also present in reticulin, which is a component of reticular fibers
  - Almost 1/3 of all proteins found in the body is collagen
    - Collagen is the most abundant protein (by weight) in the human body
  - Collagen biosynthesis
    - **Intracellular events include**
      - **translation, hydroxylation, glycosylation, and peptide bond formation**
    - Extracellular events include
      - Intermolecular cross-linkage
        - **Fibrin Formation**
        - **Another Q: Intermolecular cross-linkage is a collagen synthesis post-translational event occurring extracellulary**
  - Mitochondria is NOT involved in Collagen synthesis, but RER, Golgi are!!

- Each collagen molecule consists of **3 polypeptide chains which are wound tightly** around each other to give a triple helix
  - This gives the molecule a structure which is very resistant to stretching, a vital property, for example, for its functions in tendons and as a component of the matrix of bone and cartilage
- Vitamin C influences the formation of collagen, which is the organic matrix found in dentin and cementum
  - Another Q: **Collagen** is the major protein produced by **odontoblasts** & is contained in the organic matrix of dentin
- Another Q: Increased aging is associated w/ increased crosslinking of collagen
- Collagen and reticular fibers make up the stroma of all lymph tissues except the thymus
  - Hydroxyproline and hydroxylysine
    - Are nonstandard AAs that are present in few proteins other than collagen
      - For this reason their concentration in a particular tissue is a good estimate of collagen content
    - Are not used directly in the reactions of protein synthesis
    - Are formed by the hydroxylation of proline and lysine
      - Proline becomes hydroxylated in the synthesis of collagen
      - Another Q: The hydroxylation occurs after translation
      - **Another Q: The hydroxylation involves α-ketoglutarate, ferrous iron, oxygen, & vitamin C (ascorbic acid)**
        - **Does not involve ergosterol**
      - Another Q : Procollagen proline hydroxylase & procollagen lysine hydroxylase require vitamin C for their activity
      - Another Q: The best explanation of why vitamin C is essential in the diet of patients recovering from periodontal surgery is that it is an essential cofactor in the hydroxylation of proline
      - Another Q: Vitamin C deficiency primarily affects connective tissue
- Collagen has a trihelical structure
- The molecular weight of collagen is above 100,000 – **tropo is the longest known protein**
- Destruction of collagen can be caused by collagenases
- Collagen contains both hydroxyproline and hydroxylysine residues

➢ Elastin:
- Is rich in small, nonpolar aliphatic residues such as glycine (1/3 of all residues), proline, alanine, valine, leucine, and isoleucine
  - **Elastin & collagen are both ~1/3 glycine**
- It contains a small amount of hydroxyproline????
- Is a CT protein with rubber-like properties, in contrast to collagen, which forms high tensile strength fibers
- Can stretch several times their normal length – gives these fibers the capacity of returning to their original lengths after being stretched
- Fibers are found in the skin, ligaments and in the walls of arteries where their elastic properties are important
- The polypeptide subunit of elastin fibrils is **tropoelastin (as opposed to tropocollagen)**
- Elastin fibers are formed as a 3D network of cross-linked polypeptides
  - The **crosslinks involve lysine and oxidized lysine residues (allysine),** which are covalently linked to produce a desmosine crosslink
    - **NOT Disulfide crosslinking == Covalent Crooslinking for Collagen**
  - The **oxidation of lysine residues in both collagen and elastin is an extracellular process catalyzed by lysyl oxidase a copper requiring enzyme**

➢ So, collagen, elastin, and reticulin are types CT fibers; chitin is not

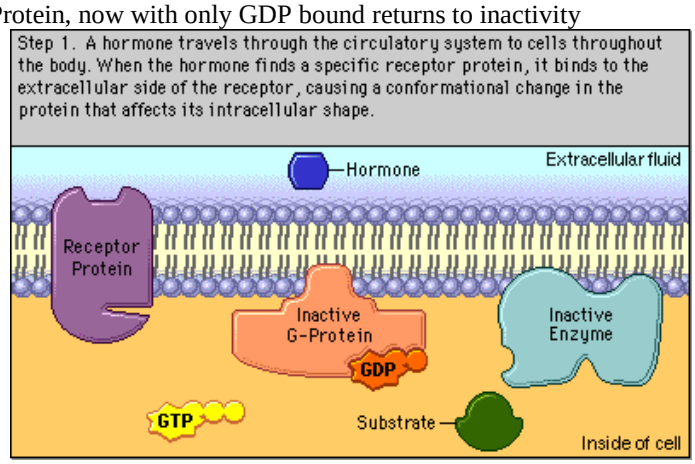
➢ Histones:
- Fairly low molecular weight and contain a large portion of the **simple, positively charged AAs arginine and lysine (Part of HAL playing the Bass→ Lysine, Arginine, and Histidine)**
- Chromatin of eukaryotic cells consists of DNA complexed with histones in nucleosomes
- There are five major classes of histones: H1, H2A, H2B, H3, H4
  - H1 connects the nuclesomes together in a string like, the others bind the DNA to form the blocks of histone
- Because of their positive charge, they form ionic bonds with the negatively charged DNA
- Histones help neutralize the large negative charge of the DNA phosphate groups
  - The major function of histones is to stabilize DNA in a compact form
- Histones are proteins rich in basic amino acids, such as lysine and arginine, which bind strongly to DNA

➢ Chromatin:
- Is the chromosomal material that is randomly dispersed throughout the nucleus
- Consists of fibers that contain protein (histones) and DNA in **approximately equal masses**
- These histones package and order the DNA into structural units called nucleosomes
  - Nucleosomes are repeating subunits of chromatin, consisting of a DNA chain coiled around a core of histones
- Gene Regulatory Proteins
  - Nonhistone proteins found in chromatin

        - These proteins are important in controlling the interactions of DNA with other molecules
    - Activation of DNA for replication or transcription requires break up of the nucleosome structure
        - Phosphorylation of serine and threonine residues in histones is part of the process for replication, while acetylation of lysine residues in the histones is used for transcriptional activation
- Plasma proteins:
    - Act as buffers that help stabilize the pH of the internal environment
    - Intracellular proteins absorb H^+ generated by the body's metabolic processes
    - Conversion of tissue protein to plasma proteins occurs in the liver
    - The three major types of plasma proteins are albumin, globulins, and fibrinogen
        - Globulin: (alpha, beta, and gamma):
            - **Main function of plasma globulin is to provide body for both natural and acquired immunity**
                - Alpha and beta function as transport molecules
                - **Gamma globulins (immunoglobulin) are circulating antibodies that act in the immune response**
        - Fibrinogen
            - A blood clotting protein
            - Synthesized in the liver (also prothrombin)
        - Albumin:
            - Simple Protein
            - Transports many small molecules (that otherwise are usually absorbed) in the blood (for example, bilirubin, calcium, Na+, Cl-, progesterone, and drugs)
                - Transports free FAs in human blood
                    - The body uses 3 mechs for transporting FAs in the blood
                        - 1) FAs to albumin
                        - 2) Chylomicrons (Cholesterol binds to fat and phospholipids to form chylomicrons)
                        - 3) Ketone bodies (aceto-acetate and beta hydroxyl butyrate)
                - Most bound **calcium** is transported in blood as an **albumin** complex
                    - Various substances are transported in the blood as protein complexes, Calcium/Albumin is an example
            - Is also of primary importance in maintaining the oncotic pressure of the blood
                - **Albumin is the major contributor to colloid osmotic pressure**
                - This is because, unlike small molecules such as Na+ and chloride, albumin is impermeable across the capillary membrane
            - Is synthesized in the liver
            - **Albumin** is most commonly associated with transport of **free fatty acids** in human blood
            - Another Q: Free fatty acid level in blood is affected by serum albumin levels, the anti-lipolytic action of insulin, and intestinal absorption of fatty acids (not by the action of calcitonin)
            - **Albumin is most commonly associated with transport of free FAs and bile acids in the blood and Colloid Osmotic Pressure**
    - Other plasma proteins include:
        - **Lipoproteins (chylomicrons, VLDL, LDL, HDL)**
            - Responsible for the transport of triglycerides, phospholipids, cholesterol, and cholesterol esters
        - Transferrin
            - The plasma protein that transports ferrous iron
            - Another Q: **The most abundant form of iron in human blood plasma is found associated with transferrin**
            - Another Q: After being absorbed from the intestine, iron is carried through the blood, associated with transferrin
        - Prothrombin
            - A blood clotting protein
            - Phospholipids and proteolysis are required for blood clotting
- Myoglobin:
    - An oxygen-storing pigment found in muscle
    - Chemically very similar to Hb as it is made up of a polypeptide chain associated with an iron-containing heme group
        - Myoglobin is also called muscle hemoglobin
    - **Has a much greater affinity for oxygen than Hb**
    - This makes it well suited for its biological function within muscle cells, **which is to store oxygen and make it available to the mitochondria**
    - Myoglobin is, in fact, much better at this than Hb because its very high affinity for oxygen at low pO_2 enables it to bind and store oxygen effectively
- Cytochrome:
    - A protein which is combined with another chemical group containing iron or copper
        - Fe is an essential element found in all cytochromes
        - Heme and prophyrine

- Found on the membranes inside mitochondria of chloroplasts
- The electron transport chain (ETC) is the final common pathway by which electrons derived from different fuels of the body flow to oxygen
- Electron transport and ATP synthesis by oxidative phosphorylation procede continuously in all cells of the body that contain mitochondria – cells in the blood do NOT contain an active mitochondrial electron transport system
- Receive electrons from the reduced form of coenzyme Q (ubiquinone)
- **Each *CYTOCHROME* contains a heme group made of porphyrin ring containing an atom of iron**
- **CYTOCHROME = IRON + HEME + PORPHYRIN , IRON for electron transport**
- This cytochrome iron atom is the electron carrier and is reduced when the cytochrome accepts an electron (Fe^{3+}, Fe^{2+})
- Are distinguished by differences in their light-absorption spectra and are designated b, c1, c, a3, & a
-
- These differences are a result of the heme prosthetic group
  - **The prosthetic groups of cytochromes have four five-membered, nitrogen-containing rings in a cyclic structure called a porphyrin**
    - The four nitrogen atoms are coordinated with a central Fe ion that can be either Fe^{2+} or Fe^{3+}
    - These porphyrins are also found in the heme proteins hemoglobin and cytochrome P450
  - Iron-porphyrin protein structures are components of cytochromes
- Cytochromes a3 & a – the terminal members of the ETC
  - They exist as a complex, which is called Complex IV or cytochrome oxidase complex
- **Glycine and succinyl-CoA are the precursors to the biosynthesis of these rings**
  - **NOTE: Glycine is the immediate precursor for creatine, purines & porphyrins**

➢ G-proteins
- SUMMARIZE http://en.wikipedia.org/wiki/G_protein, & include the answer to the 2000 Exam, Q 110
  - The biologically active conformation of trimeric G-protein requires the alpha-subunit to bind GTP
    - Steps:
      1. Hormone binds extracellularly and causes conformational change intracellulary
      2. Then the Inactive G Protein moves laterally and interacts with the "changed" receptor protein
         - This causes a change of so GDP is kicked off and GTP is then bound and Activates the G Protein
      3. Then the active G Protein moves back laterally on the membrane, and with its terminal Pi from GTP activates an enzyme
      4. The Active Enzyme is now able to catalyze other reactions, i.e. 2nd messengers
      5. The G Protein, now with only GDP bound returns to inactivity



❖ **Carbohydrates**

➢ Fructose, glucose & glyceraldehyde are all monosaccharides; **amylose is not**

➢ Another Q: Saccharin (Nutri-sweet) is a non-nutritive, non-cariogenic sweetener

➢ Monosaccharides:
- Common monosaccharides – fructose, galactose, glucose, mannose, ribose, and xylose
- The simplest of carbohydrates, which are classified according to the # of carbon atoms they contain:
  - Trioses: those with three carbons, EX – glyceraldehydes and dihydroxyacetone
  - Tetroses: four, EX – erythrose
  - Pentoses: five, EX – ribose
  - Hexoses: six, EX – glucose, fructose
    - **Fructose has 1 anomeric carbons present**
      - **BUT Sucrose is the sugar that is NOT a reducing sugar**
      - Naturally occuring fruit sugar D-fructose has a specific rotation of -88.5°.
        - It is a sugar in spite of the negative rotation because of its structural relationship to D-glyceraldehyde
- Aldoses

        - Monsaccharide with an aldehyde as their most oxidized functional group
        - For example glyceraldehydes
    - Ketoses
        - Those with a keto group as their most oxidized functional group
            - For example dihydroxyacetone
    - Naming
        - Based on the absolute configuration of glyceraldehydes
        - **The symbols L and D refer to the absolute configuration of the four consitituents around a specific chiral carbon (asymmetric carbon) in monosaccharides and AA**
        - In a Fisher projection the D form has the hydroxyl group on the right, the L form has it on the left
        - **Sugars of the D form, which are related to D-glyceraldehyde, are the most common in nature**
            - **Don't get clowned → AAs are mostly L form**
- Disaccharides:
    - A carbohydrate whose molecules contain two sugar units
        - Maltose:
            - Consists of two glucose molecules jointed together by a reaction **(condensation reaction)** in which a molcules of water is removed
            - This reaction produces a bond between two glucose molecules call a **glycosidic bond**
            - The intestinal enzyme **maltase** promotes the conversion of maltose into glucose
                - Maltose must be digested before being in a form that can be absorbed by enterocytes
        - Lactose:
            - Consists of glucose and galactose
            - The intestinal enzyme **lactase** promotes the conversion of lactose into glucose and galactose
        - Sucrose:
            - Consists of glucose and fructose
                - **Fructose has 1 anomeric carbon**
            - **Is a glycoside to a-D-glucopyranosido-B-D-fructofuranoside**
            - The intestinal enzyme **sucrase (invertase)** promotes the conversion of sucrose into glucose and fructose
- Carbohydrate Digestion
    - Salivary Amylase
        - Starts digestion, hydrolyzes the alpha 1,4 linkages to give maltose, maltotriose, and alpha-limit dextrans
    - Pancreatic amylase
        - Highest concentration in duodenal lumen, hydrolyzes starch to oligosaccharides, maltose, and maltotriose
    - Oligosaccharide hydrolases
        - At brush border of the intestine, **the rate-limiting step in carbohydrate digestion**, produce monosaccharides (glucose, galactose, and fructose)
    - The final digestion of these substances (disaccharides) to absorbable monosacharides is completed by enzymes of the small intestine (maltase, sucrase, and lactase).
        - These monosaccharides can then be absorbed by enterocytes
- Monosaccharides can be linked by glycosidic bonds to create larger structures (disaccharides, oligosaccharides, and polysaccharides)
    - These bonds form when the hydroxyl group on the anomeric carbon of a monosaccharide reacts with an -OH or -NH group of another compound (typically an alcohol, purine, pyrimidine, or in this case another sugar)
    - Maltose, lactose and sucrose consists of monosaccharides joined by an O-glycosidic bone
        - **If oxygen is involved, this bond is classified as O-glycosidic, if nitrogen is involved this bond is classified as N-glycosidic**
- Polysaccharides (aka 'glycans'):
    - Carbohydrates which are polymers of monosaccharides
    - Made up of many sugar units joined by condensation reactions (which results in glycosidic bonds)
        - Polysaccharides are converted to monosaccharides by hydrolysis of glycosidic bonds
    - Since they have large molecules, they are insoluble
    - Their main functions in living organisms are to act as storage molecules (starch and glycogen) or as structural materials (cellulose)
    - Homopolysaccharides (starch, glycogen, dextrans, and glucans) contain only a single monosaccharide species
    - Heteropolysaccharides (glycosaminoglycans) contain a number of different monosaccharide species
    - The two most important storage polysaccharides are starch and glycogen
        - Starch:
            - A large, insoluble carbohydrate which forms an important energy store in plants
            - It is a polymer and consists of a large number of alpha glucose molecules joined together by condensation reactions

- It consists of two main components which may be present in different proportions
  - Amylose:
    - Is unbranched & forms long straight chains (alpha-1,4 linkages)
  - Amylopectin:
    - A glucose polymer (alpha-1,4 linkages) with highly branched chains (alpha-1,6 linkages)
  - **Both amylose and amylopectin are rapidly hydrolyzed by alpha-amylase, which is secreted by the parotid glands and the pancreas**

- Glycogen:
  - 1,4 = glucose residues linked in glycosidic bond (sugar to o sugar)
  - 1,6 = branching in glycosidic bond
  - More highly branched (with alpha-1,6 linkages) and very compact
    - The predominant linkages between glucose units are alpha-1,4 linkages (these linkages make linear chains)
  - Carbohydrate is stored in the body principally as glycogen
  - The two major sites of glycogen storage are the liver & skeletal muscle
    - Another Q: The major storage form of carbohydrates in the liver is glycogen
    - **Glycogen is the CHO in highest concentration in resting muscle**
  - Glucose units of glycogen can enter the glycolytic pathway after removal by the action of glycogen phosphorylase
  - The cleavage of glycogen beyond a branching point requires the activity of **glucantransferase and amylo-alpha-1,6 glucosidase**

- Dextrans:
  - Water soluble, High molecular weight Polysaccharides of glucose obtained from yeast and bacteria
  - Dextrans are produced from sucrose (by *S. mutans*)
  - Is a sticky polymer of glucose molecules linked together in alpha 1-6 linkages with some **alpha 1-3 branches**
  - It is produced outside of bacterial cells by the enzyme **dextran sucrase (glycosyl transferase)**
    - **Substrate for GTF is sucrose (glucose and fructose)**
  - This enzyme **splits sucrose into glucose and fructose and links the glucose molecules into a dextran polymer**.
  - The dextran is deposited as a thick **glycocalyx** around the cell and seems to be essential for the cariogenicity of *S. mutans*
    - **The glycocalyx is located extracellularly**
  - Dextran-like glucans are extracellular polysaccharides synthesized by cariogenic streptococci in the presence of excess sucrose

- **Levans (fructans):**
  - Also increase the adhesion of bacteria to surfaces of the teeth and promote the formation of dental plaque
  - **A polyfructose synthesized by plaque bacteria**
  - **Stimulator of B cells and an individual with periodontal disease exhibits greater response to this polysaccharide than do normal control individuals**
  - A soluble polysaccharide found in dental plaque that is formed from the fructose moiety of sucrose by the enzyme **levan sucrase**
  - Considered to be reserve nutrients for bacteria

- Polymer and their components??
  - Dextran → Sucrose
  - Levan → Sucrose (Fructose moiety of sucrose)
  - Glycogen → UDP-Glucose
  - Glycogen → Fructose
- Reducing Sugars:
  - Lactose, Maltose, Glucose, Galactose, and Fructose
  - Contain one free anomeric carbon that can be oxidized
    - **A fructose molecule has one anomeric carbon present**
  - The anomeric carbon itself becomes oxidized
  - **If the oxygen on the anomeric carbon (the carbonyl group) of a sugar is not attached to any other structure, that sugar is a reducing sugar**
  - A reducing sugar can react with chemical reagents and reduce the reactive component
  - This reaction is the basis of a reducing sugar test (that is, free glucose test), which was classically used by clinical laboratories to screen for diabetes and other inborn errors involving the inability to metabolize other reducing sugars
  - Most current clinical tests for blood glucose utilized glucose oxidase-linked reactions
  - **Some carbohydrates convert Cu2+ ions to Cu+ ions; this property is related to their ability to act as a reducing agent**
    - **Remember the reducing agent gets oxidized and the oxidizing agent gets reduced**
  - **Because the reducing groups of both glucose and fructose are involved in the glycoside bond,**

- **Sucrose is not a reducing sugar.**
  - **In other words, sucrose contains no free anomeric carbon**

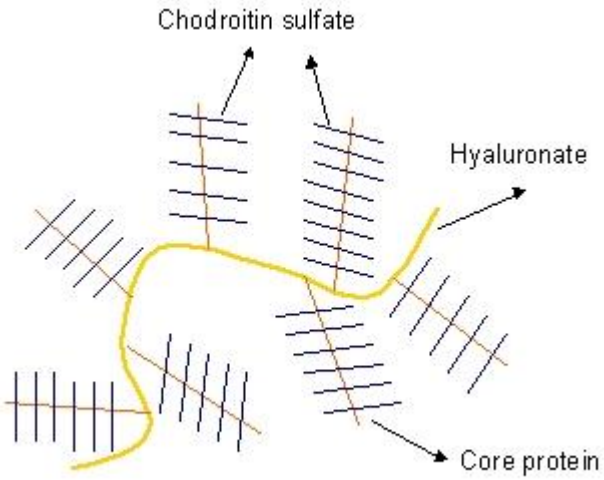
- Glocusuria
  - The presence of glucose in the urine
  - Can be caused by low insulin levels, high blood sugar levels, impaired tubular reabsorption, or a high GFR
- Glycosaminoglycans (GAGs):
  - **Contain mostly carbohydrate (95% or more)**
  - **Most abundant heteropolysaccharide in the body**
  - Are long unbranched polysaccharides containing a repeating disaccharide unit
    - ½ of the disaccharide is always an amino sugar derivative, either NAM or NAG
      - *** Bacterial cell walls contains a heteropolysaccharide made up of alternating NAG and NAM units
    - The other ½ is usually a uronic acid, such as glucuronic acid, giving a negative charge
  - GAGs are highly negatively charged molecules, with extended conformation that imparts high viscosity to the solution
  - Located primarily on the surface of cells or in the extracellular matrix
  - Along with the high viscosity of GAGs comes low compressibility, which makes these molecules ideal for a lubricating fluid in the joints
  - At the same time, their rigidity provides structural integrity to cells and provides passageways between cells, allowing for cell migration
  - GAGs function as important structural components of CT (which includes adipose tissue, cartilage, and bone as well as collagenous, elastic, and reticular fibers)
  - **Most important physicochemical property of CT which is regulated by its mucopolysaccharide molecule is Viscosity**
- The extracellular space
  - In animal tissues is filled with a gel-like material, the extracellular matrix, also called ground substance, which holds the cells of a tissue together and provides a porous pathway for the diffusion of nutrients and oxygen to individual cells
    - Chondroitin sulfate & hyaluronic acid are components of extracellular matrix
      - **Hyaluronidase** is most likely to promote depolymerization of the ground substance or Extracellular Matrix (different Q)
  - The ground substances is composed of an interlocking meshwork of heteropolysaccharides (glycosaminoglycans) most covalently linked to protein forming proteoglycans and fibrous proteins

GAG	Localization	Comments
Hyaluronic acid	Synovial fluid, vitrous humor of the eye, ECM of **loose CT**	Large polymers, serves as a lubricant and shock absorber
Chondroitin sulfate	Cartilage, tendons, ligaments and aorta	**Most abundant GAG of extracellular matrix**
Heparin sulfate	Basement membranes, components of cell surfaces	Contains higher acetylated glucosamine than heparin
Heparin	Component of intracellular granules of mast cells that line the arteries of the lungs, liver and skin	**Serves as an anticoagulant**
Dermatan sulfate	Skin, blood vessels, heart valves	
Keratan sulfate	Cornea, bone, cartilage aggregated with chondroitin sulfates	**Most heterogenous GAG**

- Which one is NOT a GAG???
  - **The are all Sulfates, Except, Heparin and Hyaluronic Acid**
  - So know all of the above!!!
  - Hyaluronic acid/Hyaluronate –
    - Is a repeating polymer of a disaccharide of glucuronic acid and N-acetylglucosamine
    - Is a lubricating material in the synovial fluids of joints such as the elbow or knee
    - Acts as the cement substance of tissue
    - Synthesized in the golgi apparatus
    - **is a highly polar polyanion**
    - **Is unique among the GAGs in that it contains no sulfur and does not covalently link to protein to form proteoglycans**
    - Is found in extracellular matrix, and is a very long filament structurally
      - So it does not have compact folded structure
    - **Another Q: Depolymerization of ground substance occurs via hyaluronidase → increase MOBILITY (not collagenase)**
      - Hyaluronidase is an enzyme that hydrolyzes hyaluronic acid

- Chondroitin sulfate:
  - Primarily found in **cartilage**, however, small amounts are found in bone
  - Fxns as part of the ECM
  - Is a polymer of a repeating unit comprising alpha (1-3) linked disaccharide of glucuronic acid and N-acetylgalactosamine
    - Galactosamine is largely sulfated on the hydroxyl of carbon 6
- Keratan sulfate (aka keratosulfate):
  - Is found in the cornea of the eye and in cartilage
    - **Occurs primarily in cartilage**
  - Consists of alternating units of sulfated N-acetylglucosamine and D-glucuronic acid
- Heparin sulfate:
  - **Occurs in the cell membrane of most cells**
  - **Is type IV collagen – Basement Membrane**
  - It consists of alternating units of a sulfated N-acetylglucosamine and either L-glucuronic acid or L-iduronic acid, which also may be sulfated
- Dermatan sulfate:
  - **Found mostly in the skin**
  - It consist of alternating units of a sulfated N-acetylgalactosamine and L-iduronic acid, which is sometimes sulfated

➢ Proteoglycans:
- **Consist of a Large Hyaluronate fiber (polymer of disaccharide) and attathed to it is core proteins with glycosaminoglycan (GAGs) attached in a brush like fashion**
- The ground substance of the extracellular matrix is a highly hydrated gel containing large polyanionic proteoglycans molecules, which are about 95% polysaccharide and 5% protein
- The linkages of GAGs to the core protein involves a specific trisaccharide composed of two galactose residues and one xylose residue
- The carbohydrate chain is referred to as a glycosaminoglycans, which can bind covalently to a protein core
  - **The protein cores are rich in serine and threonine residues (-OH groups)**, which allows multiple GAG attachments
- **The large # of alcohol groups on the polysaccharide chains contributes to the water-binding properties of proteoglycans via hydrogen bonding**
- Another Q: Each of the following applies to proteoglycans:
  - Polyanion
  - Hydrophilic
  - Highly charged
  - Sulfated sugars
  - Linear structure



➢ Glycoproteins:
- Are proteins that have a carbohydrate covalently attached to them
- **The carbohydrate portion of most glycoproteins differ from that of proteoglycans in that it is shorter and branched**
- **Serve as enzymes, hormones, antibodies, and structural proteins**
- Are often components of cell membranes and are involved in cell-to-cell interactions

➢ **Glycolipids (or sphingolipids):**
- Are found in the cell membrane with the carbohydrate portion extending into the extracellular space
- Found in Schwann cells
- **Are derived from the lipid ceramide; this class of compounds includes cerebrosides and gangliosides (gangliosides are found in the cell membrane)**

❖ **Minerals/Vitamins**

➢ **A person who lacks fruits & vegetables in his/her diet is likely to develop a dietary deficiency in Vitamins A & C**
- NOT
  - Vitamin B1 – found in cereal, unpolished rice, and wheat products
  - Vitamin B12 – Animal origin
  - Vitamin K – K1 is from VEGETABLES but K2 is from intestinal bacteria

➢ No vitamins have been shown to influence the dental caries rate, if given in amounts greater than the RDA

- Fat Soluble vitamins: **ADEK**
  - A
    - Vitamin A (retinol):
      - Dietary sources:
        - Widely distributed in green and yellow vegetables and fruits
      - Major body functions:
        - Think Retin-A (Skin/acne medicine)
        - Antioxidant
        - Constituent of rhodopsin (visual pigment
          - Structural component of rhodopsin
        - Maintenance of epithelial tissues, has a role in mucopolysaccharide synthesis, bone growth, and remodeling
          - Vitamin A functions to promote differentiation of epithelial cells
        - A deficiency of rhodopsin is most likely caused by decreased dietary intake of vitamin A
        - **Vitamin A and C are required for osteoblasts to form the organic matrix of bone prior to calcification of the tissue**
      - Deficiency:
        - Xerophthalmia (keratinization of ocular tissue), night blindness
      - Along with vitamin C & D, it is required for the normal production of sound dentin and enamel
        - A deficiency of vitamin A will most likely affect enamel more than dentin **(Epithelial origin)**
        - A deficiency of vitamin C will affect the dentin more due to the role of vitamin C in collagen synthesis
          - **Involved in the formation of the gingival collagen**
      - **Is the most toxic of all vitamins**
  - D
    - Vitamin D
      - Involved in calcium metabolism along with PTH increasing serum calcium
      - D3 = Cholecalciferol (sun-exposed skin)
      - 7-dehydrocholesterol, an intermediate in cholesterol synthesis, is converted to cholecalciferol in the dermis and epidermis of humans exposed to sunlight
        - The metabolite, 25-hydroxycholecalciferol, is derived MOST immediately from 7-dehydrocholesterol
        - Cholecalciferol is converted to 25-hydroxycholecalciferol in the liver
        - 25-hydroxycholecalciferol is converted to 1,25-dihydroxycholecalciferol in the kidney (active)
          - This conversion consists of hydroxylation at the 1 position of 25-hydroxycholecalciferol in the kidney
          - Another Q: The conversion of circulating vitamin D metabolite to its most active form take place in the kidney
      - In short
        - UV activation in skin
        - Hydroxylation in the liver
        - Hydroxylation in the kidney
        - ****24,25-(OH)2 is the Inactive Form**
      - Dietary sources: (D2 = ergocalciferol)
        - Plants
        - Fish-liver oil, eggs, diary producs, fortified milk, margarine
      - Major body functions:
        - **Promotes growth & mineralization of bones and teeth, calcium and phosphorous metabolism (bone formation)**
      - Deficiency
        - Causes a net demineralization of bone resulting in Rickets in children and Osteomalacia in adults
      - Vitamin D can be supplied to humans by the normal action of intestinal flora
      - Vitamin D is a steroid hormone and acts on nuclear receptors
  - E
    - Vitamin E (tocopherol):
      - **Is the least toxic of all vitamins**
      - Dietary sources:
        - Vegetable oil and seeds, green leafy vegetables, margarines, shortenings
      - Major body functions:
        - An antioxidant preventing free radicals from oxidizing compounds such as polyunsaturated fatty acids
        - E is for Erythrocytes
      - Deficiency:
        - Is almost entirely restricted to premature infants

- Supplementation has been proposed to be a benefit in prevention of heart disease and cancer, however controlled studies have been unable to show a link

- K
  - Vitamin K: phylloquinone or antihemorrhagic factor
    - Is synthesized in the **intestinal bacterial**, therefore Vitamin K deficiency **can occur with prolonged use of broad-spectrum ABX**
    - The Vitamin K clotting factors are II, VII, IX, X, Protein C and S
    - Warfarin is a synthetic analog of Vit K, which acts as a competitive inhibitor of prothrombin formation
      - **Warfarin is a vitamin K antagonist**
    - **A derivative of Vit K is the coenzyme for the carboxylation of glutamate side chains (Glu→Gla), NOT crosslinking of fibrinogen – that would be Factor XIII**
    - Vit K decreases coagulation time and is present in low concentrations in milk
    - Dietary sources:
      - Green and yellow vegetables, small amount in cereals, fruits, and meats
    - Major body functions:
      - Required for synthesis of prothrombin and certain other clotting factors in the liver
      - **Vit K serves as a coenzyme in the carboxylation of inactive prothrombin to form active prothrombin**
    - Deficiency:
      - Leads to increased bleeding time
      - Would affect blood clotting chiefly by decreasing prothrombin production

- Water Soluble Vitamins:
  - B-complex
    - This complex occurs chiefly in yeast, liver, eggs, and some vegetables
    - Thiamine (B1) **(IT's the Beri-beri 1st Vitamin B)**
      - Dietary sources:
        - Meat (especially pork and organ meats), grains, dry beans and peas, fish, poultry
      - Major body functions:
        - Involved in the metabolism of carbohydrates and many amino acids
        - **In thiamine pyrophosphate, a cofactor for oxidative decarboxylation of alpha-keto acids (pyruvate and alpha-ketoglutarate)**
        - Cofactor for the transketolase in HMP shunt
      - Deficiency:
        - **Adult Beriberi** – characterized by
          - **Polyneuritis, muscular atrophy, edema, and cardiovascular changes**
          - **Dry skin, irritability, disorderly thinking, and progressive paralysis**
        - Beriberi is associated with a deficiency in thiamine
          - Seen in alcoholism and malnutrition
      - Converted to the coenzyme thiamine Pyrophosphate, TPP
        - TPP (thiamine Pyrophosphate) is required for the key rxns catalyzed by pyruvate and alphaketoglutarate dehydrogenase
          - **It's the 1st, so 1st thing needed to start KREB's**
    - Riboflavin (B2) **(It's the Rival, so 2nd best)**
      - Dietary source:
        - Milk, leafy vegetables, fresh meat, egg yolk
      - Major body functions:
        - Constituent of two flavin nucleotides, coenzymes **(FAD – Fatty acid Degradation and FMN)** that function with some enzymes (flavoproteins) which catalyze oxidation-reduction reactions
        - A function of riboflavin is to form part of the coenzyme FAD
          - **Vitamin B2 = 2 ATP (FAD)**
        - Derivatives of riboflavin and niacin function as coenzymes in redox reactions
      - Deficiency:
        - **Cracks at corner of mouth** (cheilosis), dermatitis, glossitis/magenta tongue (tongue appearing smooth and purplish)
        - **Cheliosis, angular stomatits, glossitis, and red, iching eyes – It's where your FLAVor is!**
    - Niacin (B3 -- nicotinic acid): **(Don't deNI-your-SINS at the PLAYGRound – of pooping and scratching and being retarded)**
      - Dietary sources:
        - Liver, meat, fish, grains, legumes, poultry, peanut butter
        - Included in a breakfast of eggs, steak, white bread & butter, orange juice, and milk
      - Major body functions:

        - NZ specific – not interchangeable
        - Component of NAD+ and NADP+, which are involved in Glycolysis, the Kreb's cycle, and other reactions
            - **Vitamin B3 = 3 ATP (NAD)**
        - Derivatives of riboflavin and niacin function as coenzymes in redox reactions
    - Deficiency:
        - **Pellagra** (The 3 D's)
            - The clinical symptoms of dermatitis, diarrhea, and dementia suggest a deficiency in niacin
    - High supplemental doses are effective in treating hyperlipidemia
    - Can be formed from the amino acid tryptophan
        - A diet rich in **tryptophan** offsets a deficiency of **niacin** **(because its derived from typtophan)**
    - A pyridine carboxylic acid
        - Converted to 2 major coenzymes (NAD+ and NADP+) which are used in oxidation-reduction rxns
        - NAD+
            - **Generally used in Catabolic processes** to carry reducing equivalents away, i.e. NADH
        - **NADPH**
            - **Generally used in Anabolic processes** as a supply of reducing equivalents
            - Produced from the HMP shunt and the malate dehydrogenase rxn
            - **Used also in Respiratory Burst and P450**
- Pantothenic acid (B5) **(Think PENTothenic)**
    - Is an integral part of coenzyme A **(Pantothen-AAA, like acetyl CoAAAA)**
    - Dietary sources
        - In all foods, eggs, liver, and yeast
    - Major body functions:
        - Component of Coenzyme A (fxns in the entry of pyruvic acid in to the Krebs cycle and in the degradation of FAs)
    - Deficiency
        - Fatigue, sleep disturbances, impaired coordination, diarrhea, GI, and renal problems
- Pyridoxine (B6) **(Think TRANS-AM has a B6 engine)**
    - pyridoxine, pyridoxal, pyridoxamine
    - All are naturally occurring forms of Vitamin B6
        - **These forms are converted by the body into pyridoxal phosphate, which is required for synthesis, catabolism, and interconversion of amino acids**
    - Pyridoxine is a vitamin
    - Are all derivatives of pyridine, differing only in the nature of the functional group attached to the ring
    - Dietary sources:
        - Meats (liver), vegetables, whole grain cereals and egg yolk
    - Major body functions:
        - All three compounds can serve as precursors of the biologically active coenzyme, pyridoxal phosphate
            - **Pyridoxal phosphate** functions as a coenzyme for a large number of enzymes, particularly those that catalyze **transamination** reactions involving amino acids (i.e. ALT and AST)
            - Another Q: A component of the coenzyme required in a **transamination** process is **pyridoxine**
            - Another Q: The coenzyme for glutamic-pyruvic transaminase is pyridoxal phosphate
    - Deficiencies
        - Rare but have been observed in women taking oral contraceptives and in alcoholics
- **Cobalamin (B12, cyanocobalamin)**
    - Dietary sources:
        - Muscle and organ meats, eggs, dairy products, (not present in plant foods)
    - Major body functions:
        - Involved in the formation of **methionine**
        - Involved in the conversion of **methylmalonyl to succinyl CoA**
    - Deficiency:
        - Pernicious anemia, neurologic disorder, glossitis
        - Usually owing to the absence of intrinsic factor
            - Intrinsic factor (produced in the stomach) is necessary for absorption of Vit B12 from the GI tract
            - **Vitamin B12 binds to R protein produced in the saliva** and which is also in gastric juice and bile
            - **R protein/B12 complex is then hydrolyzed by pancreatic NZs**
            - B12 then binds to intrinsic factor, which is produced by oxyntic cells of the glandular mucosa of the stomach

        - Then the B12/Intrinsic factor complex binds to receptors on the **terminal ileum** for absorption into the bloodstream
    - Vit B12 is used to treat pernicious anemia
        - **Pernicious anemia is frequently associated with a deficiency of vitamin B_{12} & folic acid**
    - **Is the only water soluble vitamin stored in the kidney (Folic acid is stored in the liver)**
    - It is the only vitamin that contains essential mineral elements and is the first substance containing cobalt that is found to be vital to life
    - May be present in inadequate quantities in a strictly vegetarian diet
    - **Symptoms that affect the gastrointestinal system include a sore and brightly red tongue, loss of appetite, weight loss, diarrhea, and abdominal cramping.**

- Biotin (vitamin H) **(Think BioTINthesis of FAs)**
    - Required as a coenzyme in the initial steps of fatty acid synthesis
    - Dietary sources:
        - Liver, kidney, milk, egg yolk, yeast
    - Major body functions:
        - **Essential for the activity of many enzyme systems that are involved in AA and protein metabolism**
        - **Required for the carboxylation of acetyl CoA to malonyl CoA, an intermediate in fatty acid synthesis**
            - Eventhough the answer was just Malonyl CoA
        - Cofactor for carboxylations (i.e. Pyruvate → Oxaloacetate, Acetyl CoA → Malonyl CoA)
    - Deficiency:
        - Fatigue, depression, nausea, dermatitis, muscular pains, loss of hair
    - Also synthesized by intestinal bacteria
    - Avidin **(Rhymes) AVIDly binds to Biotin**
        - is a protein found in uncooked egg whites that **binds to and inactivates biotin and which**, when present in abundance, can result in a deficiency of biotin
        - Avidin is an important dietary component because of its influence on biotin
    - **WEIRD ? → What does N-terminal glutamic acid do??? I think it acts in the synthesis of Biotin**
- Folic acid (folate or folacin) **(SEAN only FrOLICs with 1 C**hica**)**
    - Dietary sources:
        - Liver, kidney, yeast, mushrooms, green vegetables
            - **Folate is from Foliage**
        - **Missing from a breakfast of eggs, steak, white bread & butter, orange juice, and milk**
    - Major body functions:
        - Involved in the synthesis of purines and thymine, which are required for DNA formation
        - Plays a key role in one-carbon metabolism, and is essential for the **biosynthesis of the purines and the pyrimidine thymine**
        - Coenzyme involved in the transfer and utilization of a the single carbon moeity
    - Deficiency:
        - **Megaloblastic anemia, diarrhea, glossitis**
    - Folic acid is stored in the liver and may be synthesized by the bacterial flora of the GI tract
    - Folic acid deficiency is probably the most common vitamin deficiency in the U.S., particularly among pregnant women and alcoholics
    - Because of folic acid's **importance in the synthesis of purines and thymine** its metabolism is the target of a number of antimetabolite drugs such as **methotrexate (Think THF)**
    - Usually occurs as polyglutamate derivatives with 2-7 **glutamic acid residues**
        - These compounds are taken up by the intestinal mucosa, and the extra glutamate residues are removed by conjugase
        - The free folic acid is then reduced to tetrahydrofolate by NZ dihydrofolate reductase
        - Then they circulate in the plasma primarily as free N5 methyl derivative of tetrahydrofolate
        - **N5-methyl THF is the immediate source of methyl groups in AA synthesis**
            - Various 1 carbon tetrahydrofolate derivatives are used in biosynthetic rxns
                - I.E. required for the synthesis of choline, serine, glycine, methionine, and purines
- C (ascorbic acid)
    - Effective reducing agent, that is essential for activating prolyl hydroxylase for collagen formation
    - Essential for normal elaboration and maintenance of bone matrix, cartilage, and dentin
    - Dietary sources:
        - Citrus fruits, tomatoes, green peppers, broccoli, spinach, strawberries, melon
    - Major body functions:

        - Synthesis of CT, essential for hydroxylation of lysine and proline in collagen synthesis, essential for integrity of capillaries and oral mucosa, needed for normal bone matrix formation, needed for normal phagocytic function and Ab synthesis in host defense system
        - **Facilitates iron absorption by keeping iron in its Ferrous 2+ state**
        - **Necessary cofactor for Dopamine → NE**
    - Deficiency:
        - **Scurvy**
            - (degeneration of skin, teeth, blood vessels, epithelial hemorrhages), delayed wound healing, anemia
            - Associated w/ sore swollen joints, bleeding swollen gums, loose teeth, anemia & improper development of dentin
            - Cessation of bone growth
    - Is an antioxidant
    - Avitaminosis of the gingiva is likely to be caused by vitamin C
- Minerals:
    - Inorganic substances that are essential to life
    - Serve for both structural and regulatory functions
        - Major minerals:
            - **> 0.005% of body weight**
            - Calcium, chloride, magnesium, phosphorous, K+, Na+, and sulfur
                - **Much of the body's sodium content is readily exchangeable except for that portion found in bone**
                - Another Q: Calcium metabolism is regulated by androgen, estrogen, thyroid hormone, PTH, but **not norepinephrine**; is also regulated by calcitonin
        - Trace minerals:
            - < 0.005% of body weight
            - Chromium, cobalt, copper, fluoride, iodine, iron, manganese, molybdenum, selenium, and zinc
    - General functions of minerals:
        - Maintenance of acid-base balance
        - Coenzyme or catalysts for biologic reactions
        - Components of essential body compounds
        - Transmission of nerve impulses and regulation of muscle contractions
        - Maintenance of water balance
        - Growth of oral and other body tissues
    - Copper:
        - Is important in the maturation of collagen and elastin as it is a cofactor for enzyme **lysyl oxidase**
            - A copper deficiency can cause collagen & elastin to be defective due to diminished activity of **lysyl oxidase**
        - The oxidized lysine residues formed in collagen and elastin by this enzyme form the cross links which stabilize these molecules
    - Zinc:
        - Fxns:
            - **Stabilizes cell membrane**
            - Taste acuity
            - Collagen formation
            - **Cell-mediated immunity**
            - **Carbonic anhydrase**
                - **Zinc is an essential component of carbonic anhydrase**
    - Calcium
        - A diet deficient in calcium will result in production of PTH and bone resorption
        - Another Q : < 50% of dietary calcium is normally absorbed from the gut of an adult man
            - **Absorption of calcium from the small intestine is increased by lowering the pH of the intestine**
            - Absorption of calcium from the small intestine through **active transport**
        - Another Q: In the regulation of calcium balance, the greatest elimination of calcium occurs in the GI tract
            - <50% absorbed and the rest eliminated
            - The main route of calcium excretion is in the feces
        - **Another Q: Recommended daily dietary allowances for Ca and P provide a Ca/P intake of approximately 1.0**
        - Calcium performs
            - Muscle contraction
            - Blood clotting
            - Nerve transmission

- **NOT** maintenance of membrane fluidity

- Calcium/Phosphate/Alkaline Phosphatase

♦ HyperParaThyroidism and Paget's Disease	↑ Ca2+ and Alk Phosphatase	↓ Phosphate
♦ **Vitamin D intoxication and Osteoporosis**	↑ Ca2+	**↑ Phosphate**
♦ Renal Insufficiency	**↑ Phosphate**	↓ Ca2+

Nutrient/Mineral	Functions
Iron	Constituent of hemoglobin and enzymes involved in energy metabolism
Iodine	Constituent in thyroid hormones, regulates energy metabolism
Calcium	Bone and tooth formation, **blood clotting** (Factor IV), nerve transmission, muscle contraction
Phosphorous	Bone and tooth formation, acid-base balance, release of energy (ADP, ATP)
Sulfur	**Constituent of active tissue compounds, cartilage and tendon**
Potassium	Acid-base balance, body water balance, nerve function, **muscle relaxant**
Sodium	Acid-base-balance, body water balance, nerve function
Magnesium	**Activates enzymes involved in protein synthesis**
Cobalt	Constituent of vitamin B12
Copper	Constituent of enzyme associated with **iron metabolism** and **nerve function, and collagen formation (lysyl oxidase)**
Zinc	Stabilizes cell MB, **taste acuity, collagen formation, & cell-mediated immunity**, **Carbonic Anhydrase**

- Some notes:
  - Proteins that contain trace elements of essential nutrients for biological action include:
    - Myoglobin (Fe), thyroglobin (I), and carbonic anhydrase (Zn)
  - Another Q: Ca and Fe are lacking in the U.S. diet
    - Iron deficiency leads to Chronic Bleeding
  - **Another Q: Major controlling factor of iron absorption is saturation of mucosal cells**
  - Another Q: Iron is an important nutrient present in low concentration in milk
    - **Lack of milk consumption leads to iron deficiency, not Ca^{2+} or protein deficiency**
- Fluoride:
  - Does not make enamel harder
  - NOT a primary or major electrolyte in the saliva
    - Sodium, Calicum, Potassium, and Bicarbonate ARE
  - Reduces the solubility of enamel due to the incorporation of fluoride into the apatite structure of the enamel
    - Fluoride acts by ion exchange
  - Increases the remineralization of incipient caries
  - Concentration in body fluids is regulated by an equilibrium relationship **between bone and urinary excretion**
    - Rate of fluoride incorporation into bone depends on
      - **water/mineral ratio, age, rate of bone remodeling, amount of ionizable F in diet**
  - Deficiency in fluoride can lead to an increased incidence of dental caries
  - Toxicity leads to tooth enamel mottling and discoloration, increased density (chalky white), and calcification
  - Other facts:
    - Excreted rapidly by the kidney
    - Deposited in calcified tissues
    - Passes the placental barrier slowly
    - 1 ppm is tasteless, colorless, and odorless
    - **NOTE: in plasma it does not only occur in the ionic form**
  - Absorption
    - In the stomach, as Hydrofluoric acid
    - In the small intestine, Fluoride
  - Flouride → Most electronegative ATOM
  - Hydroxyapatite
    - Calcium Phosphate/Calcium Hydroxide Compound
    - Fluoroapatite
      - The substitution of F- for OH ions makes enamel less susceptible to caries attack
      - can form during hard tissue formation by a substitution of OH ions by F- ions
  - Fluoride calculation
    - determine % F in compound

- multiply by molecular weight ratio for the compound
- multiple F by 10 to convert to mg/ml
- convert to ppm by multiplying mg/ml by 1000
- **(1ppm = 1mg/liter)**
- Example
  - 1 mL of 2% NaF * 1/2.2 = .91% F
  - .91% * 10 = 9.1 mg F/mL
  - 9.1 * 1000 = 9100 mgF/L = 9100 ppm
    - **SHORTCUT → Multiply by ratio, then multiple by 10,000 = ppm**
    - 0.2% NaF → 900ppm
    - 2% NaF → 9100ppm
    - 1.23% APF → 12,000ppm
    - 8% SnF2 → 19,369 ppm

% Fluoride Product	Molecular Weight Ratio
NaF	1/2.2
SnF_2	1/4.1
(APF) Na_2FPO_3	1/7.6

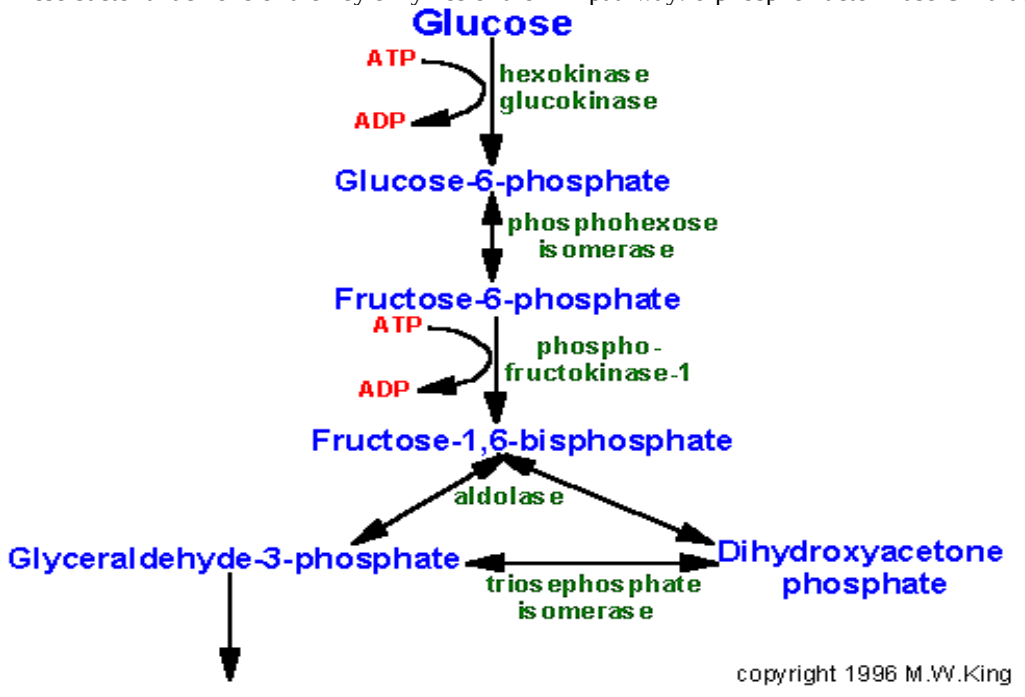
STUDYYY

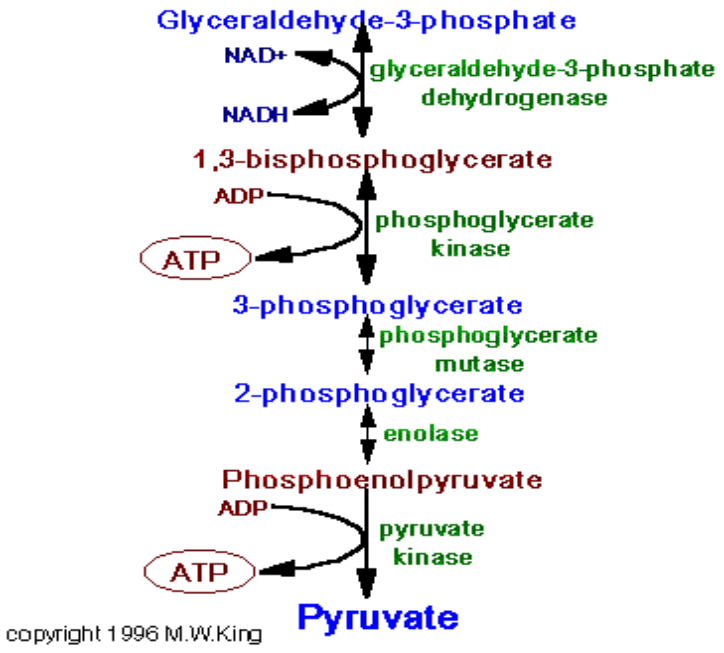
Metabolism

- Overview
  - Substrate-level phosphorylation:
    - *More details below
    - **High-energy phosphate intermediates are formed and are transferred to ADP to produce ATP**
      - Glycolysis
      - The Citric Acid cycle (Krebs cycle)
  - Oxidative phosphorylation:
    - *More details below
      - ETC
    - Electrons move down the electron transport chain and chemiosmosis occurs because the electrochemical gradient generated by the transfer of electrons through the ETC to O_2 is used in the production of ATP
      - ADP, inorganic phosphate, an electron donor, and O_2 are all required (CO_2 is not) for cellular respiration
        - **Cellular Respiration** = **Coupled respiration**
    - Energy for ATP synthesis is derived from the electron transport system by the process of oxidative phosphorylation
    - It is the third and final phase of the respiratory metabolism of glucose and other substrates
    - **Reduced coenzymes (NADH and $FADH_2$)** generated earlier in Glycolysis and the Krebs cycle are reoxidized
      - The electrons they release are transported through a serires of MB-bound carriers (flavoproteins, iron sulfur proteins, coenzyme Q, and cytochromes) to establish a proton gradient across a membrane
        - The energetically unfavorable proton gradient is created using energy from electron transfers
        - A terminal acceptor such as **oxygen is reduced**, and ATP is synthesized by **chemiosmosis**
          - Chemiosmosis is the diffusion of ions across a membrane, specifically the synthesis of ATP with the H+ gradient
    - Oxidative P is the major source of ATP in aerobic organisms
  - Photophosphorylation:
    - Occurs as a result of photosynthesis (which also involves an ETC)
  - Aerobic breakdown of a single molecule of glucose produces a net profit of:
    - **36–38 ATP**
      - 4 ATP are produced by substrate level phosphorylation
        - (2 ATP) Glycolysis
        - (2 ATP) Krebs cycle (From GTP)
      - 32–34 ATP are produced by oxidative phosphorylation during electron transport
        - Oxidation of one NADH = 3 ATP, closer to 2.5; of $FADH_2$ = 2 ATP, closer to 1.5
        - **38 Total ATP if use Malate Shuttle**
        - **36 Total ATP is use G3P Shuttle**
      - **NOTE: ATP yields the most energy per mole**
  - Anaerobic only produces 2 ATP per glucose molecule
- ATP → Made of Adenosine + Deoxyribose + 3 Phosphates

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

- Glycolysis:
  - Occurs in the cytoplasm
  - **Embden-Meyerhof pathway**: glucose is converted to pyruvate **(THE OXygen is in the Mirer – you can't get it)**
    - Most common pathway and is used by a large number of **anaerobic and facultative anaerobic** bacteria
    - Oral bacteria use this pathway
      - Pyruvate is reduced to lactic acid via fermentation
        - Lactic acid is a cariogenic product of bacterial glycolysis
        - **Another Q: In fermentation, the final electron acceptor is an organic compound** (not O_2, as in the ETC)
    - This glycolytic pathway results in the net production of **2 lactic acid & 2 ATP** per glucose metabolized
      - BE CAREFUL, the end products of alcohol fermentation are 2 molecules of Ethyl alcohol and 2 ATPs
        - This pathway is found in many yeasts and certain bacteria
    - During strenuous exercise, the energy required for the skeletal muscles is supplied largely from anaerobic transformation of glucose to lactic acid from glycogen
      - (Lactic acid = CH_3-CHOH-COOH)
  - Entner-Doudoroff pathway:
    - A glycolytic pathway used by many **obligate aerobic** bacteria
    - Results in the net production of **only 1 ATP per glucose metabolized (compared to 2 ATP in Embden-Meyerhof)**
    - Pathway ends with the formation of a pyruvate and a glyceraldehyde-3-phosphate, which is converted by enzymes outside the pathway to pyruvate
    - These bacteria lack one of the key enzymes of the EM pathway: 6-phosphofructokinase OR aldolase



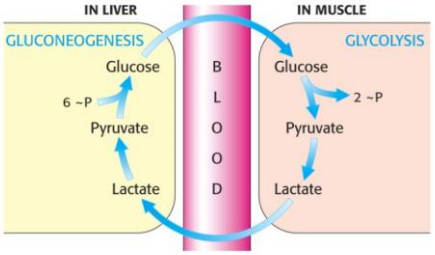


- Enzymes of Glycolysis:
  - ATP involved steps (aka the "kinases") → 1,3,6,9
  - NADH involved steps → 5
  - 1) Hexokinase (Glucokinase in Liver): ATP used
    - G → G6P
  - 2) Phosphoglucose isomerase:
    - G6P → F6P
  - 3) Phosphofructokinase: ATP used
    - AMP Increase Glycolysis
    - F6P → F1,6BP
    - The most important control point in glycolysis
      - **Rate-limiting step**
      - This is a physiologically irreversible
    - Does **not** function in association with a membrane
    - Allosteric enzyme stimulated by ADP or AMP & inhibited by high energy molecules (ATP and citrate)
      - **ATP inhibits phosphofructokinase** even though **ATP is also a substrate** for the enzyme; this is an example of **allosteric inhibition**
    - SIDEBAR: **Fructose-2,6-bisphosphate**
      - Allosteric activator of phosphofructokinase
      - Allosteric inactivator of fructose-1,6-bisphosphatase
      - ***(In other words, it **promotes Glycolysis** & **inhibits Gluconeogenesis**)
  - 4) Aldolase:
    - F1,6BP →GA3P + DHAP (One 6C into Two 3Cs)
    - This is called the aldolytic reaction
    - Aldolase is the enzyme that brings about the transition from 6-carbon metabolites to 3-carbon metabolites
    - Converte fructose ester into triose sugars
    - Plentiful in skeletal & heart muscle
      - 4a) *Triose phosphate isomerase:*
        - *DHAP → GA3P*
  - 5) Glyceraldehyde 3-phosphate dehydrogenase: NADH made
    - GA3P → 1,3BPG
    - (high energy phosphate compound is formed)
  - 6) Phosphoglycerate kinase: ATP made
    - 1,3BPG → 3PG
    - 1st ATP generating step
  - 7) Phosphoglyceromutase:
    - 3PG → 2PG
    - A mutase is an enzyme that catalyzes an intramolecular shift of a chemical group
  - 8) Enolase:

- 2PG → PEP
- **Sodium Fluoride inhibits enolase (hence inhibiting glycolysis)**

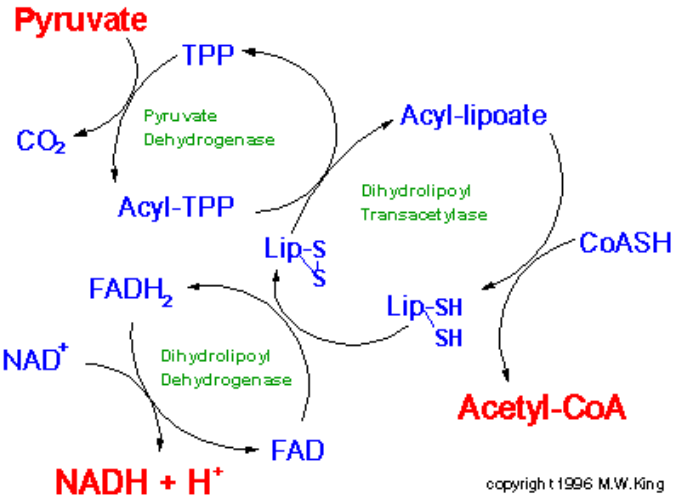
- 9) Pyruvate kinase: ATP made
  - PEP → Pyruvate
  - (2nd ATP generating step)
  - **Irreversible NZ**

- Possible **fates of pyruvate**:
  - Branch point molecule of Glycolysis is pyruvate
  - 1) Conversion to **lactate**:
    - **Lactate dehydrogenase (LDH)** converts pyruvate to lactate in the cytosol
    - **Major fate for pyruvate in RBC, the lens and cornea of the eye, the medulla of the kidney, the testes, and leukocytes**
      - The Cori Cycle



        - The cycle refers to the recycling of lactate produced by muscle during anaerobic metabolism
          - During recovery, the lactate formed in muscles is transported to the liver and used to form glucose, which is released to the blood and returned to the muscles to replenish their glycogen stores
          - This pathway (glucose→lactate→glucose) is called the Cori cycle
          - **Nets 2 ATP**
        - **The pathway resulting in glucose formation in the liver from lactate produced in muscle is the Cori cycle**
        - Anaerobic Glycolysis:
          - Enzymes that catalyze the anaerobic processes of CHO metabolism are found predominantly in the cytoplasm
          - Provides ATP energy quickly, supplementing the basal ATP production resulting from the aerobic oxidation of other fuels via the citric acid cycle
          - The end-product of **glycolysis** under **anaerobic** conditions is **lactic acid**
          - Another Q: Anaerobic glycolysis yields 2 ATP per glucose degraded **(& 2 lactic acid molecules)**
          - Another Q: Under strenuous exercise, the stored muscle glycogen is broken down to lactate by anaerobic glycolysis
          - **Another Q: During the period following exercise (when ventilation is in excess of the metabolic requirement), the level of lactic acid in blood decreases**
            - Another Q: During exercise, muscle tissue accumulates lactic acid.
            - As a result, erythrocytes passing through capillaries in the muscle absorb more CO_2 & release more O_2
          - Another Q: After prolonged muscular exercise (when oxygen debt is being repaid), most lactic acid undergoes gluconeogenesis in the liver
    - NOTE: nicotinamide (in the form of nicotinamide adenine dinucleotide = NAD) is a vitamin (B_3) derivative concerned with conversion of glucose to lactic acid
    - **Another Q: Adenine is a molecule common to NAD^+ & FAD**
  - 2) Conversion to **acetyl CoA**:
    - **Pyruvate dehydrogenase converts pyruvate to acetyl CoA in the mitochondria**
      - Formation of Acetyl-CoA from pyruvate is best described as Oxidative Decarboxylation
        - Don't be clowned because the NZ is called Dehydrogenase, whereas the 1st NZ for Gluconeogensis is Pyruvate Carboxylase to get Oxaloacetate from Pyruvate
      - **Causes backup of substrate (pyruvate and Alanine) causing lactic acidosis**
      - Can be seen in alcoholics due to B1 deficiency (Beriberi)
        - **Tx with increasing ketogenic nutrients (Lysine and Leucine are the only 2 purely ketogenic AAs)**
      - Rxn = Pyruvate + NAD+ + CoA → Acetyl-CoA + CO2 + NADH
      - Cofactors –
        - **B 1-5**

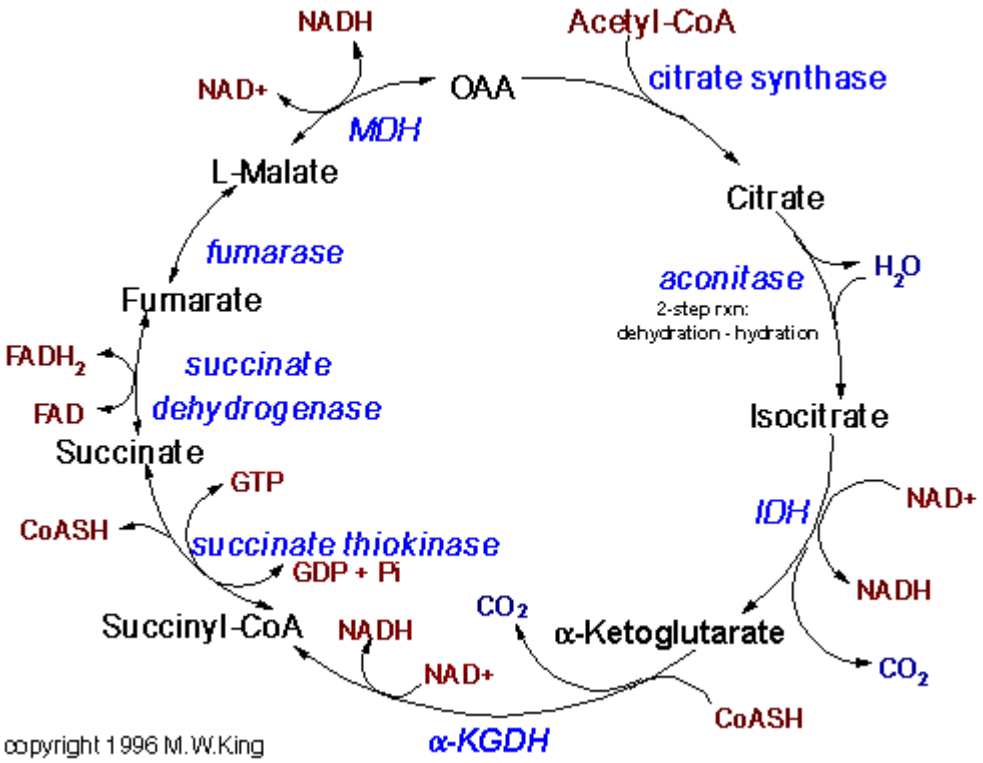
        - thiamine pyrophosphate (B_1-decarboxylation),
        - FAD (B_2-riboflavin),
        - NAD^+ (B_3,),
        - Pantothenic acid (B_5)
    - **Lipoic acid,**
    - Coenzyme A
        - **Biotin (Pyridoxine) is NOT a cofactor** – ***repeated again & again!!!!!***
- This acetyl CoA can then enter the **Kreb's cycle or be used as the building block for fatty acid synthesis**
    - Acetyl CoA is the immediate precursor for fatty acid synthesis
- **Acetyl CoA is the principal allosteric regulator of pyruvate metabolism in the liver**



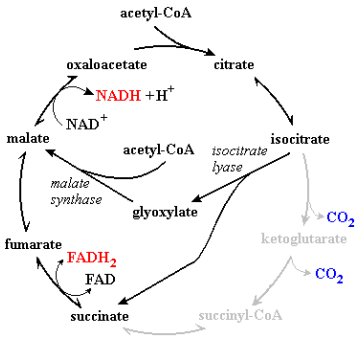
- 3) Conversion to **oxaloacetate**:
    - **Pyruvate carboxylase** converts pyruvate to oxaloacetate
        - This is not the irreversible step of gluconeogenesis, the next step, i.e. **Oxaloacetate → PEP via PEP carboxykinase is the rate limiting/committed step of gluconeogenesis**
    - This replenishes the citric acid cycle intermediates and provides substrate for gluconeogenesis
    - Pyruvate carboxylase is found in the liver and kidney, but not in muscle
- 4) Conversion to **ethanol**:
    - Pyruvate is reduced to ethanol
    - **Yields only 1 ATP – whereas the Lactic and Glycolysis yield 2 ATP**
    - Occurs in yeast and certain microorganisms, but not in humans

❖ Krebs cycle:
- Aka 'tricarboxylic acid cycle (TCA)' or 'citric acid cycle'
- Starts with the **4-carbon compound oxaloacetate**, adds 2 carbons from acetyl CoA, loses 2 carbons as CO2, and regenerates the 4-carbon compound oxaloacetate
    - The TCA cycle is initiated by the condensation of acetyl coenzyme A & oxaloacetate
    - **Malonate is an effective inhibitor of metabolism**
        - **Its competitive inhibition can be overcome by succinate**
- Pyruvate that enters this cycle is generated by the Glycolysis of glucose or protein catabolism
- Oxaloacetic acid and a-ketoglutaric acid are acids found in the citric acid cycle
- This cycle is controlled by regulation of several enzyme activities
    - **The most important of these regulated enzymes are citrate synthase, isocitrate dehydrogenase, and alpha ketoglutarate dehydrogenase complex**
- Final step in complete metabolism of fat carried out by the Krebs or TCA cycle
- Aspartic acid and oxaloacetic acid are interconvertible
    - **Aspartic acid is the most immediate source of oxaloacetic acid during metabolism**
- Enzymes of the citric acid cycle are found in the mitochondria
- CIKSSFMO = **Citrate Is Kreb's Starting Substrate For Mitochondrial Oxidation**
    - Citrate→ **Citrate**
    - Is → **Isocitrate**
        - OUT = CO2 and NADH
    - Kreb's → **α-Ketoglutarate**
        - OUT = CO2 and NADH
        - ****The alpha ketoglutarate dehydrogenase complex uses the same cofactors as pyruvate dehydrogenase**
    - Starting → **Succinyl-CoA**

        - OUT = GTP and CoA
    - Substrate → **Succinate**
        - OUT = FADH2
    - For→ **Fumarate**
    - Mito. → **Malate**
        - OUT = NADH
    - Oxidation → **Oxaloacetate**
- **THE MATH:** 3 NADH + 1 FADH2 + 2 CO2 + 1 GTP/per acetyl CoA = **12 ATP (then x2 per glucose)**



- **Glyoxylate cycle**
    - Replenishes Kreb's cycle intermediates
    - Acetate
    - Done in many bacteria, including **Azotobacter vinelandii**



❖ Oxidative Phosphorylation
- Biologic oxidative-phosphorylation enzymes occur in the cell primarily as highly organized multi-enzyme units in the mitochondria
- Electron Transport Chain (ETC):
    - The final steps in the aerobic generation of ATP:
        - Involve the transfer of electrons from the **reduced coenzymes NADH and $FADH_2$** to oxygen and the combination of protons (H+) with the oxygen to form water and regenerate NAD^+ and FAD
            - These coenzymes pass electrons to the ETC
            - In this chain, **flavin mononucleotide (FMN) and coenzyme Q (ubiquinone) pass the electrons to heme-containing cytochromes, which transfer the electrons to oxygen**
                - Ubiquinone is a lipid that participates in mitochondrial electron transport
            - During the movement of the electrons along the ETC, H^+ is moved across the inner membranes to the space between the inner and outer membrane
                - **In respiration, the removal of hydrogen ions from a substrate is always accompanied by the removal of electrons**
                - Chemical energy generated by e^- transport results from an H^+ gradient across the inner MB
            - The electrochemical gradient created provides the energy for the production of ATP from ADP and Pi by the oxidative phosphorylation complex
                - FMN is derived from riboflavin; NAD is derived from niacin
                - **Coenzyme Q is not derived from a vitamin (the body synthesizes it)**
                - **Each cytochrome consists of a heme group associated with a protein; cytochrome a + a_3 (aka cytochrome oxidase)**

- Oxygen is the ultimate electron acceptor and is reduced to water
- A coenzyme is a nonprotein substance (organic cofactor) that combines with an apoenzyme (the protein portion of a complex enzyme) to form a haloenzyme (a complete, catalytically active enzyme system)

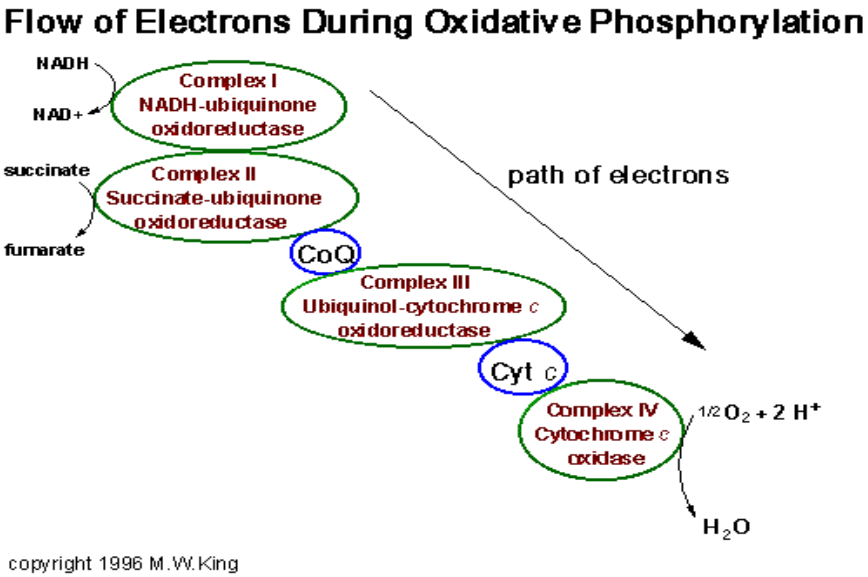
♦ Electron transport complexes:

- There are four, each representing a fraction of the entire respiratory chain
- Each is separate and has its own unique composition, and each is capable of catalyzing electron transfer through a portion of the chain
- **Complexes I and II catalyze electron transfer to ubiquinone from two different electron donors: NADH (Complex I) and succinate/FADH2 (Complex II)**
- **Complex III carries electrons from ubiquinone to cytochrome c**
- **Complex IV completes the sequence by transferring electrons from cytochrome c to oxygen**
- **Remember all of them are associated with membranes (i.e. succinate dehydronase and q reductase)**

- **THE MATH =** 1 NADH → 3 ATP; 1 FADH2 → 2 ATP

Complex	Protien components
I (NADH dehydrogenase complex)	**NADH dehydrogenase**
II (Succinate/$FADH_2$ dehydrogenase complex)	**Succinate dehydrogenase**
III (Ubiquinone-cytochrome c oxidoreductase complex)	**Ubiquinone-cytochrome c oxidoreductase**
IV (cytochrome oxidase complex)	**Cytochromes a and a3**

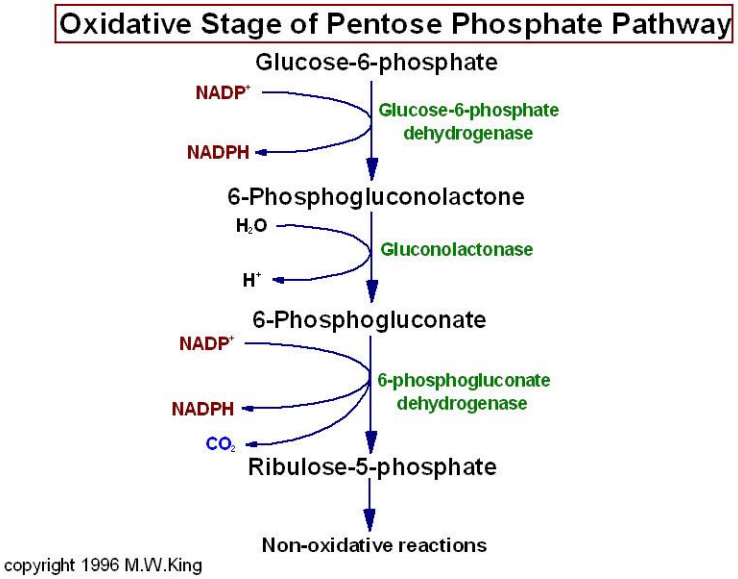
♦ The last stage of biological oxidation is accomplished with cytochrome oxidase

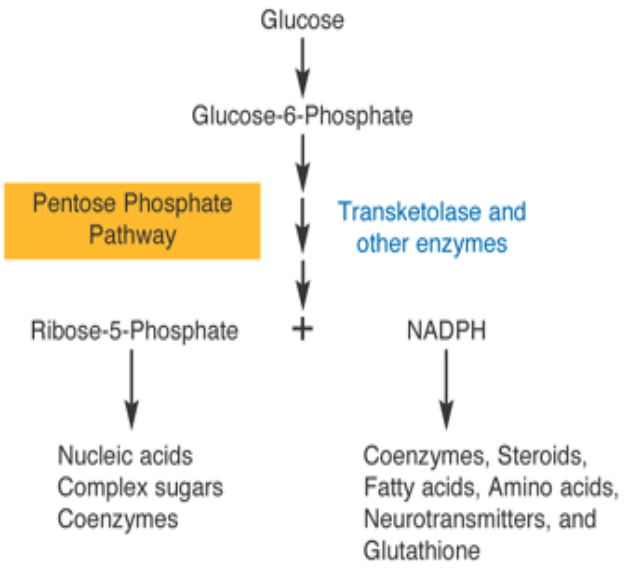


➢ Pentose phosphate pathway: **(Think nadPH as in PHATTY acid synthesis)**

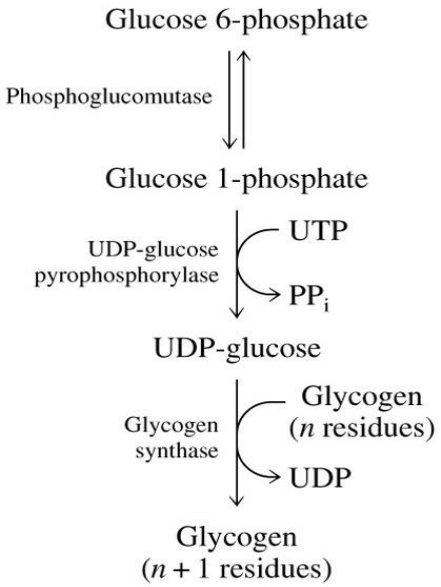
- Other names: the pentose shunt, the hexose monophosphate shunt, or the **phosphogluconate pathway**
- The major role – production of **NADPH** for reductive biosynthetic reactions (e.g., fatty acid synthesis) and the production of essential pentoses, particularly **D-ribose**, used in the biosynthesis of nucleic acids
- Another Q: The pentose phosphate pathway is a metabolic pathway that generates significant amounts of NADPH
- Ribose phosphate needed for nucleic acid synthesis can be derived from Pentose phosphate p-way
- **Produces CO_2**
- Can produce 5-carbon sugars (used for DNA and RNA) for nucleic acids
- ALL rxns of this pathway **occur in the cytoplasm**
- Occurs in all sites of FA or steroid synthesis, i.e. Lactating mammary glands, Liver, Adrenal cortex
- Controlled by inhibition of glucose-6-phosphate dehydrogenase by NADPH (SEE PIC BELOW)
  - ♦ (Normally G6PDH makes NADPH)
  - Deficiency of glucose-6-phosphate dehydrogenase results in reduced NADPH
    - ♦ NADPH is needed to keep Glutathione reduced, which in turn detoxifies free radicals and peroxides
    - ♦ Reduced NADPH lead to hemolytic anemia, due to poor RBC defense against oxidizing agents
    - ♦ NOTE: Any glycolitic NZ deficiency is associated with hemolytic anemia because RBCs metabolized glucose anaerobically and solely depend on glycolysis
- In the **irreversible oxidative reaction** of the pathway, **one carbon of G6P is released as carbon dioxide; NADPH is generated; and ribulose-5-phosphate is produced**
- In the reversible nonoxidative reaction, pentose phosphates produced from ribulose-5-phosphate are converted to the glycolytic intermediates fructose-6-phosphate and glyceraldehyde-4-phosphate
- Prominent pathway in tissues actively carrying out biosynthesis of fatty acids & steroids from small precursors
  - Particularly the mammary glands, adipose tissue, the adrenal cortex, and the liver

- Large amounts of NADPH are required in the reductive synthesis of fatty acids from acetyl CoA→specifically the reduction of double bonds and carbonyl groups
- **Other tissues less active in synthesizing fatty acids, such as skeletal muscle, are virtually lacking the pentose phosphate pathway**



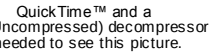


- Glycogen synthesis:
  - UDP glucose is the substrate for glycogen synthesis
    - **Fructose is also a component precursor of glycogen**
    - **Glucose enters the cell and is phosphorlyated to glucose-6-phosphate by hexokinase (in most tissues) or by Glucokinase (in the liver)**
  - To initiate glycogen synthesis,
    - 1st, the **glucose-6-phosphate** is reversibly converted into **glucose-1-phosphate** by **phosphoglucomutase**
      - This takes us away from Glycolysis and starts us up the path of Glycogen synthesis
    - 2nd, This **glucose-1-phosphate** is then converted to **UDP glucose** by the action of **UDP glucose pyrophosphorylase**
    - 3rd, **Glycogen Synthase** transfers glucose residues from **UDP glucose to the nonreducing ends of the glycogen molecule**
  - **Glycogen synthase**
    - The key regulatory enzyme for glycogen synthesis
    - **Transfers glucose residues from UDP glucose to the nonreducing ends of the glycogen molecule**
    - **Is responsible for making the 1,4 linkages of glycogen**
    - Occurs in both phosphorlyated and dephosphorylated forms
    - The active enzyme glycogen synthase A is the dephosphorylated form
      - Remember
        - A's are always on
        - Insulin (House is warm, takes off Pis)
        - Glucagon (Tags Pis for breakdown)
    - Glycogen synthase B is the phosphorylated form – inactive form of the enzyme
    - Kaplan states
      - The I form is the active form (ADP) **(Just think I for insulin initiated!!!)**
      - The D form is the inactive form (ATP)
      - Phosphorylation of some enzymes by ATP results in conversion of the enzyme from an active to an inactive form. This is illustrated by the conversion of glycogen synthetase I to glycogen synthetase D???
      - **VOWELS are turned ON**



QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

- Glycogenolysis
  - **Glycogen phosphorylase (Phosphorylase and Kinase add phosphate, but Phosphatase take away kinase)**
    - **Breaks down glycogen into Glucose-1-Pi**
    - Works only on linear chains, and breaks glycogen down until you get to within 4-5 glusoce units of a branchpoint
      - For full degradation of glycogen you would still need an alpha 1,4 glucan transferase, then an alpha 1,6 glucosidase
        - **Last NZ in Glycogenolysis? – FOR sure Last Step of Gluconeogeneis**



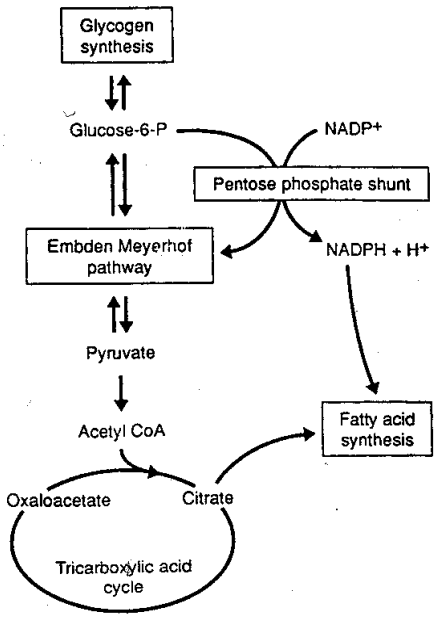
- **G-6-Phosphastase??**
- **OK, if the ? asks for the last NZ in glycogenolysis of the LIVER, then yes G-6-Phosphatase,**
- **BUT if it's just in muscle, then its Phosphoglucomutase (G-6-Pi → G-1-Pi) to then be used in Glycolysis**

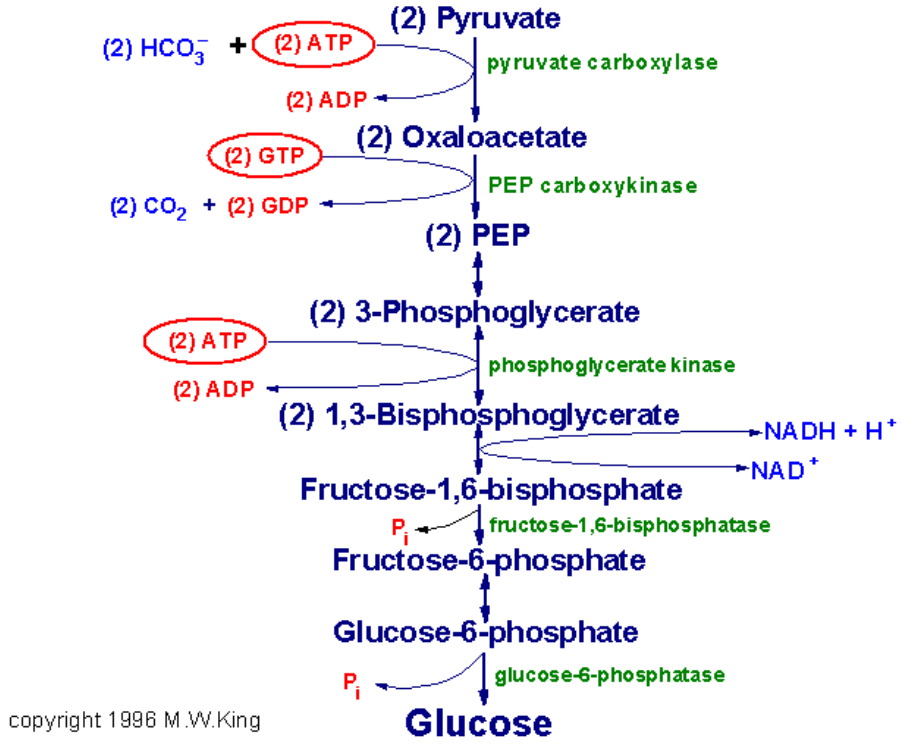
- Breaks down glycogen, also has two forms (A) and (B)
- **Phosphorylation of this enzyme forms the active enzyme (A); dephosphorylation forms the inactive enzyme (B)**
- **Muscle glycogen phosphorylase is activated by epinephrine, not glucagons**
  - **Glucagon knows muscle can't release glucose anyway!**
- **Liver** glycogen phosphorylase is activated by **both Glucagon and epinephrine**
  - Another Q: Epinephrine causes a rise in cAMP levels in muscle cells, which in turn activates glycogen phosphorylase
  - Keep a carpule of glucagon in the office for Hypoglycemic attacks
  - If insulin decreases, the glycogenolysis increases in the liver and Glycogen decreases
- Both enzymes glycogen synthase and phosphorylase are phosphorylated at **specific serine residues**
- The following are required for the activation of glycogen phosphorylase:
  - ATP, adenylate cyclase, glucagon or epinephrine, phosphorylase kinase (but not phosphofructokinase)

- **The ATP is needed to create the cAMP, from the activated adenylate cyclase**

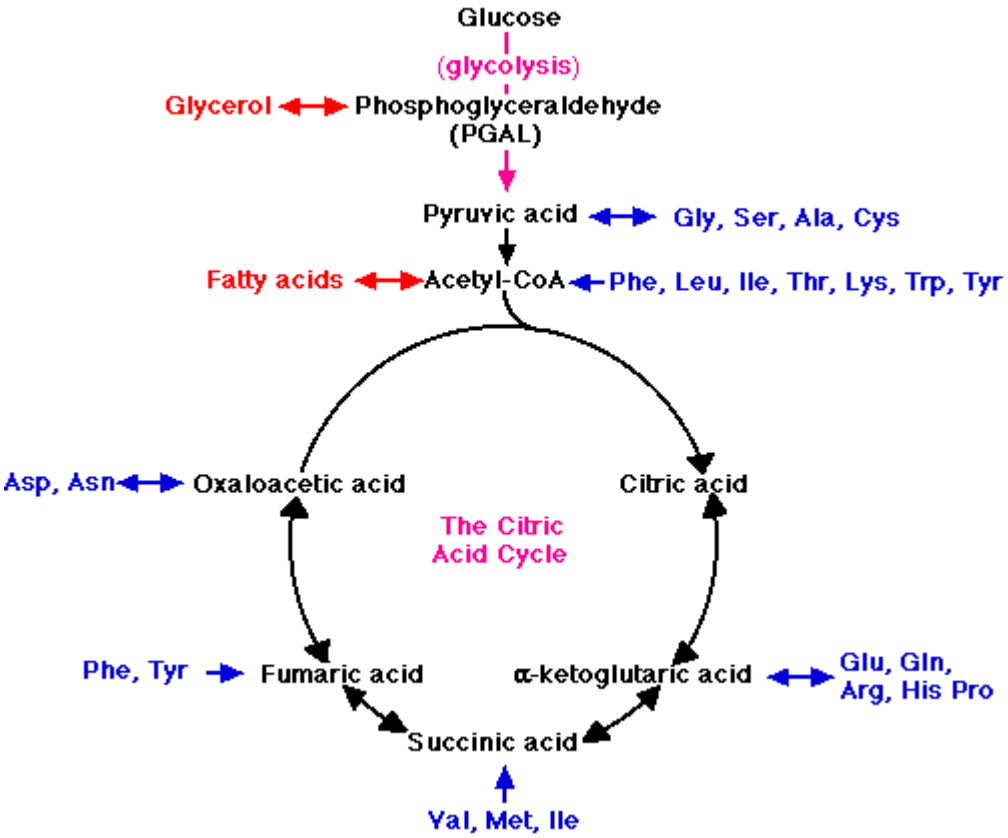
❖ **Glycogen storage diseases**
- Type I
  - Von Gierke's disease
    - Glucose-6 phosphatase deficiency
- Type II
  - Pompe's disease
    - Lysosomal alpha 1,4-glucosidase deficiency
- Type III
  - Cori's
    - Alpha 1,6-glucosidase deficiency (debranching NZ)
- Type IV
  - McArdle's Disease
    - Skeletal muscle glycogen phosphorylase deficiency
    - Can't break down glycogen to in muscle
- **VPCM = Very Poor Carbohydrate Metabolism**

❖ Gluconeogenesis:
- Biochemical process in which glucose is made from molecules which are **not CHOs (primarily from AAs but not FAs)**
- Process occurs primarily in the liver, and its role is to provide glucose for export to other tissues when other sources of glucose are exhausted
  - **Occurs in Liver, Kidney, Intestinal Epithelium,** BUT NOT Muscle!!
    - **Glucose-6-phosphatase is found associated with the Liver AND Kidney**
  - Hypoglycemia can be caused by a deficiency in any of the below NZs (Von Gierke's Glucose-6-phosphatase)
- Typically it involves the conversion of lactic acid or amino acid into pyruvate or phosphoenolpyruvate, which is then converted to glucose.
- **Irreversible NZs (PPFG-Pathway Produces Fresh Glucose)**
  - Pyruvate Carboxylase (irreversible, just not the committed step)
    - **In Mitochondria**
    - Pyruvate → Oxaloacetate
  - PEP Carboxykinase
    - In Cytosol
    - Oxaloacetate → Phosphoenolpyruvate
  - Fructose-1,6-bisphosphatase
    - In Cytosol
    - Fructose-1,6-bisphosphate → Fructose-6-Phosphate
  - Glucose-6-phosphatase
    - In Cytosol
    - Glucose-6-phosphatase → Glucose
    - **Last Step of Gluconeogenesis**
    - Essential for this transformation, it catalyzes the last step of this process in which glucose-6-phosphate is hydrolyzed into glucose
    - Is found associated with the liver *(primarily)* and the kidney (NOT in muscle)
      - Essentially absent from normal mammalian muscle (and brain)
      - Muscle glycogen does not yield blood glucose directly because glucose-6-phosphatase is not present in muscle
    - **Does not contain a high energy bond**

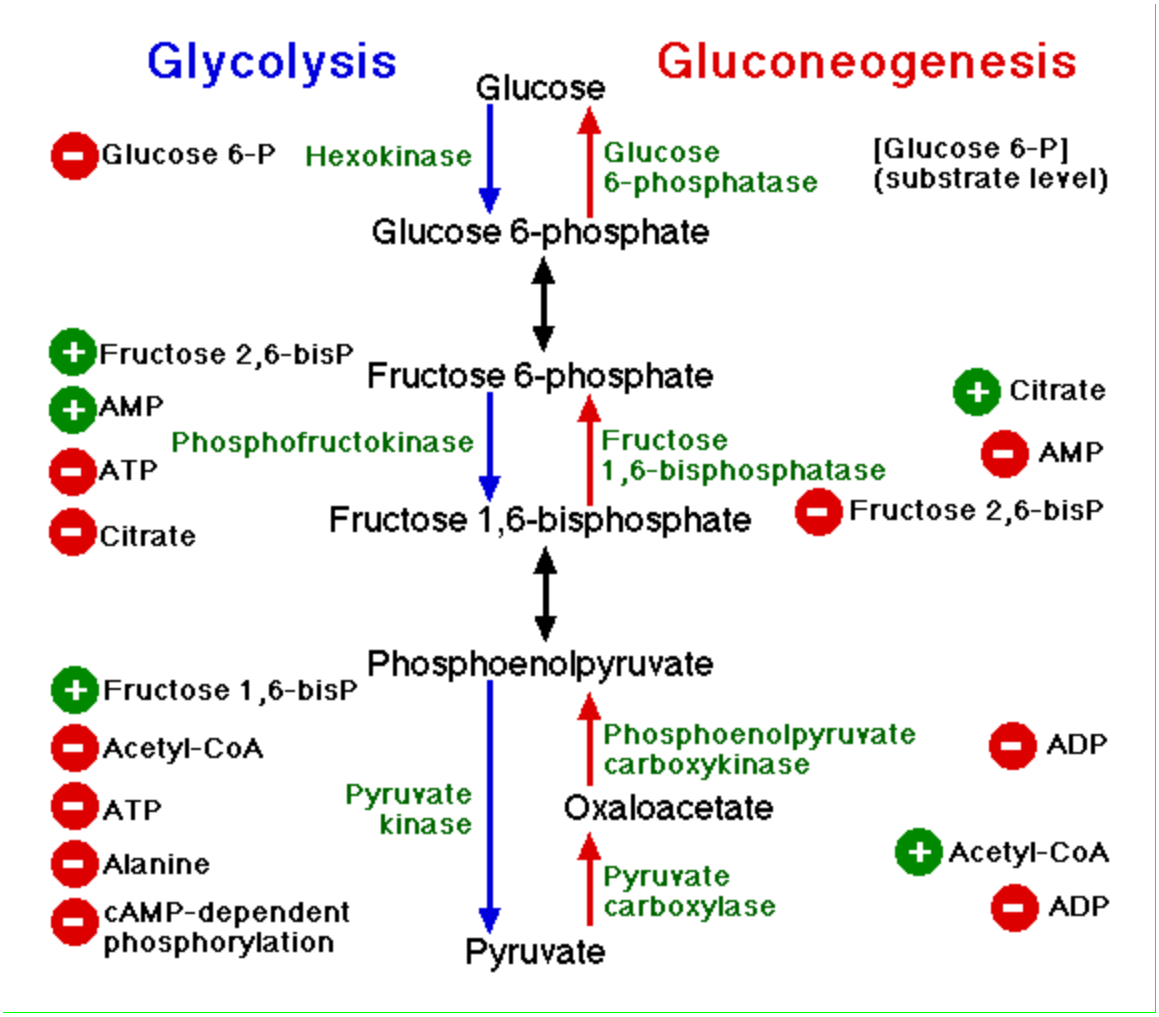




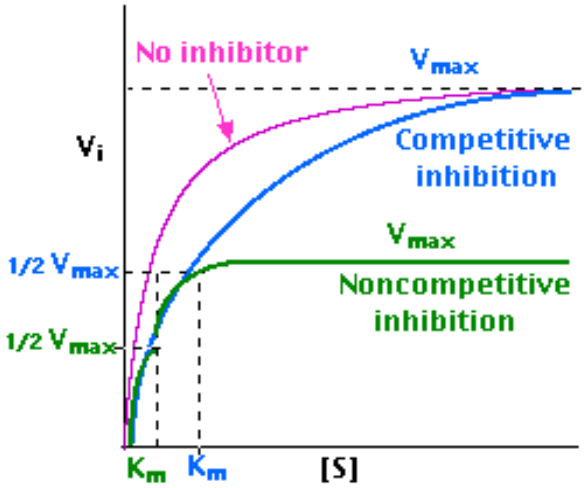
- Key reactions of Gluconeogenesis:
  - Pre-step
    - Some amino acids to Oxaloacetate
    - Some amino acids or Lactate to Pyruvate
      - EX of an amino acid that can be used is alanine
        - **The conversion of [Alanine→Lactic Acid→Glucose] is an example of gluconeogenesis**
  - 1)Pyruvate→oxaloacetate (catalyzed by pyruvate carboxylase)
  - 2)Oxaloacetate→phosphoenolpyruvate (catalyzed by phosphoenolpyruvate carboxykinase)
    - **Phosphoenolpyruvate carboxykinase production is inhibited by insulin**
    - Phosphoenolpyruvate Carboxykinase is the Rate-limiting step in gluconeogeneis
    - **Remember Insulin is for storage, except it stimulates glycolysis**
      - **Think Gluconeogenesis only happens when we're out of energy, Insulin says hey, we have energy, so don't go playing me like that!**
  - 3)Fructose-1,6-bisphosphate→fructose-6-phosphate (catalyzed by fructose 1,6 bisphosphatase)
  - 4)[Last Step] Glucose-6-phosphate→glucose (catalyzed by glucose-6-phosphatase)
    - **CAREFUL – in glycolysis it's Hexokinase that gets Glucose to Glucose-6-phosphate**



- Pyruvate
  - Directly can go to:
    - Gly, Ser, Ala, Cys
    - Acetyl-CoA
    - Oxaloacetate
    - Lactic Acid
    - Ethanol



- **Enzymes**
  - General Properties:
    - Enzymes have enormous catalytic power – accelerate reactions by factors of at least 10^6
    - Highly specific, both in the reaction catalyzed and in their choice of reactants
    - Their activity is somewhat regulated
    - **The rate of product formation is affected by: pH, temperature, ionic strength, [substrate] (but not isoelectric point)**
    - Enzyme-catalyzed reactions are characterized by formation of a complex between substrate & enzyme (an ES complex)
      - The binding occurs in a pocket on the enzyme called the active site
    - Equilibrium of a reaction is unaffected by the enzyme
      - This means that an enzyme accelerates the forward and reverse reaction precisely by the same factor
    - Enzymes function is to lower the activation energy for the reaction they catalyze and thereby enhance the reaction rate
    - Many enzymes require cofactors that frequently are metal ions or derivatives of vitamins
    - Boards Q: Methods of regulating enzyme activity: allosterism, zymogen activation, competitive inhibition
      - **NOT induction and repression**
  - Each of the following represents a key regulatory feature of an ezymatic cascade:
    - Amplification of an initiating signal
    - Coordinated control of enzyme activity in the target cell
    - Enzymes controlling the activity of other enzymes
    - ***Secretion of protein kinases outside the cell does NOT
  - Michaelis-Menton Kinetics



- **$V = V_{max}*([S]/([S] + K_m)$**
- Constant K_m:
  - Numerically equal to the [substrate in moles/liter] that gives half-maximal velocity, expressed as K_m = [S], when V_o = ½ V_{max}
  - K_m is equivalent to that substrate concentration at V_o (initial reaction velocity) is one half of V_{max}
  - K_m has units in molarity
  - Values range widely: from most enzymes K_m lies between 10^{-1} and 10^{-6} M
  - K_m value for an enzyme depends on the particular substrate and also on environmental conditions such as the temperature and ionic strength
  - Frequently **incorrectly** said to be the equivalent to the dissociation constant of the enzyme substrate complex
    - For most reactions it is a complex function of many different reactions constants, but it does give a means of comparison of the affinity (reciprocal of dissociation) of an enzyme for different substrates or different enzymes for the same substance
    - **The lower the K_m the higher the relative affinity**
  - K_m values for substrate reactions:
    - Increase in the presence of competitive inhibitor
      - Another Q: If the presence of a specific compound, C, increases the K, for an enzyme-substrate reaction, C would be a competitive inhibitor of the enzyme
    - Are **not** affected in the presence of noncompetitive inhibitor
- EX problem: for K_m = 1mM, when the [S] doubles from 10mM to 20mM, the velocity of the reaction increases slightly
  - NOTE the math: $V = V_{max}*(10/(10 + 1) = V_{max}*0.90 \rightarrow V = V_{max}*(20/(20 + 1) = V_{max}*0.95$ (slight increase)
- The velocity of a reaction increases with the substrate concentration if the enzyme concentration is constant
- At V_{max}, all of the active sites of the enzyme are saturated with substrate
  - So, the limited value of V_{max} of the reaction rate is due primarily to saturation of the enzyme with substrate
- The velocity of a reaction i
- ncreases with temperature until a maximum is reached, above which the enzyme will denature
- Lineweaver-Burk plot: (SEE ABOVE GRAPH)
  - **The y-intercept of a Lineweaver-Burk plot represents V_{max}**

➢ Inhibition Types: (SEE GRAPH)

- Competitive inhibition:
  - The competitive inhibitor resembles the substrate and binds to the active site of the enzyme
    - The substrate is then prevented from binding to the same active site
  - Inhibitor and substrate compete for the same binding site on the enzyme
  - Is overcome by increasing substrate
    - In other words, it just takes a bunch more substrate to get to half the max velocity!
  - V_{max} is unchanged
  - K_m is increased
- Noncompetitive inhibition:
  - The inhibitor and substrate both can bind to the NZ on different sites
  - Cannot be overcome by increasing substrate and is by definition an allosteric inhibitor (SEE BELOW)
  - The noncompetitive inhibitor binds to either a free enzyme or the ES complex
    - In other words, we blocked off and "ruined" allosterically some NZs, so we still can get to half velocity just fine with substrate, but even if we keep adding substrate we'll never hit our max velocity
  - V_{max} is decreased

- K_m is unchanged
- Uncompetitive inhibition:
  - Like noncompetitive, the inhibitor and substrate bind at different sites which do not overlap
    - But, uncompetitive inhibitors only bind to an enzyme which has a substrate already attached (ES complex)
- Irreversible inhibition:
  - Those that combine with or destroy a functional group on the enzyme that is essential for its activity
  - **Classic EX – irreversible inhibition of cyclooxygenase (COX) by aspirin (acetylsalicylate) which acetylates the active site serine residue**

➢ Allosteric enzymes:
- Frequently catalyze a committed step early in the metabolic pathway
- Often have two or more subunits each with substrate binding sites that **exhibit cooperativity**
- An allosteric modifier alters enzymatic reaction rate by interacting with the enzyme at non-active sites
  - Allosteric activators cause the enzyme to bind substrate more readily
  - Allosteric inhibitors cause the enzyme to bind substrate less readily
- A number of catabolic pathways are allosterically inhibited by an increase in the concentration of ATP
- Show a complex relationship between the velocity and substrate concentration
  - **Do NOT follow Michaelis-Menton kinetics – Because we altered NZ**
- The most common form of covalent modification is phosphorylation / dephosphorylation
- Kinases and phosphatases involved are themselves allosterically regulated
  - Protein kinases are the enzymes that phosphorylate certain AA residues in specific proteins
  - Through this process of phosphorylation, protein kinases act to regulate the activities of other enzymes

➢ Zymogens
- Inactive precursors of proteolytic NZs (i.e., digestive NZs)
  - Become active by removal of a peptide fragment
- EXs: pepsin, trypsin, chymotrypsin area all secreted as zymogens (amylase is not)

➢ Phosphatases
- Are any of a group of enzymes that liberate inorganic phosphate from phosphoric esters
- **Alkaline phosphatase and pyrophosphatase are two enzymes that play an important role in calcification**
  - Pyrophosphatase also may play a role in the mineralization of bone
- Alkaline phosphatase: (ALP)
  - Believed either to increase the local concentration of inorganic phosphate or to activate the collagen fibers in such a way that they cause the deposition of calcium salts
  - Involved in bone mineralization, hydrolysis of phosphoric esters, and functions optimally at pH 8.6
  - **Secreted from osteoblasts** that are actively depositing bone matrix
  - **High levels are seen in Paget's disease and osteosarcomas; low levels are seen in cases of hypophosphatasia**
- Acid phosphatase:
  - A phosphatase with optimum functioning at pH 5.4 and is present in the prostate gland
  - High levels are seen in carcinoma of the prostate gland
- Creatine phosphate:
  - Aka 'phosphocreatine'
  - An organic compound found in muscle tissue and capable of storing and providing energy for muscular contraction
  - During increased muscle activity, ATP is resynthesized from phosphocreatine

➢ Oncogene
- Produced when a mutation occurs in an NZ controlling a signal pathway involved in cell growth processes

❖ **Miscellaneous**

➢ Heat
- Principle energy laws:
  - Govern every organization; are derived from the two famous laws of thermodynamics
  - First Law of Thermodynamics (Energy Conservation)
    - Heat, being a form of energy, is subject to the principle of energy conservation
    - Total energy, incuding heat, in a closed system is conserved
  - Second Law of Thermodynamics: (restriction for heat)
    - Heat, being a form of energy, can be transformed into work and other forms of energy and vice versa
    - This transformation of heat energy is subject to a very important restriction:
      - ➢ Heat flows spontaneously from a hot body to a cool one
      - ➢ One cannot convert heat completely into useful work
      - ➢ Every isolated system becomes disordered in time
        - Entropy
          - is a measure of the degree of randomness or disorder in a system

- *Enthalpy
  - Heat content of a system (Heat has an "H" in it)
- Gibbs Free energy change:
  - In thermodynamics, GFE is the energy portion of the thermodynamic system available to do work
  - This is thermodynamic potential and is a state function
  - $\Delta G = \Delta H - T\Delta S$
    - Final – Initial = Δ
    - G = gibbs energy
    - H = Enthalpy
    - T = Temperature
    - S = Entropy
  - When is the free energy of a system at a minimum?
    - When the free energy of the final state is less than the free energy of the initial state
  - Certain chemical reaction proceed spontaneously until equilibrium is reached
    - Exergonic
      - Reactions that proceed with the release of energy
      - **Because the products of such reactions have less free energy than the reactants, the free energy change is negative**
    - Endergonic
      - Chemical reactions in which the products have more free energy than the reactants are endergonic
      - For these reactions the positive free energy change
      - **Reactions that have unfavorable energetics (+ delta Go) in metabolic pathways may be driven to completion by coupling**
      - Remember Positive ΔG is going uphill, and – ΔG is going down!!
- Calorimetry:
  - Method of measuring heat loss or energy loss
  - Putting a person in a tank of water and noting the temperature change in the water can measure human body heat
    - The body heat causes this change
  - Direct calorimetry:
    - The measurement of the amount of heat made by the body's processes

    This is a method of measuring energy released by the cells
  - Oxidative reactions (e.g., evaporation, radiation, conduction and convection) produce heat
  - Indirect calorimetry:
    - Human calorie use can also be measured in terms of the amount of oxygen inhaled and the amount of carbon dioxide exhaled during a given time
    - HENCE:
      - RQ = CO2/O2 → remember the 0.8
      - RQ quotient for a person taking pure glucose as food source is → higher than normal (normal is 0.8, with pure glucose is 1.0)
        - NOTE the RQ may be used to calculate the basal metabolic rate via the technique of indirect calorimetry
- Heat regulation:
  - Heat generating mechanisms – increased voluntary activity, shivering, and increased secretion of epinephrine from the adrenal medulla
    - **Shivering is the most important**
    - Vasoconstriction of cutaneous blood vessels prevents heat loss (does not generate heat)
  - Another Q: Mechanisms that raise body temperature include shivering, ATP hydrolysis, exothermic reactions, and increased thyroxine release (not peripheral vasodilation)
  - Heat loss includes – vasodilation of cutaneous BVs & increased sympathetic outflow to the sweat glands
  - **Both heat generating and heat loss mechanisms are activated by the posterior hypothalamus**
    - Mechanisms of panting, sweating, loss of appetite & cutaneous vasodilation are activated in response to heat
  - Human body temperature generally remains constant, thus heat gained equals heat lost
  - Heat is transferred between the body and environment via:
    - Radiation:
      - Emission of heat in the form of infrared rays
      - The body is continually exchanging heat by radiation with objects in the environment
      - Surface body temperature is usually higher than the surface temperature of most objects in the environment
    - Conduction:
      - Transfer of thermal energy as a result of direct contact between two objects; aided by convection
      - Body only loses heat when outside air is cooler than body heat

- Convection:
  - When air molecules exchange heat with the body surface and move away to be replaced by other molecules
- Evaporation:
  - Conversion of a liquid into a vapor
  - Heat is lost when water evaportates from the body surfaces
  - Water is lost from body surfaces in two ways:
    - **1) Insensible water loss – occurs by way of exhaled air and through the skin**
    - **2) Sweating – active fluid secretion by the sweat glands**
      - It must evaporate to produce its cooling effects
      - More effective means of cooling in low humidity than in high humidity environments
        - If the air temperature is 105o F and the relative humidity is 10 percent, evaporation is the primary cause for loss of body heat
      - Another Q: Someone working under conditions of high temperature should increase NaCl intake
      - Another Q: In prolonged sweating, the the extracellular fluid compartment experiences a decrease in volume & an increase in osmotic pressure
    - Man sweats a lot, you see → Low sodium retention (Right then, not what happens next to maintain BP)

- Osmosis:
  - The net diffusion of water through a semipermeable membrane caused by a concentration difference
- Osmotic pressure:
  - The pressure that develops in a solution as a result of net osmosis into that solution
  - It is affected by the number of dissolved particles per unit volume of fluid
  - Intracellular and extracellular fluids have similar total osmotic pressures
  - Another Q: The distribution of fluids between intracellular and extracellular compartments is mainly achieved by unrestricted movement of water to achieve osmotic balance
  - **Albumin affects osmotic pressure the most**
  - NaCl and KCl will ionize two ions therefore their osmotic pressure will differ from a single mole of glucose
  - One side contains 0.2 mol NaCl and other side has 0.2 mol glucose, which way does the water go → toward NaCl
- Osmolarity:
  - Osmotic pressure of a solution expressed in **osmols/kg** of solution
  - Calculating Molarity
    - Molarity = # of particles in solution x [] of each particle in solution
    - Ex: What is the molarity of 1M CaCl2 solution?
      - 1 Ca2+ x 1M + 2Cl- x 1M = 3 M/Liter
  - If a solution of 700 mOsm/L & one of 500 mOsm/L are separated by a membrane only permeable to water, there will be a net movement of water from the 2nd solution to the 1st
- Osmolality:
  - Osmotic pressure of a solution expressed in **osmols/kg** of water
- Tonicity:
  - Due to the presence of solutes which are impermeable across the cell membrane, which determine cell volume
  - Isotonic solution
    - A solution that when placed on the outside of a cell will not cause osmosis
    - **The cell neither shrinks nor swells: 0.9% NaCl or 5% glucose solutions are both approximately isotonic to plasma**
      - A 0.9% solution of NaCl is isotonic to blood since it exhibits the same osmotic pressure (osmolarity) as blood
      - Another Q: a 0.85% solution of NaCl is isotonic with respect to blood. It would also be isosmotic.
  - Hypertonic solution
    - A solution that when placed on the outside of cell will cause osmosis out of the cell and lead to shrinkage of the cell
    - NaCl solutions of > 0.9% concentration are all hypertonic
    - Infusion of hypertonic NaCl solution will decrease intracellular volume and increase extracellular volume
  - Hypotonic solution
    - A solution that when placed on the outside of a cell will cause osmosis into the cell & lead to swelling and cell lysis
    - Any solution of NaCl with < 0.9% concentration is hypotonic
- Systems of diffusible ions **(Gibbs-Donnan equilibrium)**
  - The presence of impermeable ions on one side of the membrane will result in
    - **Osmotic pressure**
    - **Transmembrane potential**
    - **Asymmetric distribution of diffusible ions across the membrane**
      - Sometimes the trapped ions are negatively charged, then the diffusible positively charged ions are drawn to them and gives an asymmetrical distribution of diffusible ions

- Because the negative proteins cannot diffuse, the potential that is set up would not disappear as the two sides cannot equilibrate

- Body Water
  - Body water:
    - Humans weight is due 50-60% because of water
    - Intracellular fluid: 2/3
      - **The largest amount of body water can be found in intracellular fluid**
        - 33% of total body water by weight
      - Major cations are K^+ and Mg^+. Major anions are protein and organic phosphates.
    - Extracellular fluid: 1/3
      - Made up of interstitial fluid and plasma.
      - Major cation is Na^+. Major anions are Cl^- and HCO_3^-
      - **Plasma ¼**
      - **Interstitial fluid ¾**
        - Largest component of extracellular fluid volume
        - 27% of total body water by weight
        - Fluid surrounding and bathing the cells
        - **Its composition is the same as that of plasma except it has a lower concentration of protein**
    - If you subtract the Extracellular Fluid, you can calculate the intracellular body fluid
- Edema:
  - Occurs when the volume of interstitial fluid exceeds the capacity of the lymphatics to return it to the circulation
  - Physical cause of edema is positive pressure in the interstitial fluid space
  - Conditions that will cause extracellular fluid edema:
    - Increased capillary pressure due, for example to blockage of a vein
    - Decreased plasma colloid osmotic pressure, due to decreased plasma protein concentration
    - Increased interstitial fluid colloid osmotic pressure (oncotic pressure) caused by a lymphatic obstruction
      - NOTE: Decreased lymphatic drainage promotes edema
    - Increased capillary permeability which may occur in certain allergic responses
    - Venous constriction and standing cause increased capillary hydrostatic pressure and tend to cause edema
    - Inflammation causes local edema by dilating arterioles and increasing permeability
      - This may be due to vasodilating kinins
  - Constriction of arterioles causes decreased capillary hydrostatic pressure and, as a result, decreased net pressure across the capillary wall. Arteriole dilation increases the likelihood of edema
  - Administration of a plasma volume expander could be beneficial in reducing edema in the arms of women who have had a radical mastectomy with removal of axial lymph nodes (this draws fluid from the interstitium to the blood)
  - Know how to calculate Net Filtration
- Immunoglobulins:
  - **Glycoproteins** found in blood serum; synthesized by plasma cells in the spleen and lymph nodes in response to the detection of a fsoreign antigen; they mediate anaphylaxis, atopic allergies, serum sickness, and Arthus reactions
  - IgG:
    - **The most abundant**; the only Ig which crosses the placenta; **main defense against various pathogenic organsisms**
  - IgA:
    - **2nd most abundant**; occurs in body secretions and protects surface tissues; synthesized by the plasma cells in the mucous membranes of the GI, respiratory and urinary tracts
    - IgA is the plasma protein subfraction that contains antibodies found bathing mucous surfaces (mouth, bronchial passages, small intestine)
    - Another Q: Secretory IgA is involved in bacterial aggregation & subsequent elimination from the oral cavity
    - sIGA is Polymeric → 2 IgAs joined by J chain
    - Another Q: IgA is the characteristic immunoglobin present in human external secretions
  - IgD:
    - Makes up < 1% of Ig's; present on MB of many ciruculating B-cells; function is unknown or not fully understood
  - IgM: (M for Massive and iMMediate)
    - **Largest Ig**; 1st Ab produced in response to infection; powerful activator of complement system
  - IgE:
    - Present only in trace amounts in serum; reagenic activity resides in this Ig; protects external mucosal surfaces;
    - **Tightly bound to its receptors on mast cells and basophils**; responsible for Type I hypersensitivity reactions (allergic and anaphylactic)
- A sound can be characterized according to its pitch, loudness, and timbre (quality)
  - Pitch:

- Related to sound wave frequency
- In general, the higher the frequency of a sound wave, the higher the pitch of the sound wave
- Frequency is measured in hertz (Hz) or cycles per second

- Loudness/Intensity:
  - Usually the greater the amplitude of a particular sound, the greater the intensity of the wave and the louder the sound
  - Intensity is measured in decibels (dB)
    - A 100 dB sound is 100,000 times greater than the human threshold for sound???
      - *I think this is right:* ***dB = 20 log (x);*** *if dB = 100, then 100/20 = log (x), which means x = 10^5 = 100,000*
      - ***The Threshold of hearing is O dB → 0 = 20 Log x → 0/20 = log x → 10^0 = x or 1***
- Timbre or quality:
  - Related to the presence of additional sound-wave frequencies superimposed on the principal frequency

➢ Bonds
- Covalent bonds:
  - Forces that hold atoms together
  - Forces are formed when the atoms of a molecule share electrons
  - Two examples of covalent bonds are peptide and disulfide
  - Hydrogen, oxygen, nitrogen, and carbon are capable of forming one, two, three, and four covalent bonds respectively
  - Carbon is very versatile and can form single, double, and triple bonds
  - Not normally broken under biologic conditions unless by enzymatic catalysis
- Weak bonds:
  - May be easily broken but are very important becaue they help to determine & stabilize shapes of biological molecule
  - **EX – important in stabilizing the 2° structure (alpha helix and beta sheets) of proteins**
  - Hydrogen bonds keep complementary strands of DNA together and also participate in enzymatic catalysis
  - These interactions are individually weak but collectively strong
  - Denaturing agents (organic solvents, urea, and detergents) act primarily by disrupting the hydrophobic interactions that make up the stable core of globular proteins
  - Are easily broken under normal biological conditions of temperature and pressure

➢ Isotopes:
- Same chemical properties but different weights
- Are stable or radioactive forms of an element
  - The radioactive forms of isotopes are often used as tracers
- Naturally occurring elements are usually mixtures of isotopes so that atomic weight is an average of values for the mixture
- Isotopes have the same atomic # but different mass #
  - The atomic # is the number of protons; mass number is the sum of protons and neutrons
  - Therefore, isotopes have the same # of protons but differ in the # of neutrons

➢ Bone matrix:
- Are affected by age, race, and gender:
  - Blacks commonly have denser bone whan whites, and men commonly have denser bones than women
  - Bone density and structural integrity (ability to withstand stress) decease after age 30 in women and 45 in men
  - Thereafter, a relatively steady quantitative loss of bone matrix
- The intercellular matrix of bone contains both organic components (glycosaminoglycans in the ground substance and collagen fibers) and inorganic salts
  - Inorganic salts consist primarily of Ca^{2+} phosphate, which is present in the form of highly insoluble HA crystals
    - According to chemical & x-ray diffraction studies, the structure of bone mineral is HA
    - These salts allow bone to withstand compression
  - Organic matrix is composed largely of collagen and GAGs
    - Collagen fibers provide bone w/ great tensile strength
  - Bone is an important calcium reservoir
- Osteoblasts:
  - Secrete the organic components of the intercellular matrix bone, including GAGs (5%) & collagen (makes up 95% of the intercellular matrix)
  - Within the period of days, the intercellular matrix calcifies via the deposition of insoluble calcium salts w/in it
- Some of the common GAGs present in the intercellular matrix of bone include hyaluronic acid and chondroitin sulfate
- Form organic matrix and require Vitamin A and C
- The intercellular matrix also contains a **calcium**-binding protein called **osteocalcin** as well as a **calcium** & **collagen**-binding protein called **osteonectin**
  - Osteonectin =

        - Bone specific protein
        - **Found in bone AND non-mineralized tissues**
        - **Provides sites of growth for the calcium crystals and anchors them to the organic matrix**
        - **Ca and collagen**
        - **What is more common in enamel??? → Hyaluronate or Osteonectin????**
    - Osteocalcin = only Calcium
    - Osteogenin
        - Matrix protein of bone
        - No binding affinity for Calcium to collagen
    - Amelogenin
        - Matrix protein of enamel
        - No binding affinity for Calcium to collagen
    - Fibronectin
        - Glycoprotein found in Extracellular matrix, on cell surface
        - Functions as adhesive-ligand like molecule
        - Promotes cell adhesion
        - Does NOT facilitate calcium and collagen binding
        - **Ehlers-Danlos syndrome**
            - a group of inherited generalized connective tissue diseases characterized by overelasticity and friability of the skin
            - hypermobility of the joints, and fragility of the cutaneous blood vessels and sometimes large arteries, due to deficient quality or quantity of collagen
                - Also associated with **Berry Aneurysms**
            - the most common is inherited as an autosomal dominant trait;
            - some recessive cases have hydroxylysine-deficient collagen due to deficiency of collagen lysyl hydroxylase, and two tentatively ascribed to X-linked inheritance.
- Coumadin
    - Rx to prevent Stroke
- Cyandide Poisoning
    - Cyanide affects virtually all body tissues, attaching itself to ubiquitous metalloenzymes and rendering them inactive.
    - Its principal toxicity results from inactivation of cytochrome oxidase (at cytochrome a3), thus uncoupling mitochondrial oxidative phosphorylation and inhibiting cellular respiration, even in the presence of adequate oxygen stores.
    - Cellular metabolism shifts from aerobic to anaerobic, with the consequent production of lactic acid.
    - Consequently, the tissues with the highest oxygen requirements (brain and heart) are the most profoundly affected by acute cyanide poisoning.
    - Acute cyanide poisoing most likely results in decreased oxygen extraction by peripheral tissue
- Fainting (Vaso-vagal)
    - Associated with Pallor, Diaphoresis, Decreased Heart Rate, Decreased Cerebral Flow
        - NOT Increased Systemic Blood Pressure

SWEET NUGGETS FROM USMLE

- Activated Carriers
    - Phosphoryl (ATP)
    - Acyl (Coenzyme A, Lipoamide)
    - Electrons (NADH, NADPH, FADH2)
    - CO2 (Biotin)
    - One-carbon units (Tetrahydrofolates)
    - CH3 groups (SAM)
    - Aldehydes (TPP)
    - Glucose (UDP-Glucose)
    - Choline (CDP-Choline)
- Metabolism Sites
    - Mitochondria (Energy)
        - Fatty acid oxidation (Beta-oxidation)
        - Acetyl-CoA production
        - Krebs cycle
    - Cytoplasm
        - Glycolysis
        - Fatty acid synthesis
        - HMP shunt
        - Protein synthesis (RER)

- Steroid synthesis (SER)
- Both
  - Gluconeogenesis
  - Urea cycle
  - Heme synthesis

- Alcohol Dehydrogenase
  - **Ethanol** → ***(via Alcohol Dehydrogenase)*** → **Acetaldehyde** → ***(via Acetaaldehyde Dehydrogenase)*** → **Acetate**
    - Both Rxns go via NAD+ → NADH
    - So NAD+ is the limiting reagent
    - Alcohol Dehydrogenase operates **via zero order kinetics**
  - Ethanol metabolism increase NADH/NAD+ ratio in the liver, causing diversion of pyruvate to lactate and OAA to malate
    - This inhibits gluconeogenesis and leads to hypoglycemia
    - **This altered NADH/NAD+ ratio is responsible for the hepatic fatty change seen in chronic alcoholics**
      - Pruvate → Lactate
        - *(Via NADH to NAD+)*
      - Oxaloacetate → Malate
        - *(Via NADH to NAD+)*
- Kwashiorkor vs. Marasmus
  - Kwashiorkor
    - Results from a protein-deficient **MEAL**
      - Malabsorption, Edema, Anemia, Liver (fatty)
    - Clinically, a small child with swollen belly
  - Marasmus
    - Protein-calorie malnutrition resulting in tissue wasting
- Cell cycle Phases
  - M
    - When is DNA conc inside a cell lowest? I phase, **between G1-S phase**, M phase
    - In what phase does nondisjunction occur most rapidly??
    - Mitosis (PMAT)
    - Usually shortest phase
    - Protein & RNA synthesis occur in each of the following phases of the cell cycle, except M (does occur in G_0, G_1, S & G_2)
  - Interphase (G_1, S, G_2)
    - G_1
      - Growth Phase
      - Rapidly dividing cells have a shorter G_1 Phase
      - Most variable phase in the cell cycle
    - S
      - Synthesis of DNA
    - G_2
      - Growth Phase
  - G_0
    - Quiescent Phase
    - Most cells are in this phase
- **S-adenyl Methionine (SAM or AdoMet)**
  - **Contains an active (labile) methyl group**
  - SAM synthetase synthesizes SAM from Methionine and ATP
  - SAM is the methyl group donor for most of the methylation reactions in all organisms
    - Examples: synthesis of phosphocreatine, high-energy phosphate active in muscle ATP production
  - Regeneration of methionine (hence SAM) is dependent on **Vitamin B12**
  - The methyl group of methionine is transferred to the substrate and then the demethylated SAM or AdoMet is released

Random Qs

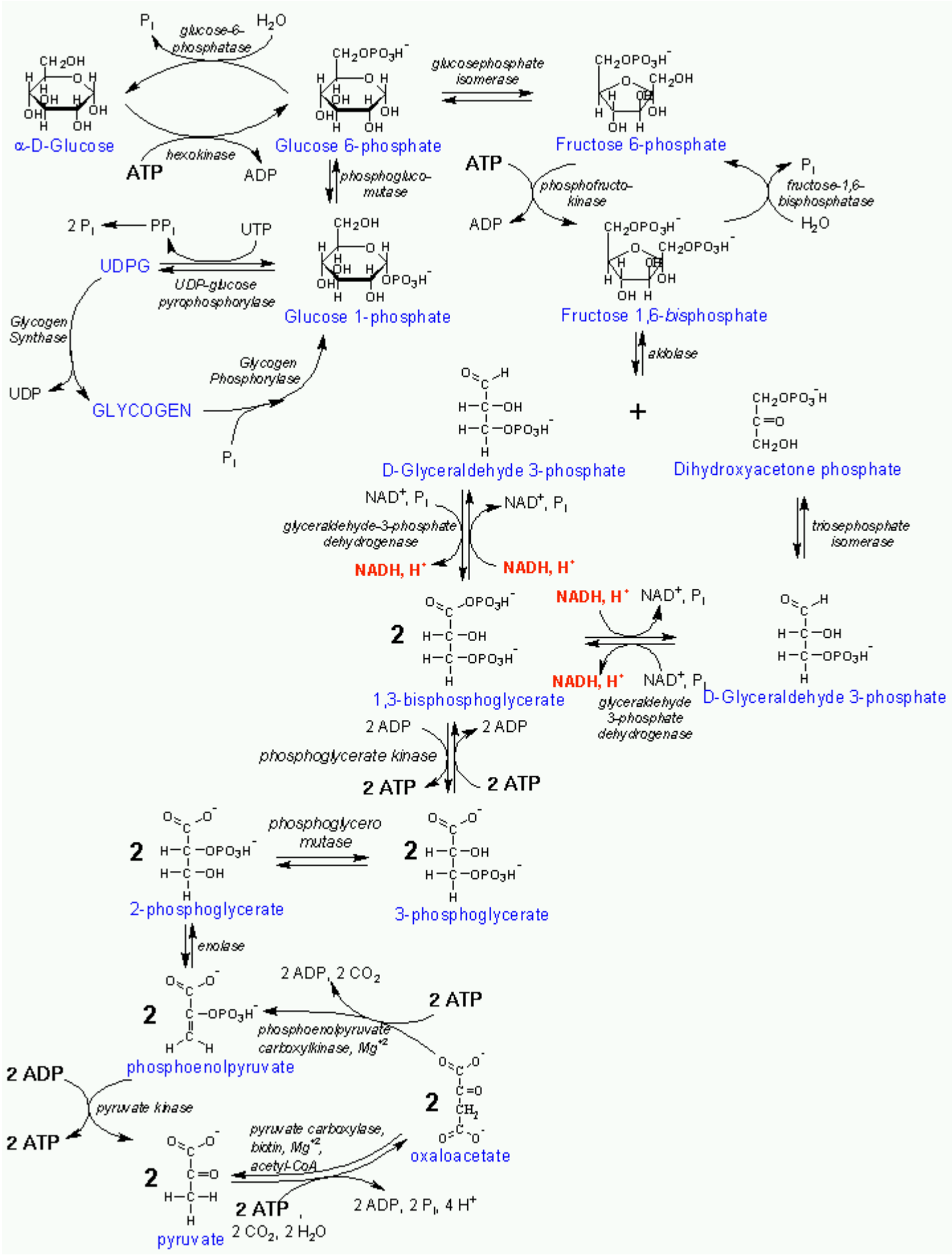
- Oncofetal antigen
  - Tumor associated antigen present in the fetal tissue, but not adult
    - Examples: alpha-feto protein (kidney) and carcinoembryonic antigen
- Cyclin proteins do what in the cell cycle?
  - Activate protein kinases (cyclin-dependent kinases) at various stages throughout mitosis
  - Allows it to go From G1 to S phase

- Destroyed by the ubiquination/proteasome pathway
  - Part of the Mitosis Promoting Factor (MPF –cyclin/cyclin DK)

- Ksp
  - A compound is soluble when what is greater than its solubility constant (Ksp)?????
- Add info on Streptomycin
  - Streptomycin is an antibiotic which inhibits the process of transcription in prokaryotes
- Add somewhere???
  - Electronegativity in living cells requires that a potential for charge separation exists

USC messed up the following questions:
1978 Q91 (options (c) & (d) should be iron & copper, respectively – then the listed answer is correct)
1979 Q03 (answer should be (c) – compare w/ '81 Q05); Q05 (the answer is in the question – it should've been option (a)) Q 89 (In the lungs, HCO3- comes in and Cl- goes out, then HCO3- goes to H2CO3 and pushes out CO2 and H20)
1982 Q25 (should be (e) decreased venous return – compare w/ '85 Q36)
Lame questions:
1979 Q88
1982 Q24 (None of the above – lame-o); Q28 (2 correct answers (b) & (d))
Huh?
1979 Q40; Q53; Q70
1981 Q22

Questions I have a problem with:
78 Q51 (ADH – cells of the posterior hypophysis? NO!) 55 (NO!, it's PTH that increases Ca absorption in intestine), 59
85 Q02 (wrong – 1,25-etc), 15 (none of the above), 66, 85 (ACTH?), 89
89 Q06 (look closely at #6 – CO_2), 26 (same problem in B), 43 (B12, not B2)
96 Q53 (should be 10^{-5})
Questions to review (add to notes)
78 Q50 (Volume per cent?) 82 Q74, 81
85 Q03, 38
87 Q17 (not covered), 53, 73, 80, 90, 91, 99
89 Q09, 14, 25 (just read), 81, 85, 89, 92
96 Q63, 84


α-D-Glucose
glucose-6-phosphatase
Pi
H2O
hexokinase
ATP
ADP
Glucose 6-phosphate
glucosephosphate isomerase
Fructose 6-phosphate
phosphoglucomutase
ATP
phosphofructokinase
ADP
fructose-1,6-bisphosphatase
Pi
H2O
Fructose 1,6-bisphosphate
2 Pi
PPi
UTP
UDPG
UDP-glucose pyrophosphorylase
Glucose 1-phosphate
Glycogen Synthase
UDP
GLYCOGEN
Glycogen Phosphorylase
Pi
aldolase
D-Glyceraldehyde 3-phosphate
Dihydroxyacetone phosphate
triosephosphate isomerase
NAD+, Pi
glyceraldehyde-3-phosphate dehydrogenase
NADH, H+
NAD+, Pi
NADH, H+
2
1,3-bisphosphoglycerate
NADH, H+
NAD+, Pi
NADH, H+
NAD+, Pi
glyceraldehyde 3-phosphate dehydrogenase
D-Glyceraldehyde 3-phosphate
2 ADP
phosphoglycerate kinase
2 ADP
2 ATP
2 ATP
2
2-phosphoglycerate
phosphoglycero mutase
2
3-phosphoglycerate
enolase
2 ADP, 2 CO2
2 ATP
2
phosphoenolpyruvate carboxykinase, Mg+2
phosphoenolpyruvate
2 ADP
pyruvate kinase
2 ATP
2
oxaloacetate
pyruvate carboxylase, biotin, Mg+2, acetyl-CoA
2
pyruvate
2 ATP
2 CO2, 2 H2O
2 ADP, 2 Pi, 4 H+