BIO 3320
Advanced Human Physiology

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BIO 3320 Advanced Human Physiology

PHYSIOLOGY: The function of the human body and its parts. The specific characteristics and mechanisms of the human body that make a living being. Physiology seeks to integrate the functions of all the different parts of the body to understand the function of the ENTIRE human body.

Cell Physiology - Each type of cell is specially adapted to perform one or a few particular functions. The body is a special order of about 100 trillion cells organized into different functional structures.

Cell - The basic living unit of the body.

All cells combine to breakdown products of fat, CHO's, or protein with 0_2 to make ENERGY.

The general mechanisms for producing energy in all cells are basically the same.
All cells deliver their end products of their reactions to the surrounding fluids.
Almost all cells REPRODUCE.
Cells are bathed in extra-cellular fluid.

Body Fluid Content = 60% human body is fluid. 1/3 is extracellular fluid; 2/3 intracellular.

Intracellular Fluid - K^+, Mg^{++}, $P0_4$; Fluid inside a cell represents 2/3 total body fluid.

Extracellular Fluid - Na^+, Cl^-, Ca^{++}, Fluid outside the cell; 1/3 total body fluid; internal environment of the body.

HOMEOSTASIS

Maintenance of static or constant conditions in the internal environment.

Two general mechanisms involved:

1) NEGATIVE FEEDBACK MECHANISMS (Most control systems of the body)
Definition: when a controlled measure opposes a disturbance to a system or
When a factor is excessive or deficient a series of changes is initiated to return the factor to normal.

Example: $C0_2$ regulation
$[C0_2]$ in extracellular fluid increases = Pulmonary ventilation increase
High $C0_2$ present = More $C0_2$ expelled

2) POSITIVE FEEDBACK MECHANISMS
leads to instability -- continues until the stimulus is removed
• 2 L of blood loss = death (positive feedback)

Examples of Positive Feedback:
The Clotting Cascade
Childbirth -Generation of nerve signals

Regulation of Body Systems

Predominantly through Nervous System and Endocrine System

The Cell and Its Function

The cell composition:
nucleus, cytoplasm and organelles

1) Protoplasm = cytosol
- H_20 = - Electrolytes: K^+, Mg^{++}, $P0_4$, $S0_4$, $HC0_3$ (Na^+,CI^-,Ca^{++})
- Protein
- Lipids = Phospholipids, Cholesterol (Fat soluble) = 2%
- CHO's = 1% - 3% (1% to 6% in liver) serve as nutrients

*except "fat cells" where triglyc. = 95% cell mass

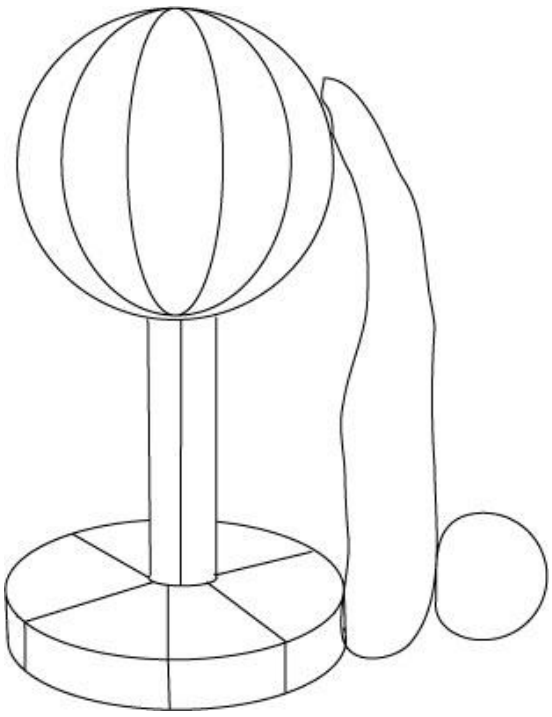
2) Organelles

A) Mitochondria

- Self replicate
- Most metabolism occurs here
- Outer membrane
- Inner membrane
- Produces ATP
- Glycolysis: Breakdown glycogen to glucose

Glucose ⇨ 2 pyruvate ⇨ acetyl CoA ⇨ TCA/Kreb's cycle ⇨ C02 + H's H's drive ETC
(Electron Transport Chain)

Rotary Catalyst Mechanism: Chemi-Osmotic Hypothesis



$F_0 F_1$ATPase Synthase

Glucose Energy Production

Four Main Functions of Energy Production
1.

2.

3.

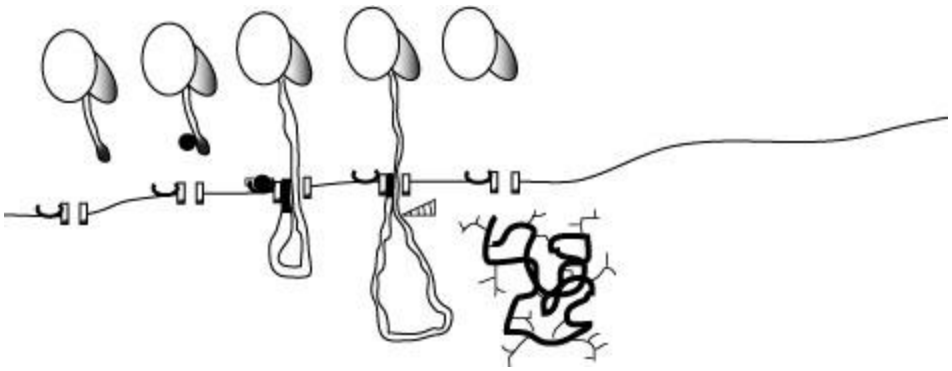
4.

Nucleotides (ATP)

B) Endoplasmic Reticulum
-a large network of tubules & vesicles penetrating the cytoplasm
-directly connected to nucleus (continuous with nuclear envelope)

Function:
Transport
-produce lipids (smooth)

-produce proteins (rough)



Two Types of Proteins

1) Structural-

2) Globular-

C) Golgi Apparatus

stores & packages products of ER (predominantly in the secretory cells)

Lysosome

intracellular digestive system
contain hydrolytic digestive enzymes

Peroxisome

oxidizes molecules to break them down

D) Nucleus

the control center of the cell and contains large amounts of DNA = genes
Nuclear membrane (envelop): separates nucleus from cytoplasm
Dual membrane:

E) Nucleolus

condensed mass of RNA within nucleus
No membrane

F) Non-membranous organelles –

Microvilli

Cilia

Axoneme

Tau proteins

GENETIC CONTROL OF PROTEIN SYNTHESIS, CELL FUNCTION, AND CELL REPRODUCTION

DNA - Deoxyribonucleic Acid
comprise genes
Genes control protein synthesis/cell function
Controls the formation of RNA (ribonucleic acid)

Nucleotide: composed of phosphate groups, deoxyribose, & a "base"

Base Pairs:	Purines	Pyrimidines
	A	T
	G	C

Genetic code
- consists of triplets of bases
- Codon: each triplet that codes for a specific amino acid
- Codon: complimentary code triplets (to DNA) formed in mRNA

TWO MAIN STEPS OF PROTEIN SYNTHESIS: Transcription & Translation

1) TRANSCRIPTION - transcribing DNA
DNA makes a complimentary copy of RNA - which leaves nucleus and travels to cytoplasm

*The DNA template is used to assemble RNA from activated nucleotides

*RNA polymerase recognizes and attaches to the promoter

*Polymerase unwinds 2 turns of DNA

*Polymerase binds complimentary RNA nucleotides to DNA

*RNA nucleotides bind to each other forming a strand

*Polymerase encounters CHAIN TERMINATING sequence - polymerase breaks off

*mRNA is released into cytoplasm

Operon - control biochemical synthesis; are activated by a promoter

RNA Polymerase

1) Adds complimentary RNA nucleotides
2) Cleaves off the 2 extra Phosphates
3) Uses this energy to bond phosphate to sugar

RNA - ribonucleic acid

Uracil is substituted for thymine (Pyrimadine subs.)

DNA Base	**RNA Base**
Cytosine	Guanine
Adenine	Uracil
Thiamine	Adenine
Guanine	Cytosine

3 types of RNA
*mRNA - messenger transcribes code from nucleus to cytoplasm

*tRNA - transfer - located in cytoplasm; brings A.A. to ribosome to help build a protein molecule; recognizes codon-anticodon

*rRNA-ribosome-where P's assembled - heavy unit/light unit is docking station for mRNA

2) TRANSLATION

function: Protein Synthesis

*mRNA enters ribosome and reads it

*tRNA selects codons

*Peptide linkages

*protein is built

*chain terminating sequence

Two methods of controlling the Cell's Biochemical Activities:

1) GENETIC REGULATION

Promoter - a series of nucleotides that has an affinity for RNA polymerase

Operon - a sequence of genes located in a series one after another on the same Chromosomal DNA strand which controls the formation of all the enzymes needed for the synthetic process

Repressor - a band of nucleotides central to the promoter; a "regulatory= repressor protein"

Activator substance or inducer substance - changes the repressor protein - activates or induces transcription

2) ENZYME REGULATION - cell activities are controlled by intra-cellular enzyme levels

A) Enzyme Inhibition - when the substance formed has a direct feedback effect

B) Enzyme Activation - enzymes that are normally inactive are activated when needed.

Protein Synthesis

1) AA Activated when ATP combines with AA to form AMP

2) This activated AA+AMP complex binds with a specific tRNA to form a AA-tRNA complex and releases the AMP

3) The tRNA-AA contacts the mRNA bound to the ribosome and the anticodon of the tRNA binds to the codon of the mRNA

4) Peptidyl transferase binds the new AA to the existing AA chain via dehydration synthesis

Protein Synthesis:

CELL REPRODUCTION - controlled genetically

Life cycle of cell - the period from cell reproduction to the next reproduction

Interphase - the intervals between mitosis

Mitosis - the process by which the cell splits into 2 new daughter cells
*lasts about 30 minutes
Bone Marrow Cells - life cycle of 10 hrs (rapidly reproduce)
Nerve cells - lifetime lifecycle (do not reproduce)

Replication vs. transcription
1) DNA Replication - both strands are replicated
DNA Polymerase; each new strand remains attached by DNA ligase.

2) Transcription -1 strand replicated; small portions replicated

After replication mitosis begins cell division.

Interphase

Prophase - beginning of mitosis; spindle forms; chromosomes condense

Prometaphase - spines of the aster puncture nuclear envelope, aster fibers attach to chromatid

Metaphase - chromatids to center of cell spine equatorial plate

Anaphase- chromatids pulled apart = 2 sets of 46 daughter chromosomes

Telophase - sets pulled apart - new cells

Cytokinesis - pinching of the cells apart to form new cells

Result of Mitosis = 2 new cells

Cell Differentiation = allows different cells of the body to perform different functions

Selective Repression - results in cell differentiation

Most mature cells in the human being produce about 8000 to 10,000 proteins rather than the potential 100,000 or more if all genes were activated.

Things can go wrong!

Cancer:
mutation or abnormal activation of cellular genes that control cell growth and cell mitosis

1) Mutation of DNA in the cell

2) Abnormal activation of cell genes that control growth/mitosis

Mutated cells usually don't produce cancer because:
*Most mutated cells have less survival capability than normal cells and they die
*Most mutated cells still have normal feedback controls that prevent excessive growth
*Mutated cells are often destroyed by the immune system
*Usually, several different oncogenes must be activated at the same time

Angiogenin – hormone that causes vessels to grow into a tissue to give it O_2 and nutritional supply, keeps it from being hypoxic

MEMBRANE PHYSIOLOGY

Functional Properties:

1)

2)

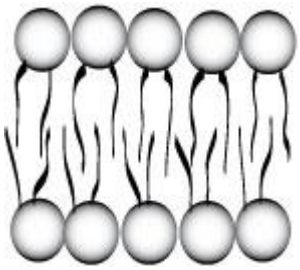
3)

4)

Components of the Cell Membranephospholipids

A) phospholipids

Phopholipid Bilayer nature of cell membrane creates a semi-permeable membrane and constitutes a barrier for the movement of most H_20 soluble substances



B) cholesterol

C) proteins

The protein molecules within the cell membrane allow passage for these water-soluble molecule

1) Integral Proteins: mostly glycoproteins
   a)
   b)

2) Peripheral Proteins:

a)

b)

c)

Transport across the membrane INVOLVING PERMEATION (through the actual membrane)

2 Mechanisms:

1) Passive transport: "Natural" process requires:

2) Active transport: requires:

Gradient:

Example:

Extra-Cellular Fluid	Intra-Cellular Fluid
Na	K (low Na^+)
Cl	Phosphates & Proteins
Glucose	amino acids / proteins

Passive Transport - uses only kinetic energy

DIFFUSION

Random movement of molecules thri intermolecular spaces in the membrane or with a carrier protein from a higher concentration to a lower concentration until the gradient is removed.

Particles/molecules naturally move from one area because of the energy imparted into the system.

Brownian Movement:

0_2, N_2, $C0_2$, -OH's, F.A.s move easily through membrane

H_20, Urea - require channels

Membrane-Bound Protein Channels

3 Main Types:

1) Voltage Regulated: Na^+ gates

2) Chemical Regulated: Acetylcholine

3) Leak Channels: Na, K

FACILITATED DIFFUSION

KNOWN AS CARRIER - MEDIATED DIFFUSION;
A SUBSTANCE TRANSPORTED IN THIS MANNER CANNOT USUALLY PASS THROUGH THE MEMBRANE WITHOUT A TRANSPORT PROTEIN

A conformational change occurs in the carrier protein that allows a molecule to pass through the cell membrane.

LIMITATIONS OF CARRIER-MEDIATED TRANSPORT:

1) Saturation

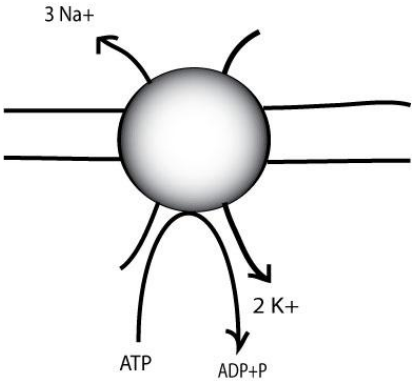
2) Regulation

3) Specificity

ACTIVE TRANSPORT

MOVEMENT OF MATERIALS BY: using additional energy or carrier proteins

Movement against the electrochemical gradient



Stepwise mechanism of PRIMARY Active transport:
1)

2)

3)

4)

Na^+ / K^+ ion pump:

MEMBRANE – BOUND PUMPS
Carrier proteins that move molecules against the concentration gradient

Examples of 3 Pumps
1) Na-K ATPase Pump:

2) Ca Ion Pump

3) H Ion Pump

2 TYPES OF SECONDARY Active Transport:

1) co-transport - the diffusion energy of anion "pulls through" another substance

2) counter-transport - a substance binds the exterior of the protein & the other substance binds interior;
1 substance pulls both through

Co-transport – transport molecules in the same direction
Usually Na and other substance

Counter transport = Na^+ -----Ca^{++}
Na^+ ---- H^+

Classic Example of Active Transport

*H_20 tend to enter cell and causes:
*BUT - as long as Na/K pump active cell does not swell. Why?

2 Types Transport Proteins

1) Channel Proteins - have a channel through their center for passage of ions

2) Carrier Proteins - conformational change of protein substance binding allows substance to pass through

Lipid solubility determines ease of diffusion across the membrane for lipid soluable molecules.

Factors affecting Diffusion Rate

1) increase membrane thickness

2) Lipid solubility; more soluble in lipid

3) Number of P channels; increase number

4) Increase temp

5) Increase m. wt.

Diffusion Coefficient

D = P x A (Permeability) x (area)

Number of molecules that pass thru membrane/time

Net Diffusion
Overall movement of a molecule towards the inside/outside of a cell membrane

C = [ ]

ND α D ($C_0 - C_1$)

ELECTROCHEMICAL CHARACTERISTICS OF THE CELL MEMBRANE

1) Polarization of the Cell Membrane
Requires energy to move charges against the concentration gradient.
Overall charge on the inside of the cell membrane is negative.
Overall charge on the outside of the cell membrane is positive.
Serves to generate an electrical potential across the cell membrane.

2) Depolarization of the Cell Membrane
An "unpolarization" of the cell membrane.
Allowing the charges (ions) to move down their concentration gradient.
The electrical potential is eliminated.

RMP (Resting Membrane Potential)
Neuron = -90 mV
Skeletal = -85 mV
Cardiac = -90 mV

Developed by Three Main Factors
1) Na/K Ion Pump

2) Na/K Leak Channels

3) Negative Protein Molecules

All 3 Contribute to the Resting Membrane Potential

ELECTROCHEMICAL GRADIENT
The effect of charges of ions on a concentration gradient.
The sum of the electrical charge and the chemical gradient that will determine which way an ion will diffuse across a membrane

NERNST Equation:

(mv) EMF (electromotive force) =
+ or - refers to the overall charge
of the inside of the cell membrane

Equilibrium Potentials

Na = +61 mV
Sodium will flow into the cell until the charge across the cell is +61 mV.

K = -94 mV
Potassium will flow outside the cell until the charge across the cell membrane is –94 mV.

GOLDMAN Equation
Determines the EMF of a semipermeable membrane for several different ions.

EMF=

Voltage/Chemically Regulated Ion Channels (General Characteristics)

1) Na^+ channel (fast)
    a) allows only small molecules through

    b) very strong negative charge

    c) precise size and geometry for Na

2) K^+ channel (slow)

a) allows K though

b) pore has neutral charge

c) precise size and geometry for K

*These 2 factors eliminate Na^+ from being attracted to channel

PROTEIN GATED CHANNELS

Voltage Controlled

1) Na^+ Voltage Regulated Gate
Regulated by voltage across the cell membrane Na^+ gate stays closed

Change membrane polarity
Na^+ voltage gate opens
Na^+ flows into cell to decrease gradient

-90 mV

+30 mV

2) K^+ Voltage Regulated Gate
With the normal negative charge inside the cell the K gates stay closed.

-90 mV

+30 mV

Chemically Controlled

Commonly located on the cell body and dendrites of the nerve.
When chemical messenger binds to the protein the gate opens or closes.
This changes the conformation to either open or close the gate.

Ex. Acetylcholine gate

Characteristics of the ACH gate
1)

2)

3)
a)

b)

The Structure of a Nerve Cell

Steps of Depolarization

1) Local Depolarization = Dep. Threshold = -60mV

2) Open V reg. Na^+ ion gates

3) Na^+ ion gates close +30mV

4) K^+ ion gates open

5) -70mV K^+ ion gates BEGIN to close (slowly)

6) Hyperpolarization (continual K^+ leak)

7) Na^+/K^+ ion pump repolarizes to -70mV

Ca^{++} Ion Pump
pumps Ca^{++} outside the cell

Calcium Ion Voltage Gated Channels
Ca^{++} rushes in @ a slower pace than Na^{+}
Ca^{++} ion gates are prevalent in smooth & cardiac tissue (norm RMP -85 to-90 mV)

What happens if Ca^{++} level decrease by 50% in extracellular fluid?

Drives membrane toward + side, so RMP approaches depolarization threshold.

Action Potential
Depolarization of a cell membrane which travels like a wave over the cell membrane.

Action Potential
Unmyelinated axon

Myelinated axon
leap frog reaction of electrical impulse down axon

OSMOSIS
MOVEMENT OF H_20 DOWN THE CONCENTRATION GRADIENT
It is the diffusion of H_20.

Capillary Hydrostatic Pressure
Pressure within the capillaries.

1) heart

2) gravity

AG ratio = Albumin/Globular Ratio

Osmotic Pressure
Amount of pressure required to stop osmosis from occurring (mm Hg).

Molar Concentration
Number of particles/unit volume of fluid, not it's mass that determines osmotic pressure.

Osmolatility - solute [conc] expressed in number of particles in solution per Kg of H_20 (aka OSMOLE)

Osmole - 1 Mwt. of undissociated solute

180 grams of Glucose = 1 gram Mwt. of glucose

Osmolarity = osmoles /L soln.

ENDOCYTOSIS
THE MOVEMENT OF VERY LARGE PARTICLES OR WATER INTO THE CELL.

1)Pinocytosis - Cell Drinking; ingestion of small vesicles that contain extracellular fluid.

Clathrin- a network of contractile fibers or filaments under the region where vesicle is ingested.

2)Phagocytosis - Cell Eating; ingestion of large particles.

EXOCYTOSIS
THE EXCRETION OF INTRACELLULAR PARTICLES AND FLUID TO THE EXTRACELLULAR SPACE

NEUROMUSCULAR PHYSIOLOGY

The skeletal muscle cell is multi-nucleated, because myoblasts fuse in embryological development to form 1 large muscle fiber/cell.

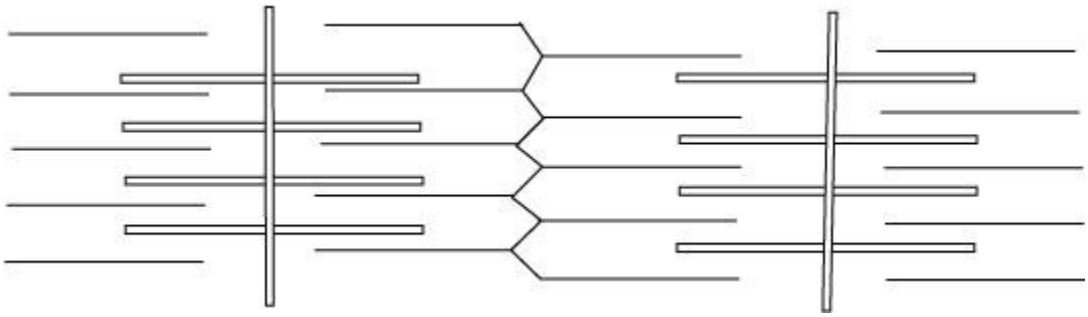
Myofibrils - filament attach from end to end of muscle cell.

Sarcomere - functional unit of myofibril from Z-line to Z-line.

Thin Fiber - actin (Narrow 5-6 nn) 1 micron long.

Thick - myosin (10-12 nm dia.) 1.6 microns long.

The Sarcomere (Functional Anatomy)



A-band = contains all of the myosin
H-band = contains only myosin
I-band = contains only actin
Overlap area = active/myosin overlap

Sarcoplasmic Reticulum
Network of tubes that surround myofibrils contain:

2-Terminal cisterna enlarge ends of S.R. that act as:

T-tubule (transverse tubule)
Extension of sarcolema which envaginates down into cell and butts up against the terminal cisternae.

Triad

Components of the Thin Filament

G Actin – globular actin

F Actin - backbone of the actin - a double strand of G – actin

Nebulin

Tropomyosin
Protein strand that covers active sites on G-actin

Troponin - rotates tropomyosin off of active sites on actin in the presence of Ca^{++}

*Troponin I -
*Troponin T -
*Troponin C –

Once troponin binds to tropomyosin it rotates tropomyosin off of the actin to initiate contraction.

Sliding Filament Theory

Myosin Molecule

1) Myosin head binds ATP to it splitting the ATP into ADP + Pi

2) Ca^{++} binds to troponin which rotates tropomyosin off of active sites of actin

3) Cross bridging between myosin head & active site on Actin

4) Power Stroke - allows the movement of myosin head

5) Cross bridge detachment

   Rigor Mortis =

6) Myosin reactivation

   Cycle stops if:

FAST TWITCH FIBERS VS. SLOW TWITCH FIBERS

SLOW	**FAST**
Myoglobin	Extensive SR
Increase storage of O_2	Increased glycogen
Lots of mitochondria	Fewer mitochondria
Smaller diameter	Larger diameter

Increased blood supply	
Sustained respiration	

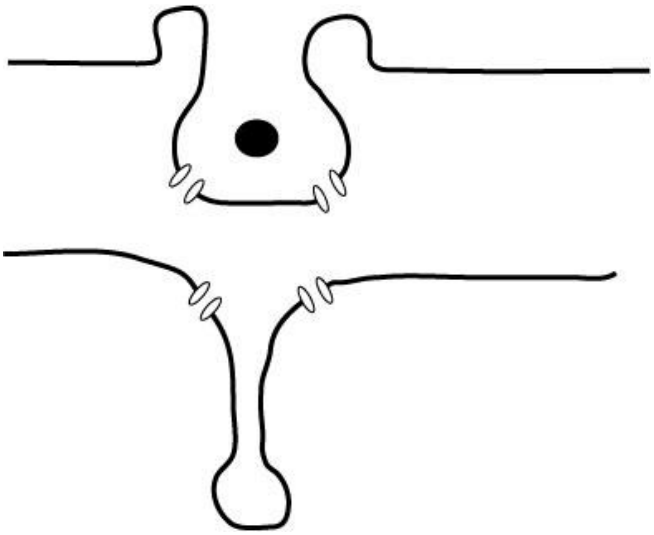
TREPPE:

Repetitive contractions do not allow Ca^{++} back into sarcoplasmic reticulum fast enough so-->

Anatomy of the Neuromuscular Junction

Release Sites
Synaptic Vesicles

Ca^{++} Channels Dense Bar



ACH Receptor Site/Channel for Na^{+}

Subneural Cleft

Motor End Plate
The junction between the synaptic Knob and the muscle (Neuromuscular Junction)

Initial Steps in Muscle Contraction

1) Action potential travels along the axonal cell membrane

2) Opens up-

3) Ca^{++} ion influx-

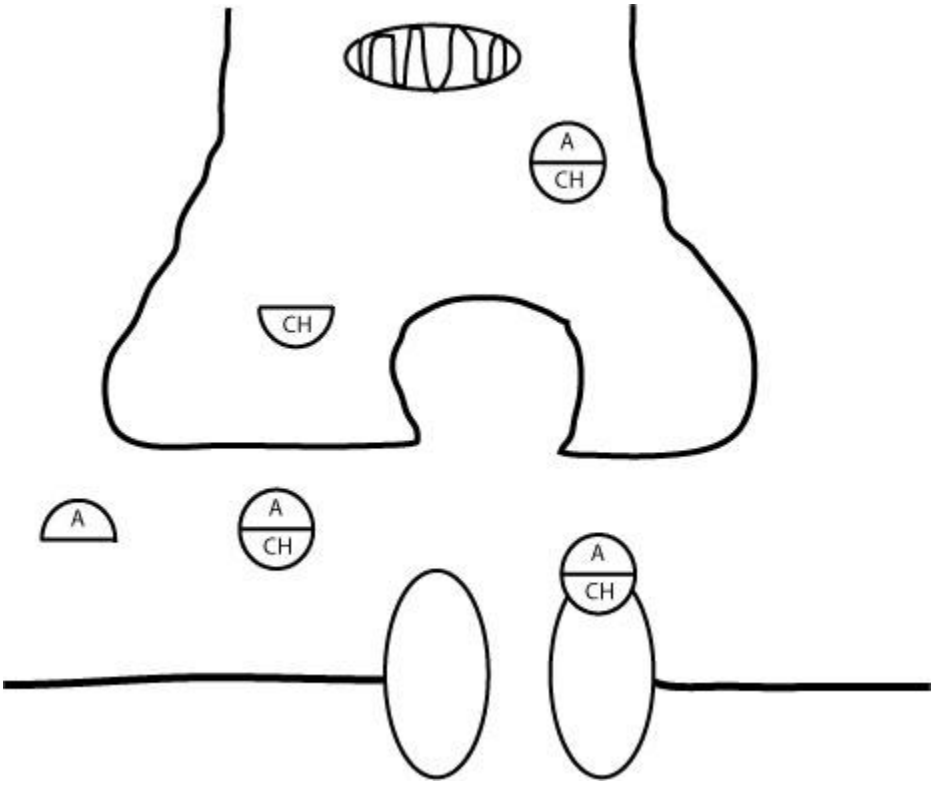
4) ACH binds-

5) Wave travels-

6) Depolarization-

ACH Degradation

About 1/2 of the ACH does not reach the receptors sites.



Drugs

Curare- blocks gating action of acetylcholine at receptor site.

Botulism Toxin (BOTOX)- decreases release of ACH from nerve cell.

Malathion- anticholinesterase drug

Nicotine- has same affect on muscle cell, but is not broken down by ACHase very quickly.

Black Widow Venom-

• Myasthenia Gravis- Auto-immune disease

SMOOTH MUSCLE

Anatomy of a Smooth Muscle

Unitary Smooth Muscle- A mass of smooth muscle (sheet) contracts together as one unit via gap junction connections.

Actin Organization- relatively unorganized

Myosin- relatively unorganized

ATPase- greatly reduced in smooth muscle tissue so the actin stays active and the muscle contraction lasts longer ~ up to 2 to 3 seconds longer

Cross-Bridge Detachment- for smooth muscle is a much longer period.

Smooth Muscle Disorganization-

Smooth Muscle Cell Signaling Pathway for Calcium Release

Smooth Muscle Contraction Cycle

Smooth muscle does not have troponin. Instead, it has a regulatory protein called calmodulin.

Calmodulin

Initiates smooth muscle contraction in the presense of Ca^{++}

Mechanism for Contraction

Calmodulin binds with Ca^{++}

Activating calmodulin

⇩⇩⇩

Myosin Kinase (light chain)

Phosphorylation adds a phosphate on the myosin head

⇩⇩⇩

Cross-bridging occurs between actin and myosin

Relaxation of Smooth Muscle Tissue

Ca^{++} levels fall, myosin phosphatase splits the phosphate off the myosin head causing contraction to stop

Smooth Muscle Receptor Sites

1) Inhibitory

2) Excitatory

The neurotransmitter could be the same. Different reactions depends on the receptor site involved.

Smooth Muscle Action Potential

Smooth muscle has a slower Action Potential. Why?

1) Voltage Regulated Ca^{++} Ion Gates

2) Gate Speed

Neuromuscular Junction of Smooth Muscle

Varicosities- enlargements along the axon where a neurotransmitter is released to specific smooth muscle cell

Local Tissue Factors Involved in Vasodilation

1) Lack of O_2

2) Excess CO_2

3) Increased H ion concentration or decrease in pH

4) NO nitric oxide

Blood Vessel Wall Vasodilation

Arginine

⇩

Nitric Oxide

⇩

Guanylyl Cyclase

⇩

GTP ⇨ cGMP ⇨ Muscle Relaxation

Smooth Muscle Overstretch

Bladder

Benign Prostatic Hypertrophy

BODY FLUIDS

Review of KCl Effects

Hypernatremia:

Daily Intake of H_20

1) Ingestion: 2100 ml/day	2100 ml
2) Synthesized from metabolism	200 ml
Total Intake/day	2300 ml

Daily Loss of H_20

1) Insensible H_20	
a) Evaporation	300 - 400 ml/day
b) Evaporation	300 - 400 ml/day
2) Sweat ~ highly variable	100 ml/day
3) Feces	100 ml/day
4) Kidneys ~ majority of lost fluids	1400 ml/day
Total Out/day	2300 ml/day

FLUID COMPARTMENTS

Total body fluid is distributed among 2 major compartments

1) intracellular- 28 liters of fluid, majority of fluid in the body

2) extracellular- 14 liters of fluid

Extra-cellular Fluid: All fluids outside the cells
- 20% of body weight
~14 liters in average adult

1) Interstitial Fluid = 11 liters (3/4)

2) Plasma = 3 liters (1/4)
   Non-cellular part of blood

Blood Volume
Blood is a separate fluid compartment

- 5 L /person
- 60% plasma
- 40% HCT (hematocrit is packed cell volume)
  40-42% in males 36-38% in females

• note: Blood conatins both intra & extra cellular components

The Donnan Effect

1) The concentration of (+) ions is increased in plasma vs. ISF (Interstitial Fluid)
Why?

2) Negatively charged ions are greater in the interstitial tissue fluid because negative proteins in the plasma repel the anions.

Measurement of Fluid Volumes

The Indicator - Dilution Principle
Measures unknown fluid volumes by injecting a known amount (volume) of solution with a known concentration into a fluid compartment and let it disperse. Then remove a small sample and measure the concentration. Enter the concentration into the equation.

$$\text{Volume B} = \frac{\text{Vol. A x Conc. A}}{\text{Conc. B}}$$

Circulation of Intra-cellular Volume

Intracellular volume = total body water – extracellular water volume
28 = (28 + 14) – 14

Circulation of Interstitial Fluid Volume

Interstitial fluid Volume = extracellular fluid volume – plasma volume
11 = 14 – 3

$$\text{Total Blood Volume} = \frac{\text{Plasma Vol.}}{\text{1- Hematocrit}}$$

Example:

Basic Principles of Osmosis
Osmosis: the net diffusion of H_20 from a region of High [H_20] to one that has a lower [H_20]

Osmolatility:

Osmolarity:

Osmotic Pressure: the precise amount of pressure required to prevent osmosis.

Osmotic pressure (II) = C•R•T

ACIDS, BASES & BUFFERS

Acid- releases H^+ into solution

Base- accepts an H^+ in solution

Strong acids/bases dissociate completely in solution
Example:

Weak acids/bases remain largely intact in solution
Example:

pH scale - used to measure the amount of acid or base in solution.

pH= log $\frac{1}{H}$ → -log [H] so pH is inversely proportional to: [H^+]

Increase [H] What happens to pH?

Normal extracellular pH is:

A change in H^+ concentration causes:
1)

2)

3)

pH of less than 6.8 or greater than 7.7=

Acidosis:

Alkalosis:

Three Systems to Regulate pH
1)

2)

3)

Buffer System can reversibly bind H and OH ions.

Help to neutralize H^+ ions produced in GI tract and via cellular metabolism

Buffer:
1)

2)

Buffer System: interacting compounds that prevent an increase or decreases in pH of body fluid.

Buffers are only temporary solutions to pH problems.

The three most important Buffer Systems
1) Carbonic Acid- Bicarbonate Buffer System
2) Phosphate Buffer System

3) Intracellular Protein Buffer System

CARBONIC ACID - BICARBONATE BUFFER SYSTEM
Important in the extracellular fluid

$NaHC0_3$ = baking soda

Because the reaction is reversible, any change in concentration can drive the reaction in the opposite direction.

• more $C0_2$ in solution:

• then H_2C0_3:

• so, an increase in $C0_2$:

• if when $C0_2$ increases then blood pH does what?

What would be the respiratory response?

If H+ increases what would happen?

$NaHCO_3 + HCl \rightarrow H_2CO_3 + NaCl \rightarrow CO_2 + H_2O + NaCl$

Add HCl increase $H^+ + HCO_3^- \rightarrow H_2CO_3 + Cl^- \rightarrow$ increase $CO_2 + H_2O + Cl^-$ (What then is the respiratory response?)

Add NaOH $NaOH + H_2CO_3 \rightarrow NaHCO_3 + H_2O$

PHOSPHATE BUFFER SYSTEM

Important in the intracellular fluid
Important in the kidney tubules, where there is a lower pH which is closer to Phosphate Buffer System's pK.
pK:

Two Ion Variables
Dihydrogen Phosphate: $H_2PO_4^-$

Monohydrogen Phosphate: $H^+ + HPO_4=$

Helps stabilize pH of urine , so this system is prevalent in the kidney tubules.

INTRACELLULAR PROTEIN BUFFERING SYSTEM

Accounts for 60%-70% of buffering system within the cell.

HENDERSON - HASSELBACH EQUATION

Allows us to calculate the pH of a solution if the molar concentration (bicarbonate ion) and the $PC0_2$ (partial pressure of $C0_2$= amount of $C0_2$ times it's solubility coefficient) are known.

$$pH = pK + \log \frac{HC0_3^-}{.03 \times PC0_2}$$

What does this tell us?

pH of normal blood is 7.35 and the pK of $HC0_3^-$ is 6.1, so $HC0_3^-$ has it's best buffering ability as the pH gets closer to 6.1.

Metabolic Acidosis- decrease in pH due to a fall in $HC0_3^-$

The body compensates by:

Common cause:

Respiratory Acidosis- decrease in pH due to an increase in $PC0_2$

The body compensates by:

Common cause:

Metabolic Alkalosis- an increase in plasma pH due to an increase in $HC0_3^-$ in plasma

The body compensates by:

Common cause:

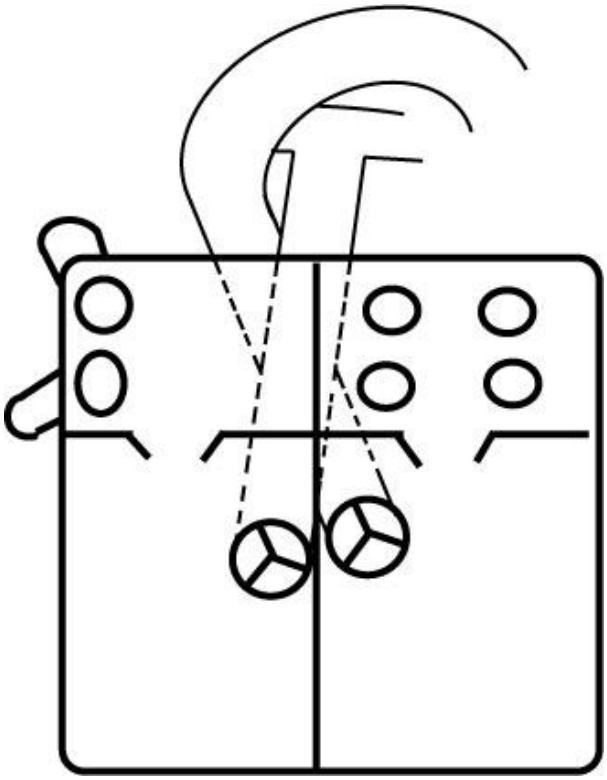
Respiratory Alkalosis- decrease in H+ from a decrease in $PC0_2$

The body compensates by:

Common cause:

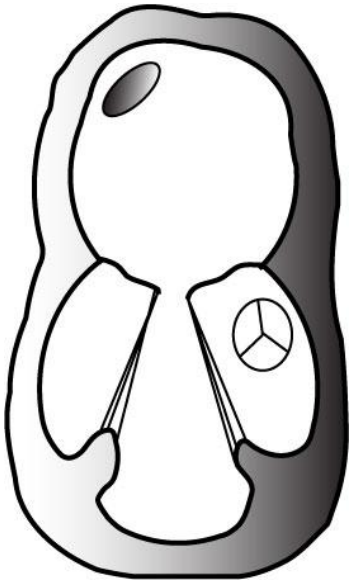
CARDIOVASCULAR PHYSIOLOGY

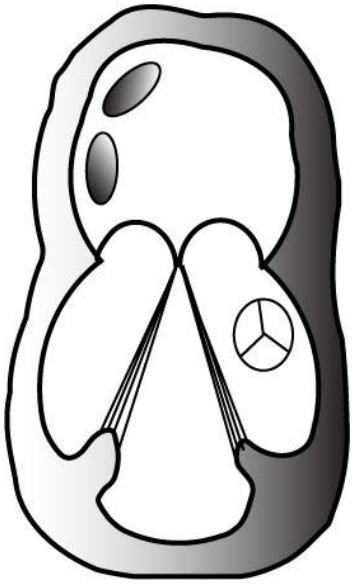
Basic Structure of the Heart



The most common location of murmurs involves:
More common in females than in males.

AV Valves = atrioventricular valves (bicuspid & tricuspid)





Cardiac vs. Skeletal Muscle Physiology

1) Cardiac muscle has intercalated disc between cardiac muscles cells. These discs have a very low electrical resistance allows the action potential to travel freely between cardiac muscle cells due to gap junctions.

2) T-tubules in cardiac muscle are much larger (5x's as large) and are filled w/negatively charged MUCOPOLYSACCHARIDES. These mucopolysaccharides bind to Ca^{++} to increase the Ca^{++} stored in the Terminal cisternae.

3) Functional Syncytium = cardiac muscle is a mass of cells that works together as 1 unit.

4) Stronger Contractions: heart muscle contractions are much stronger than skeletal muscle.

Heart Muscle
3 types

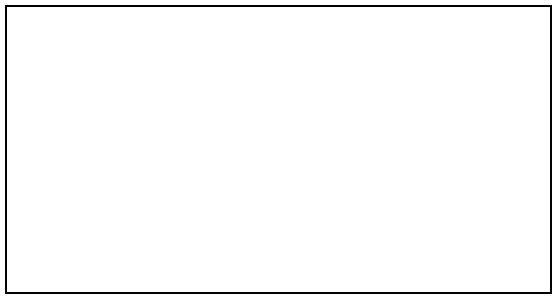
1) Atrial muscle fibers, walls thinner than ventricular
2) Ventricular muscle fibers
(both are like skeletal muscle except for the intercalated disc)
3) Excitatory/Conductive fibers
- These muscle contract feebly (very few contractile fibers).
- Their function is excitability and transmission of the impulse.

Action potentials in Cardiac Muscle
- normal resting membrane potential for cardiac muscle =

Ventricular Action Potential

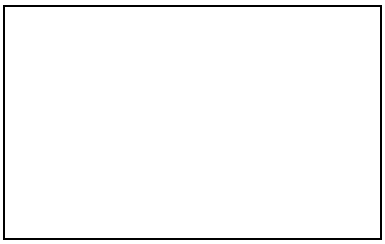
+20

-80



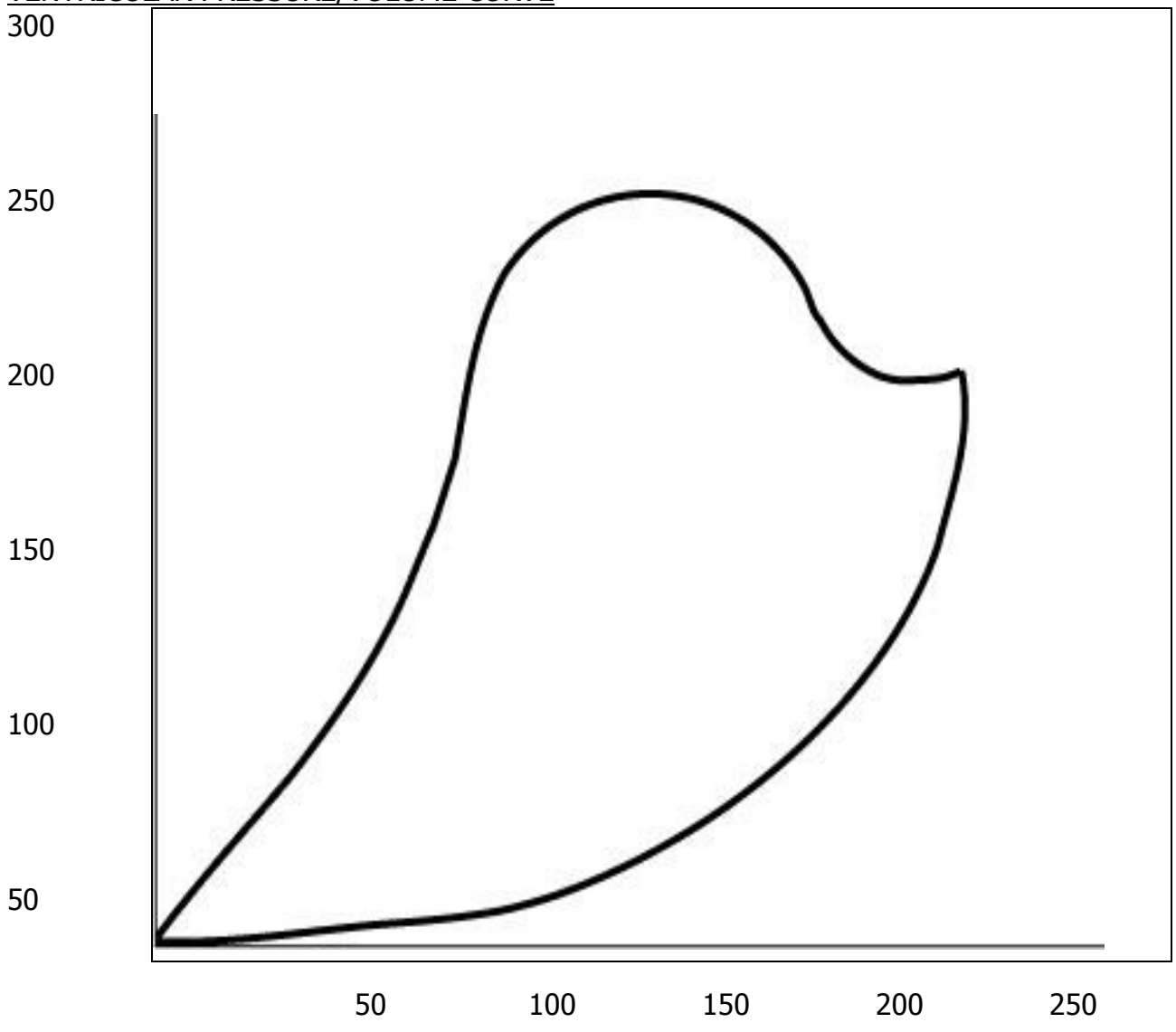
*This plateau causes the cardiac muscle to contract 3 - 15 times longer than a skeletal contraction.

Absolute Refractory Period
-inactivation gates are closed so NO additional action potential can occur.



Relative Refractory Period
-can contract but harder due to membrane hyperpolarization

VENTRICULAR PRESSURE/VOLUME CURVE



EKG (Electrocardiogram)- The Cardiac Cycle

EKG - is an electromyographical tracing which reflects the electrical impulses that travel through the heart and is picked up by electrodes on the surface of the body.

P-Wave
Caused by the spread of Depolarization of ATRIA (this is followed by atrial contraction) .16 sec

QRS Wave
Depolarization of the ventricles (initiates ventricular contraction) QRS begins at the onset of ventricular systole

T-Wave (Ventricular T-Wave)
Repolarization of the ventricles, occurs at end of ventricular contraction.

*note: atrial repolarization is located where on the EKG?

Heart sounds: "Lubb-Dupp"

S1 Lubb = softer sound

S2 Dupp = crisp sound

Blood Volumes

SV (stroke volume) = volume of blood pumped out during ventricular contraction.
average resting adult =

EDV (end diastolic volume) = the amount of blood in the ventricles prior to ventricular contraction.

ESV (end systolic volume) : the amount of blood remaining in the ventricle after contraction.

Ejection Fraction:
Usually - 60%

*The ventricles fill passively @ the beginning of ventricular diastole.
70 - 75% of the blood "Flows" in during atrial diastole
Because the atrial contraction only provides 25%

ATRIA PRESSURES - DIASTOLE

1) P-Wave =

2) A-Wave =

3) AV Valves Close!

4) C -Wave = ventricles begin to contract
Some Pressure increase due to back pressure of blood toward atria

V -Wave = results from slow flow of blood from the great veins into the atria

VENTRICULAR PRESSURES – SYSTOLE

1)Isovolumic (isometric) Contraction:
AV valves close
Vent. Pressure increase due to onset of contraction. There is contraction but no emptying at this point.

An increase in pressure leads to:

2)Period of Ejection

P = 80 mm, SL valves forced open
Blood pours out
Rapid ejection
Slow ejection -

3)Isovolumic Relaxation

2° increase due to pressure in large arteries (aorta) blood is pushed back toward the ventricles resulting in the SNAPPING of the aortic & pulmonary valves shut.
Ventricles relax causing:

AORTIC Pressures

- Aortic Pressure is dropping before the aortic valves open
- Aortic valves open; blood enters arteries
- Valves close, elastic recoil

Dicrotic Notch (incisura)

- Brief increase in aortic P when the aortic valve closes.

<u>Cardiac output = CO</u>
Stroke Volume x HR / 100
80 x 70 =

<u>Factors influencing C.O.</u>

1) Exercise - sympathetic nervous system can increase CO up to:

2) Body Temperature (increase activity of ion gates)

3) Ions (K+, Ca++, Na+)

(HCM)Hypertrophic Cardiomyopathy
Genetic
Hypertrophy of muscles results in a disarray of myofibril which affects conduction pathways.
Increase ventricular size
Protein synthesis problems
Cardiac hypertrophy also occurs due to hypertension

IONS EFFECT

1) increase K^+ = excess K^+ in extra-cellular fluids produces slow HR

2) increase Ca^{++} excess Ca^{++} = spastic contraction

3) increase Na^+ ---- hyperpolarization (nml = 142 meq/L)

4) decrease Na^+ = hypopolarization

Intrinsic Regulation of Heart Pumping

The FRANK-STARLING MECHANISM
Input must equal output
The intrinsic ability of the heart to adopt to changing volumes of inflowing blood.
The increase heart muscle stretch

Disease state = CHF(Congestive Heart Failure)

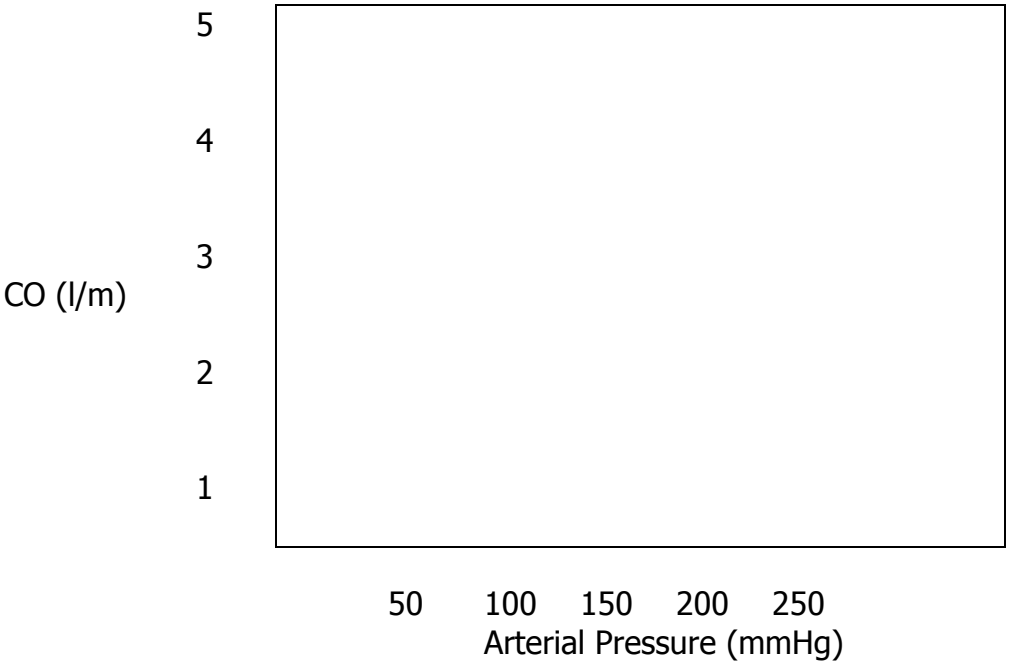
Theory - the increased stretch puts the myofibrils (actin and myosin) in:

Also stretching of the atrial wall causes HR increase by 10 - 20%.

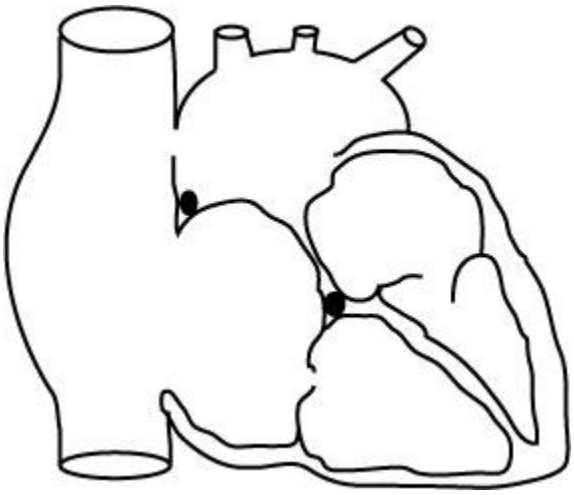
*If arteriolar pressure > 160mmHG, then the ventricles LOOSE their ability to contract.

Cardiac Output Curves

Increase arterial pressure = increased stroke output until pressure gets too high.

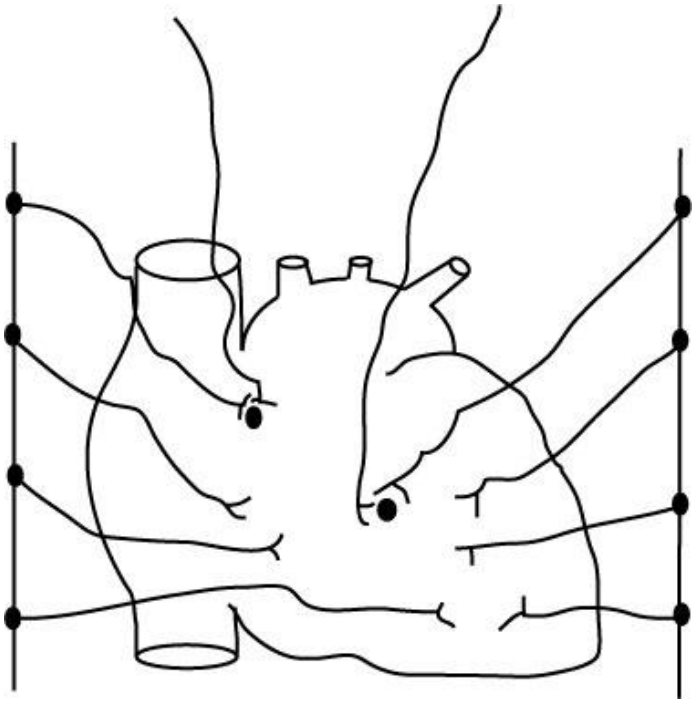


Conduction System of the Heart



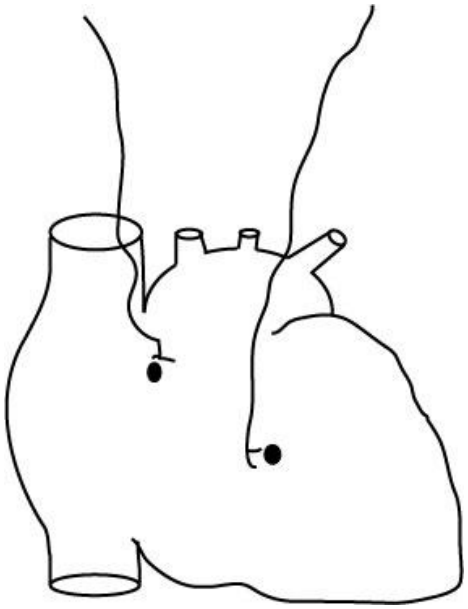
Autonomic Control of Heart Rate

1) Sympathetic



Cardiac Output can be increase by more than 100% (sometimes 2 to 3 fold) due to sympathetic stimulation.
However, at HR >150 cardiac function begins to fail.

2) Parasympathetic (VAGAL) stimulation



Strong vagal stimulation can stop heartbeat for a few seconds.

Vagal stimulation also decrease strength of contraction.

SA NODE (Sinoatrial Node)
Generates normal rhythmical pulse 3mm wide; 15 mm long; 1 mm thick- superior lateral wall of right atrium

RMP = Resting Membrane Potential

Three channels play role in the Depolarization/Repolarization Cycle

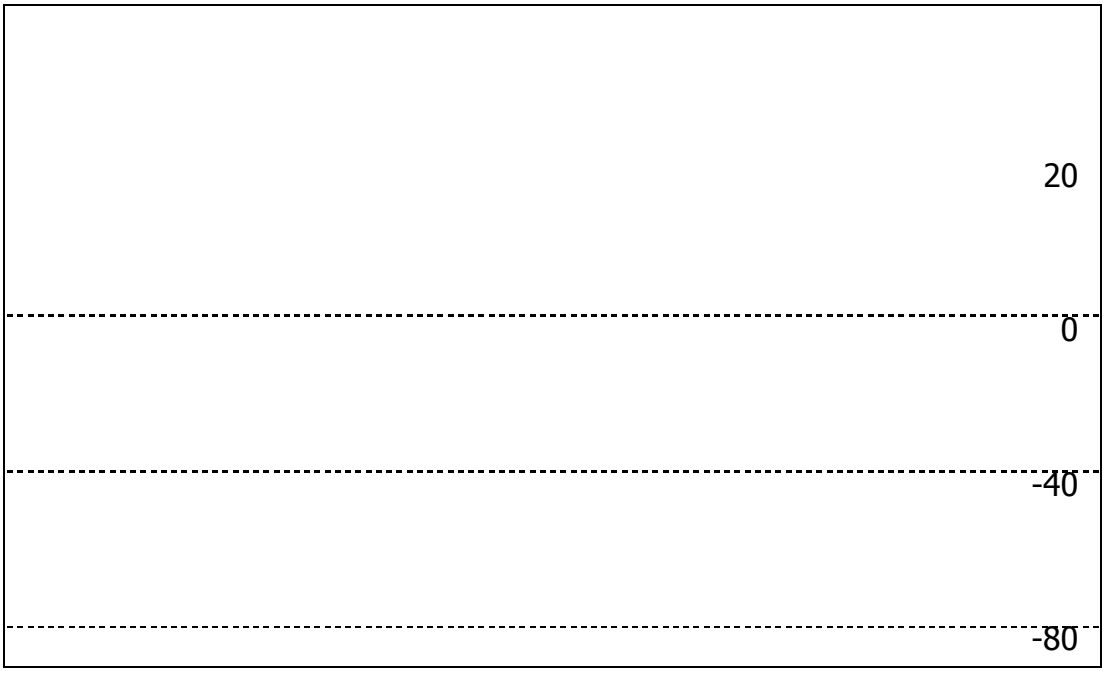
1) Fast Na^{++} channels

2) Slow Ca^{++}/Na^{+} channels

3) K^{+} channels

Lesser negativity (RMP = -55mV)

SINUS NODAL RHYTHMICITY



Repolarization of the SA Nodal cells is the same: K^{+} channels hyperpolarize"reset" at ~ -55 – 60mV. Then Na^{+} leak starts to increase again.

CARDIAC CONDUCTION

Internodal Pathways

Transmission of the cardiac impulse through the atria.
These pathways consist of small bundles of atrial muscle fibers.

1) anterior interatrial band

2) anterior
3) middle All internodal pathways
4) posterior

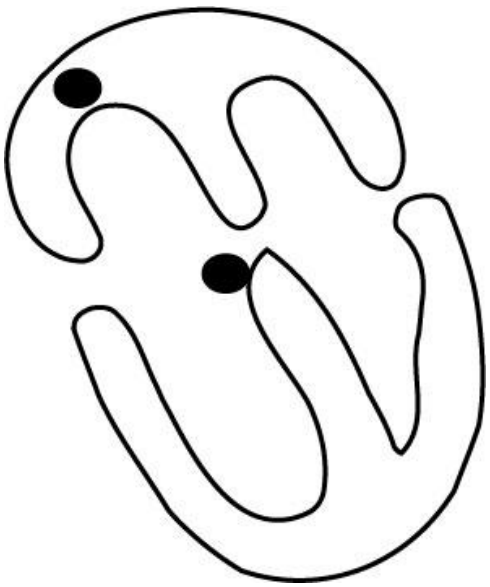
AV-Node Action Potentials

1) No fast Na^+ channels
2) Slow Na^+/Ca^{++} channels
3) Depolarization process is the same as in SA node
4) A-V nodes intrinsic rate is slower that the SA node

A-V Nodal Blocks

If the impulses from the SA Node –

The SA node continues to stimulate the atria @ a rate of 70 bpm, but the A-V node will develop its own rate of 15-40bpm.
The result is an atrial rate that is:



Stokes - Adams Syndrome

5-30 sec. Delay from a sudden AV block before the purkinje/AV node generate a rhythm.

Parasympathetic Nerves & Heart Rhythmicity

PSN stimulation can cause decrease HR and/or interruption of conduction producing ventricular escape.

1) ACH (acetylcholine) is released at the vagal endings
   a)decrease rate of sinus node
   b)decrease excitability of A-V fibers

   ACH binds causing:

   Ventricular Escape = 15 - 40 bpm

Remember the characteristics regarding the PNS and vagal stimulation:

Sympathetic Stimulation (has the opposite effect of PSN - stimulation)

1) increase rate of sinus nodal discharge
2) increase rate of conduction — All can triple heart rate
3) increase level of excitability in entire heart

4) increase force of both atrial & ventricular contraction (double)

Mechanism:
Release of Norepinephrine @ the SNS Nerve endings:

Electrocardiogram: EKG
A recording of the electrical potentials generated by the heart.

P-Wave = atrial depolarization
QRS = ventricular depolarization
T = ventricular repolarization

The height of each tracing correlates with the strength of the electrical potential generated.

Einthoven's Triangle
A triangle drawn around the area of the heart. The 2 arms & the left leg form the apicies of a triangle surrounding the heart. We can determine the strength and direction of the unknown third lead if the other two leads are known.

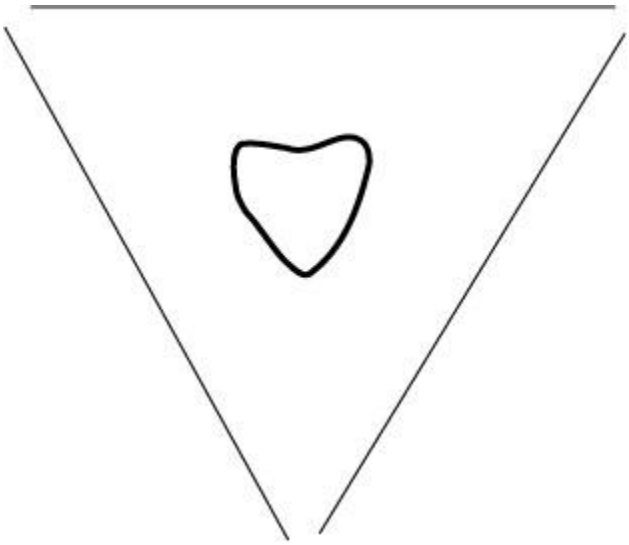
Lead: a lead is the electrical potential generated or electrical potential difference between two electrodes.

Lead I : RA- ---------- LA+

Lead II : RA- ---------- LL+

Lead III : LA- ---------- LL+

Leads one, two and three allow us to measure the electrical activity in the vertical plane.



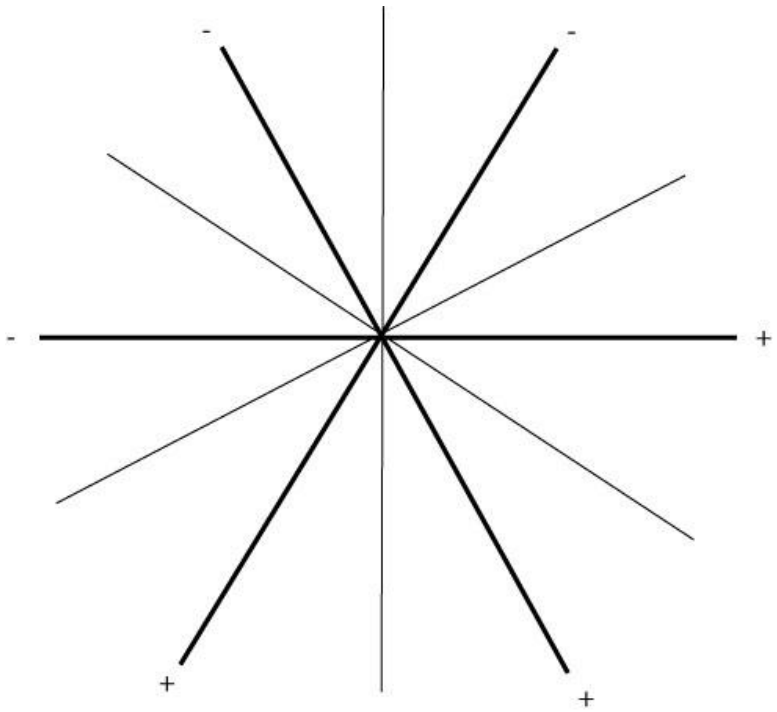
EINTHOVEN'S LAW

If the electrical potentials of any 2 of the 3 bipolar limb electrocardiographic leads are known at any given instant, the 3rd can be determined mathematically from the 1st two.

Example:

Lead I :	+ .5mV
Lead III:	+ .7mV
Product = Lead II	+1.2 mV

Modified Einthoven's Triangle



Used to determine the vector of depolarization through the heart muscle tissue = Vector Analysis

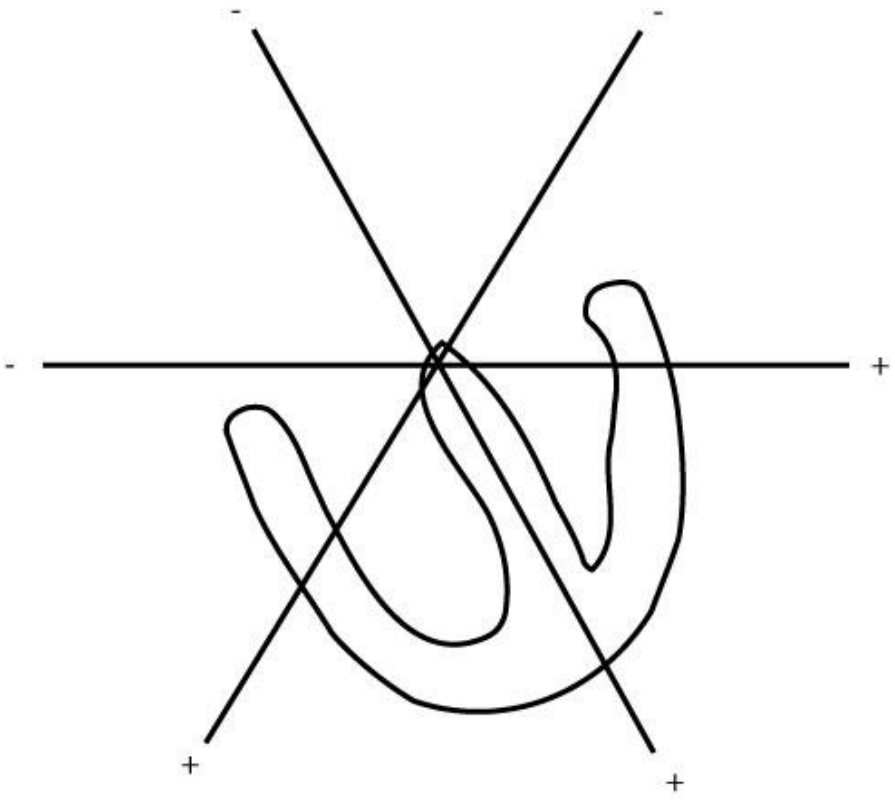
Direction of Vector Arrow

As the cell depolarizes the outside turns from electropositive to electronegative. The arrow points from electronegative to electropositive.

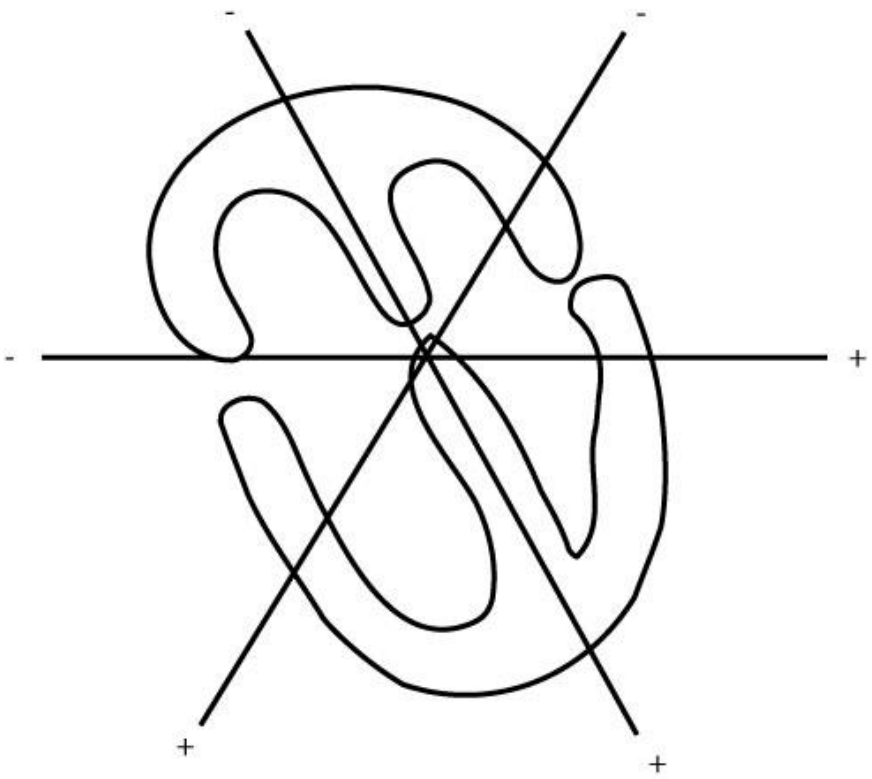
Vector: It is an arrow that points in the direction of the electrical potential generated by the current flow with the arrowhead IN THE POSITIVE DIRECTION, also the length of the arrow is drawn proportional to the voltage of the potential. Length = strength

VECTORAL ANALYSIS

Overall Mean Vector: the summated vector of the generated potential. The overall general direction of electrical potential traveling from the base of the heart to the apex. A longer arrow equals a stronger current in millivoltage flowing in the direction of that vector.



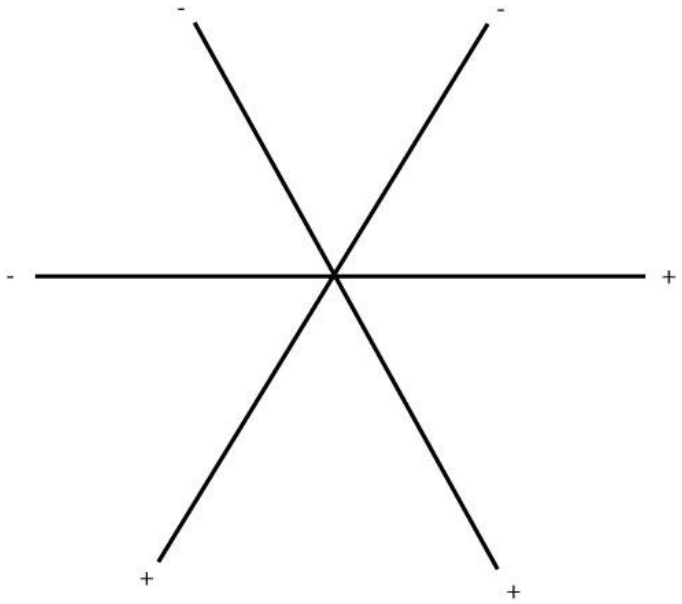
Mean QRS vector is normally + 59°, because of the placement of the ventricles. This "Overall Mean Vector" travels from the base to the apex.



How do we determine the Mean Vector? By summing up the millivoltage of the QRS complex.

Projected Vector - a line drawn perpendicular to the axis of the lead, this vector has direction & strength

Lead I



Vector A = instant mean by adding up the QRS complex for Lead I

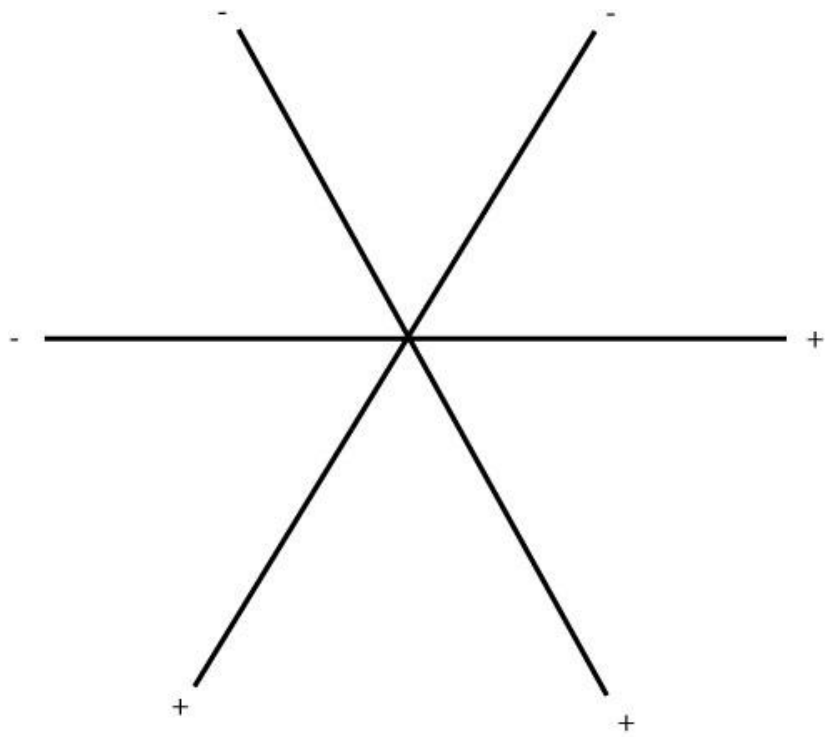
Examples: Lead I

Q deviates: - .05mV
R deviates: +.35mV
S: <u>- .1mV</u>
Net : .20mV = Lead I

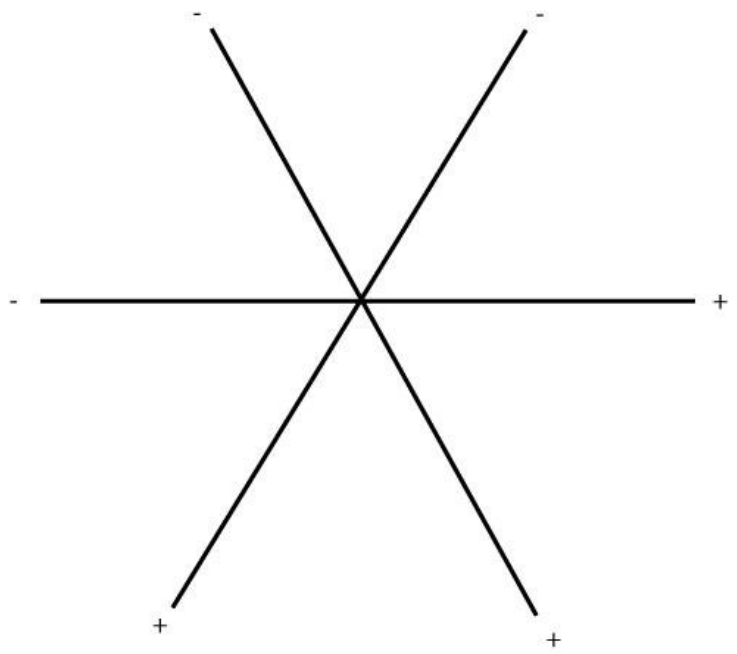
.20mV
RA •----|----|----|----|----|----•LA

Lead II- Adding

Q deviates: -.10
R: +.45
S : -.05
Net: +.30



Example:
Given
Lead I = 4
Lead II = 9



Ventricular Depolarization

1) Q wave- initial depolarization of the left half of the septum before the right half (more mass) creating a weak vector from left to right for a fraction of a second.

2) R wave- largest vector in the positive direction because about half of the ventricle is depolarized

3) S wave- deflects toward the negative direction, because the last part of the ventricle to depolarize is the upper portion of the left ventricle.

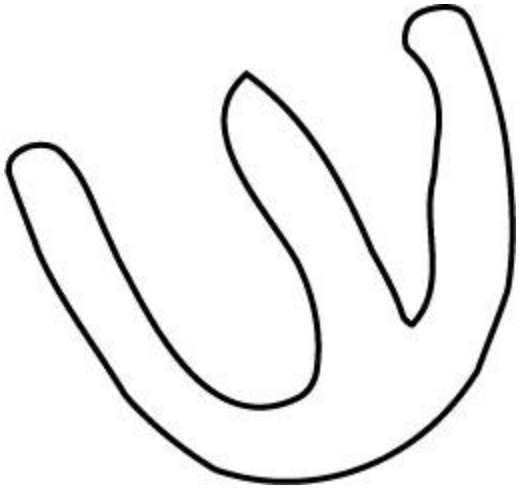
4) Isoelectric line- when all of the ventricle is depolarized Then we are at OmV.

Ventricular Repolarization - (T wave)

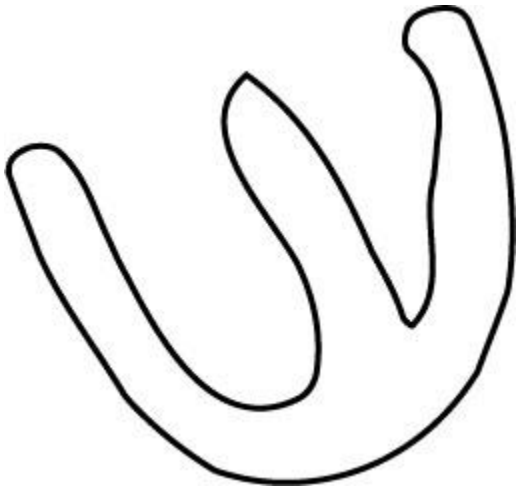
1) The greatest portion of the ventricular muscle to repolarize first is that located over the entire outer surface of the ventricles and especially near the apex of the heart.
2) The last to depolarize is the ventricular apex and the outside of the ventricles.
3) First to repolarize is the apex of the ventricles. Why?

Conclusion: repolarization occurs from the apex to the base.

Depolarization

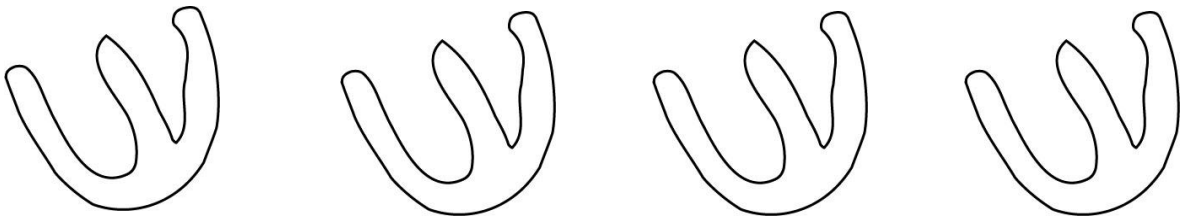


Repolarization

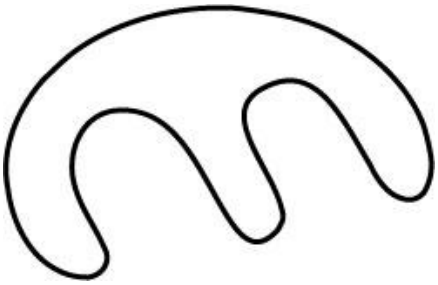


The predominant direction of the vector through the heart during repolarization of the ventricles is from BASE → APEX
(the opposite direction as depolarization).

Ventricular
Repolarization

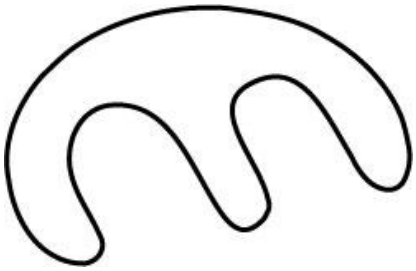


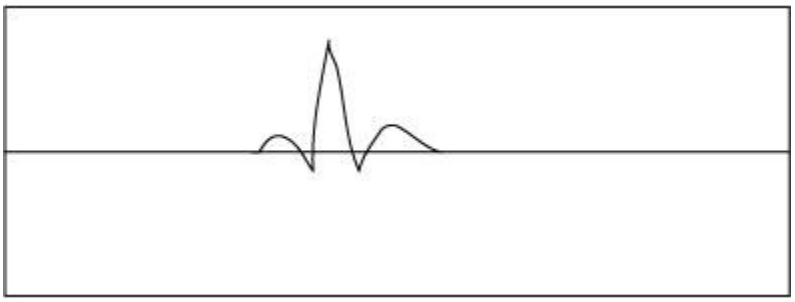
Atrial Depolarization (P wave)
Begins @ the SA node
And spreads over the atria



Atrial Repolarization

The area in the atria that becomes repolarized lst is the SA node region, which is also the area that becomes repolarized first.
(due to the refractory period)





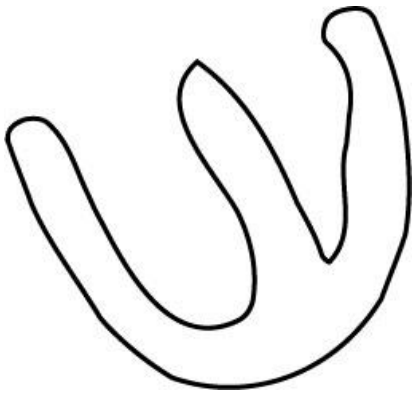
AXIS DEVIATION
Shifts to the left - if the heart is angulated to the left.

So the mean axis
1) Changes heart position
    a) during expiration
    b) lying down such that abdominal contents press on the diaphragm
    c) stocky, or overweight individuals whose diaphragm press against the heart at all times
    d) L ventricular hypertrophy. Why?

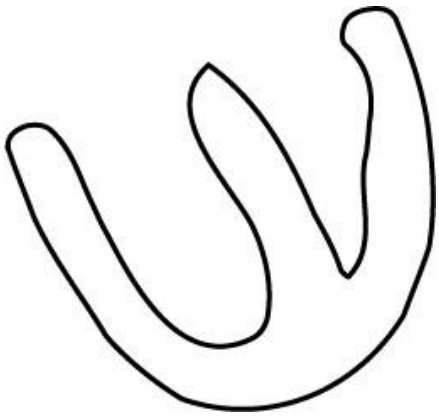
Shifts to the Right
1) changes in position
    a) inspiration
    b) standing (diaphragm decrease)
    c) tall, lanky people whose heart "hangs down"
    d) pulmonary stenosis
    e) right ventricular hypertrophy

<u>Bundle Branch Block</u>
Cause axis deviation -If one major bundle branch is blocked, the cardiac impulse will spread through the normal ventricle long before the blocked side.

R Bundle Branch Block



L Bundle Branch Block



Cardiomyopathies

Decreased Voltage

1) Old MI's which resulted in decrease muscle mass

2) Fluid in the pericardium (pericardial effusion)
   - the fluid conducts impulses much easier than muscle, so the fluid "short circuits" the conduction system

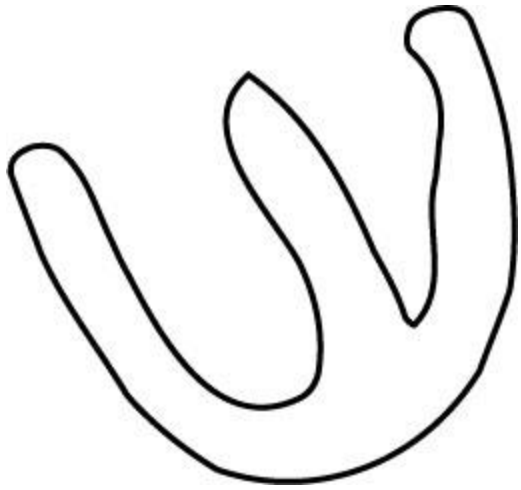
3) Pleural Effusion - see above

4) Pulmonary Emphysema (effects EKG but does it effect heart conduction? Lungs filled w/ excess air and act as an insulator to the heart --- so the electricity generated by the heart does not flow to the body, which decreases electricity reaching superficial leads.

WIDENED QRS IS ALWAYS prolonged conduction of the impulse through the ventricles.

Current of Injury

Due to abnormality a part of the heart (ectopic focus) remains depolarized {hypopolarized (-)} all the time.
This injured part emits (-) charges into the surrounding fluids whereas the normal heart is positive.
Why? Injured tissue such as from ischemia, infection and trauma is not able to create a stable resting membrane potential.



By itself, or combined with the SA node, a current of injury will cause abnormal vector patterns.

EKG

1 mm vertical line = .1 mV
1 mm horizontal line = . 04 sec. @ standard paper speed of 25mm/sec.
Each heavy line = .2 sec.

Determining Beats/Minute

1) 25mm/sec. x 60 sec./min. = bpm
   # of mm between beats

2) 300 150 100 75 60 bpm / each section

3) The 3 sec. mark How many beats between each mark x 20 =

Cardiac Arrhythmias

Such as varied rhythm, extra beats, rapid/slow heart rate, heart blocks.
Normal sinus rhythm: regular rhythm set by SA node

Causes of Arrhythmias

1) Abnormal rhythmicity of pacemaker
2) Shift of pacemaker from SA node to other parts
3) Blocks of normal impulse transmission
4) Abnormal pathways of impulse transmission
5) Spontaneous generation of abnormal impulses

1) Widened QRS Complex

Causes ectopic foci through the ventricles slow/alter ventricular conduction

2) Increase R-Waves = one ventricle is not conducting normally. If one side is not firing normally, the vector becomes larger toward the electropositive side.

3) Inverted T-Waves
Slowness of contraction over the surface of the ventricle or slow travel of depolarization over the muscle allows the first area to depolarize to be the first area to repolarize.

4) Sinus Arrest
Losing the SA node
P-Waves drop
Ventricular escape
If a P-Wave does appear = vagal stimulation is the culprit

5) Paroxysmal Atrial Tachycardia (PAT)
Often seen in normal, healthy adolescent
A sudden Tachycardia (increase T, sympathetic stimulation, toxicity)
Blurring of the T & P waves

6) Paroxysmal Nodal Tachycardia (PNT)
No P Wave due to AV Node going crazy
Also seen in normal, healthy young adults, usually grow out of them, but can be seen in various toxicities, or sympathetic stimulation.
From aberrant AV node rhythm.

7) Paroxysmal Ventricular Tachycardia
Ventricle contract as a whole
*note EKG looks like cardiac cell depolarization
looks like premature ventricular beats, without any normal beats interspersed in between.

8) Atrial Flutter
Damaged atrial tissue stretches out causing reentry of contraction cycle. Observe good QRS complexes. Rapid continued contraction of atria with ventricular beats interspersed.

9) Ventricular Fibrillation

Injuries produce multiple vectors. Areas of ischemia cause disorganization of depolarization pathways. "Bag of Worms presentation". Utilize electric shock to attempt to correct this condition. Due to pockets of depolarization and repolarization that occur simultaneously.

10) Atrial Fibrillation

Resembles V-fib. - atria and ventricles are separated by a fibrous connective tissue layer.

11) SA Node Block:

No P-Waves; ventricular rhythm, escapes at 15-40 bpm. Shows blockage to the vagus nerve.

12) AV Nodal Block:
Delay or a complete block between SA node and AV node

Causes:
AV node ischemia
AV node compression from scar tissue
Inflammation

1st Degree: Prolonged PR interval (normally. 16 sec., now >.2 sec.)
A delay in conduction

2nd Degree: Delay of SA ----AV node
P --- R interval > .25 sec.
Dropped Beats

3rd Degree: Atria & ventricles are contracting completely independently.
Atria beat at their normal rhythm.

12) Premature Ventricular Contractions (PVC)
Causes: ischemia, local plaques, toxic irritation

Characteristics
1. QRS complex is prolonged. Why?

2. QRS Voltage is high. Why?

3. Inverted T wave. Why?

CIRCULATION

The function of circulation is to service the needs of the tissues: nutrients, waste, hormones, tissue, blood gases

ARTERIES
Vessels traveling away from the heart

1) Large elastic = have lots of elastin & collagen fibers; function under high pressure from the heart

5) Small arteries = have a large middle muscular layer (tunic) Giving them ability to expand & contract to some extent

6) Capillaries = one cell layer thick = allow 1 RBC through @ a time

Pre-capillary Sphincters
Regulates the flow of blood through the capillaries giving the tissues the minimum amount of blood needed.

VENULES - SMALL VEINS - LOW PRESSURE
VEINS - large venules
1) Highly stretchable (Distensible)
2) Thinner middle muscle (tunic)

Blood Volume Distribution
Veins serve as a large blood reservoir
Cross section of veins is 4 X's the area of the arterial system

*clinical note: if the MEAN arterial pressure is < 100mmHg the SNS starts to stimulate contraction (constriction) of the vascular tree to increase pressure.

PRESSURE - (P)
Force exerted by blood against any vessel wall measured in mmHg.

Pressure Gradient: difference in pressure between 2 ends of a vessel

Flow= (Q or F) volume of blood moved per unit of time (ml/Min or L/Min)

Resistance ®

The force that opposes movement of blood

1) can be due to friction between blood and vessel walls
2) measured in mmHg/ml/min
3) inversely proportional to blood flow
4) also due to turbulence

Increase resistance = decrease flow; increase pressure = increase flow

Flow=Q $R = \frac{1}{Q}$

VISCOSITY

THE THICKNESS OF A FLUID (η) Increase viscosity = decrease flow

OHMS LAW:

$Q = \frac{\Delta P}{R}$

Comparison of Pressure in Different Vessels

1) Aorta = has a high blood volume and pressure because it is right on the heart
2) Arteries = have high pressure that decrease w/ branching. The further from Heart we see a decrease in pressure
3) Arterioles = as they branch have less volume per vessel

Surface Area:	aorta's:	4.5 cm^2
	Capillaries:	5000 cm^2

4) Veins= low pressure

POISEUILLES LAW

The velocity of blood flow will be different depending on the size of the vessel (tube) diameter.

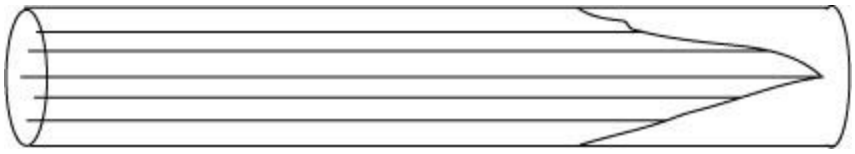
$$Q = \frac{\Pi \Delta P r^4}{8 l \eta}$$

1= vessel length
η= viscosity

Increase diameter (2r) = increase Q

Laminar Flow

The fluid flowing at the perimeters of a vessel is moving slowest due to friction with vessel wall. Fluid in the center of a vessel moves fastest.



HCT (Hematocrit) = % cells in the blood (45 - 47%)
Increase HCT; decrease Plasma
Increase HCT; Increase dehydration

Increase HCT = Polycythema = condition where the bone marrow produces an excess/increased # of RBC's. Increase in viscocity affect capillaries less than large vessels due to Roleaux effect- cells line up single file in capillaries.

Turbulence:
A disruption in laminar flow, causing heavier particles to precipitate out of the plasma.

How does atherosclerosis starts?

Decrease volume = decrease pressure

Vascular Distensibility
Measure of the stretch capacity of a blood vessel (vein stretch 8 x's more than arteries)
Veins stretch immensely -arteries have thicker walls, less stretch

Vascular Capacitance
The amount of blood that can be stored per length of vessel.
The more expandable, the more capacity
Veins (aka compacitant vessels)

Compliance of a Vessel

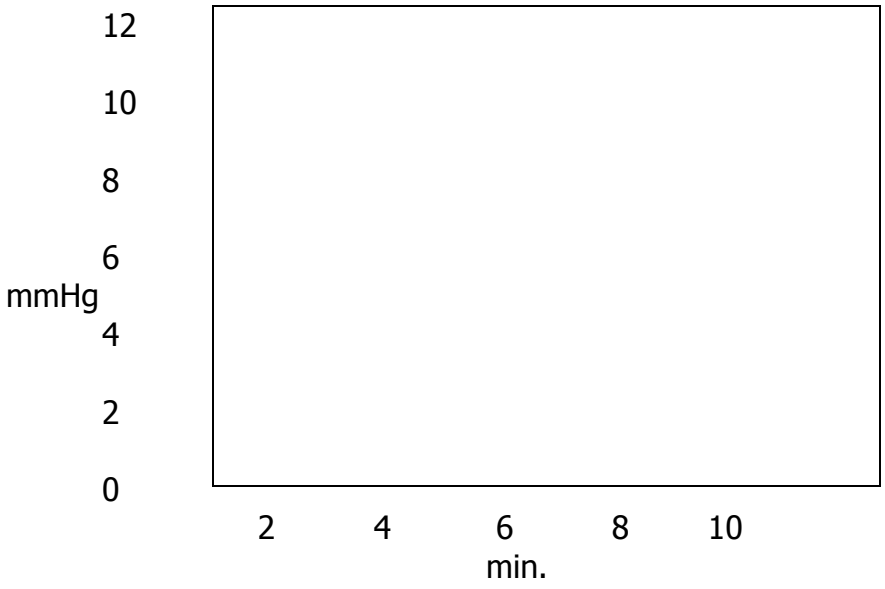
Arteries: increase pressure, volume remains constant

Veins: Increase Pressure, increase volume because veins stretch under pressure

Veins serve as blood reservoir
SNS can stimulate veins to constrict due to blood volume loss

<u>Orthostatic Pressures</u>
BP laying down } If change l OmmHg or increase HR 10 bpm is indicative
BP sitting } of blood loss or compensation
BP Standing }

*Children compensate better, but crash quicker. Why?



Pulse/Pulsation: There is pulsation in arteries due to lack of distensibility & high pressure.

Resistance: The narrower the vessel = increase resistance. Capillaries do not pulsate due to low pressure & they are connected to venules which are distensible.

Pulse Pressure: The difference between systolic & diastolic pressure.
120/80, pulse P = 40. If pulse pressure = 30 Worry! Why?

Central Venous Pressure (CVP)
The pressure measured in the R atrium (blood from all systemic veins flows to RA).

CVP normal = 0 mmHG

If CVP = 4 mmHG indicates volume is backing/damming up on the venous side.
Increase CVP due to heart damage (ventricular).

*CVP is regulated by a balance between the ability of the heart to pump blood out of the RA & the tendency for blood to flow from peripheral vessels back to the RA.

A weak heart increase CVP.

Function of Venous Valves
Valves allow blood to flow only in the direction toward the heart.

*Prolonged standing (10 min without movement) can cause the venous pressure (hydrostatic) to increase to +90mmHg (normal = 25).

Increase venous pressure -fluids to leak into the interstitial spaces.
10 -15% of blood volume can leak out in a 10 min. period.

Intrathecal (Abdominal) Pressures
Respirations affect the abdominal cavity pressures and can cause "contraction" propelling blood through the inf. & sup vena cava.

Varicose Veins/Valve Incompetence
Large, bulbous protrusions of the veins beneath the skin of the entire leg.

Caused by incompetency of the valves due to extreme vessel distension.
Tretment: They can be stripped & other vessels will assume function.

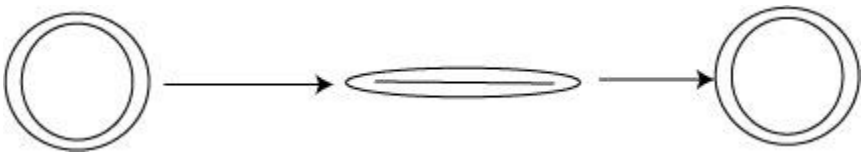
VEINS ARE A BLOOD RESERVOIR = 60% blood volume

Ausculatory Method of Taking Blood Pressure
Inflated cuff partially collapses brachial artery producing an audible tone is produced during part of the arterial pressure cycle.

Korotkoff Sounds
Created by turbulent flow of blood through collapsed vessel.

First heard - opening of the vessel as cuff is loosened.

Last heard - sounds disappear as a decrease in cuff pressure allows the vessel to open completely.



Microcirculation
Function: transport of nutrients & removal of cellular excreta.
Tissues control/dictate their own blood flow.

1 Billion capillaries/body
1) Arterial a) arteries - have a thick middle muscular tunic = decrease distensibility
2) meta-arterioles - do not have continuous muscular tunic
3) capillaries - walls a 1 cell layer thick (fenestrated)

Pre-capillary sphincters: found @ the point where true capillaries originate from metarterioles.
A smooth muscle fiber encircling the capillary - serves to open & close the entrance of the capillary.

Example: During exercise the GI tract capillaries are constricted to divert Blood flow elsewhere

Flow of Blood in the Capillaries

VASOMOTION: The intermittent contraction of the metarterioles & precapillary sphincters to help regulate blood flow to an area.

Regulation of vasomotion:
The concentration [02] in the tissues Increase 02 use = increase frequency & duration of capillary flow.

Interstitial Tissue
Spaces between cells
Makes up 1/6 of the body space

1) Solid Structures
   a) Collagen fibers bundles - provide tensional strength of tissues
   b) Proteoglycan filaments - "brush pile" - 90% hyaluronic acid - 2% protein

2) Gel Component – "tissue gel" - the combination of proteoglycan filaments & the fluids trapped w/in them.

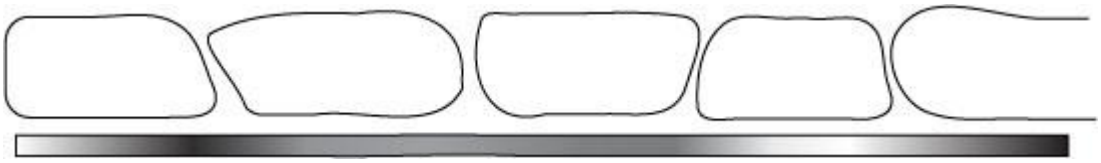
Fluid is composed much the same as plasma except less proteins –
95% diffusion rate of H20 through Gel

So, 95% as permeable as H20

Things diffuse very rapidly through Gel: H20 molecules, electrolytes, nutrients, cellular excreta, 02, C02 etc.

12 L of interstitial fluid/body

Capillary/Interstitial Tissue "Junction"



80 x's as much material flows across/through the membrane than actually through the capillary

Diffusion rate is affected by 2 Factors:
1) size of the molecules (increase size decrease rate)
2) Permeability of the membrane

Liver tissue = has large intercellular clefts — Lots of diffusion for both
Kidney = glomerular cells have lots of clefts

Blood Brain Barrier = tiny clefts; few in number — Little diffusion

FILTRATION

The movement of fluid across a membrane whose pores restrict the movement of solute.

Hydrostatic Pressure

The pressure produced by the weight of the blood in the vessels.
Forces the H_20 out of capillaries and into the interstitial tissue fluid of the legs.

Osmotic Pressure

The pressure generated from diffusion of H_20 from an area of increase [H_20] to decrease [H_20].

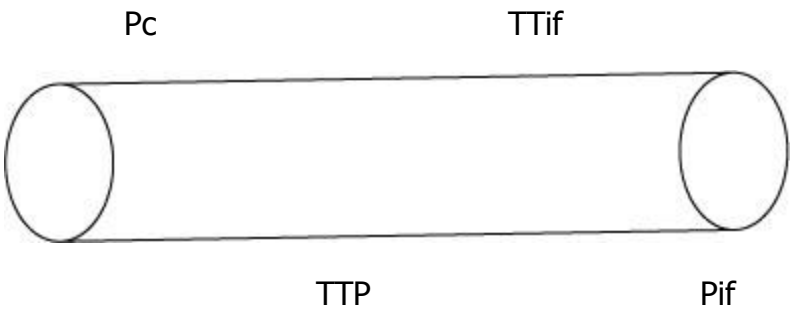
Forces that determine fluid movement through the capillary membrane (4)

1) Capillary Hydrostatic Pressure (Pc): tends to force fluid out through the capillary membrane.

2) Interstitial Fluid Pressure: (PiF) forces fluid into the capillary membrane when PiF is positive, but outward when PiF is negative, - (Pressure in the interstitial tissues forces fluids into the capillaries).

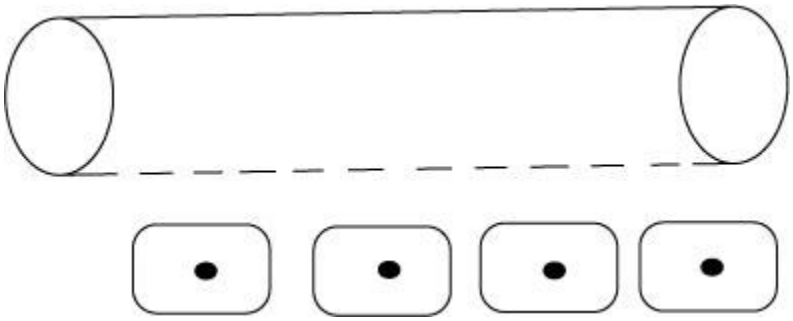
3) Plasma Colloid Osmotic Pressure (TTP) tends to cause osmosis inward through the capillary membrane (P molecules in the Plasma attract H_20) Also attracts Na, K increase pressure.

4) Interstitial Fluid Colloid Osmotic Pressure (TTif) tends to cause osmosis of fluid outward through the capillary membrane toward the solute molecules in the interstitial tissue fluid.

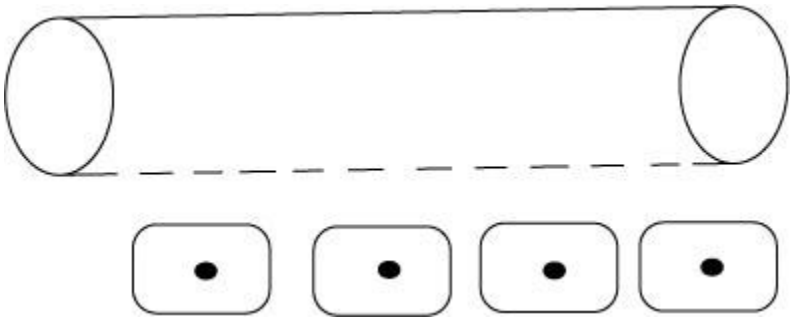


Examples:

1) Capillary Pressure: Forces Fluid outward
P in > P Out
Pressure within capillary > interstitial Pressure

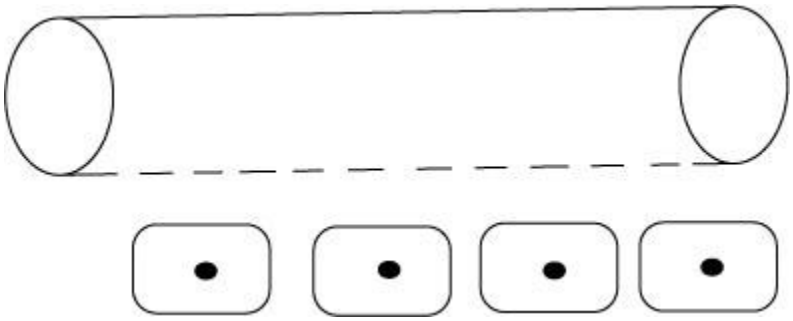


2) Interstitial Fluid Pressure
P Out>P In

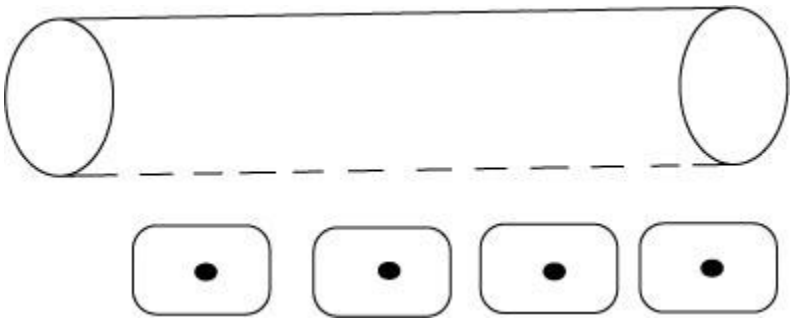


3) Plasma Colloid Osmotic Pressure
Osmosis In

H_20 is attracted to the Proteins
Plasma has > P's than I.F.

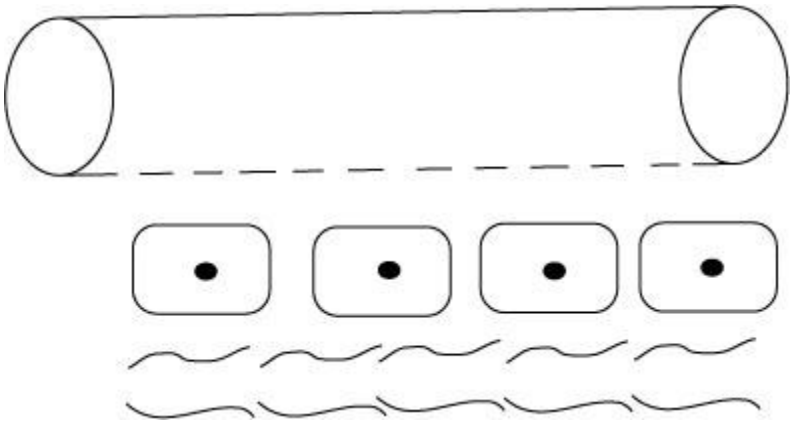


4) Interstitial Fluid Colloidal Osmotic Pressure
Osmosis Out
P In > P Out
The net movement is toward equilibrium



The Lymphatic System
Lymphatic Fluid: resembles plasma composition except that there are fewer proteins.

1° Function of Lymph: Lymph channels drain excess fluid from the interstitial spaces and return it to the blood.
The pores in lymph channels are much larger than capillary pores, therefore lymphatics can carry proteins and large particulate matter away from the tissue spaces.
Capillary [P] > interstitial tissue [P} > lymph [P]



Lymph channels have valves and a "pump system"

Lymph Fluid → Lymph nodes
↓
Filtered
↓
Subclavian Veins
↓
heart

REGULATION OF BLOOD FLOW

1) Local control of blood flow in response to tissue need

Each tissue has the ability to control its own blood flow in proportion to its metabolic needs
Blood flow is regulated by the tissues via
-vasoconstriction
-vasodilation

Blood flow to each tissue is usually regulated at the minimal level that will supply its requirements ----no more no less.

Local Autoregulation
Hyperemia: the presence of an abnormally large blood supply
1) active = increase blood flow due to increase metabolic activity

2) reactive = increase blood flow due to previous blockage example: decrease flow to an area results in an increase flow by 5 - 7 x's after the blockage is resolved

Vasodilator Theory for local blood flow regulation
The greater the rate of metabolism or the less the availability of 0_2 or other nutrients the greater the rate of formation of VASODIALATOR SUBSTANCES: (released by tissues) Adenosine, CO_2, lactic acid.

These substances act on the precapillary sphinters, metarterioles & arterioles and cause dilation.

Mechanism of Adenosine
ATP →ADP → AMP → Adenosine = VD → increase energy (more ATP, 0_2)

Oxygen Demand Theory
for local blood flow control
Aka. Nutrient Demand Theory: 0_2 & nutrients are required for vascular muscle contraction; if 0_2/nutrients are lacking, then vessels relax/dilate naturally; Increase 0_2 = constrict; decrease 0_2 = dilate

Long Term Blood Flow Regulation
Develops over a period of hours, days, weeks...
Involves a change in the degree of vascularity

ex. If arterial P to a region falls for an extended period, the body responds by increasing vascularity to that region; this is ...

ANGIOGENESIS : making of new vessels
Occurs for 3 reasons
1) Tissue Ischemia
2) Rapidly growing tissues
3) Tissues w/ excessively high metabolic rates

Angiogenin: hormone produced by tissues under above conditions.

Retrolental Fibroplasia:
1) Presence of excess 0_2 (from 0_2 tents) causes cessation of vascular growth (in neonatal retina)
2) Excess 0_2 removed = explosive OVERGROWTH of new vessels
3) Overgrowth invades eye structures and causes blindness

2) Humoral Regulation

The effect of hormones or ions on blood flow (AKA. Endocrine Control)

Local Vasoconstrictors

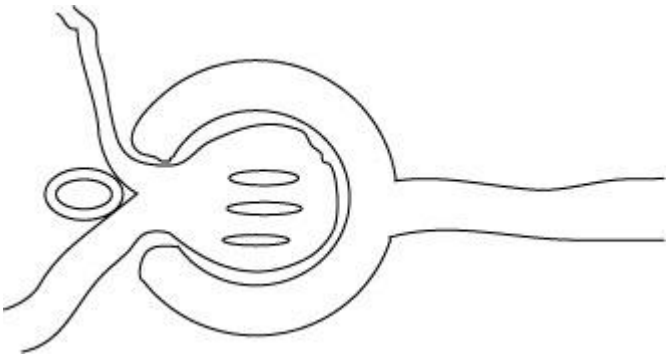
Epinephrine (EPI)
1. is a relatively mild vasoconstrictor
2. secreted by adrenal medulla
3. is a vasoconstrictor at high concentrations
4. in low concentrations can act on the heart as a vasodilator on coronary arteries during increased heart activity

Norepinephrine (NE)
1. is a more powerful vasoconstrictor
2. secreted by sympathetic NS endings and adrenal medulla
3. excites heart, veins and arterioles
4. causes vasoconstriction in veins and arterioles

Beta receptors: Receptors found on the cell surface that when bound to a hormone can cause various effects depending on surface receptors on the target cell.

Angiotensin II
1) a very powerful vasoconstrictor
2) acts on arterioles
3) systemic constrictor, not just local
4) increases total peripheral resistance
5) responds to decrease in renal blood pressure

Angiotensin II (cont)
Production from decrease renal BP → secretion of REN1N by the JUXTAGLOMERULAR CELLS



Renin converts angiotensinogen → angiotensin (milder VC) → angiotensin II results in an increase renal BP, increase flow to glomerulus from vasoconstriction of whole body.

<u>Vasopressin</u>
aka. ADH Anti Diuretic Hormone
Press = constrict
- more powerful VC (more than angiotensin II)
- produced in the hypothalamus and travels down to the posterior pituitary to be released

Has 2 general effects:
1) causes peripheral vasoconstriction
2) reduces H_20 amounts lost in the collecting ducts of the nephron

*responds to decrease BP, decrease blood volume, decrease HR

*ADH is the last renal mechanism for controlling the amount of urine (H_20) excreted ADH prevents loss of urine (H_20)

*ETOH inhibits ADH -

Endothelin

A powerful VC in damaged blood vessels
Found in the endothelial cells of blood vessels
Produces Local VC in response to damage (like crushing injuries)

VASODIALATORS

1) Endothelial-Derived Releasing Factor
released in response to rapid blood flow
due to rapid blood flow, the endothelial cell can be "sheered off' the vessels wall.
These "sheered" cells produce NITRIC OXIDE which is a very powerful VD.
This will decrease peripheral resistance and sheering.

2) Bradykinin
Active for only a few minutes!!
causes very powerful VD (arteriolar)
increased capillary permeability
activated via inflamation/breakdown of tissue

Mechanism of BradykininAction
1) tissue inflammation/breakdown of tissue (due to ischemia or trauma)
2) α-2 globulins split from blood
3) activation of kallikrein
4) kallikrein + α-2 globulin → kallidin
5) kallidin converted by tissue to bradykinin

α-2 Globulins → kallikrein → kallidin

Carboxy peptidase breaks down Bradykinin

3) Serotonin (5- hydroxytryptamine) = CNS Neurotransmitter

Causes VD or VC depending on circumstance/area
Effects are local
We are unsure of it's role as a "Circulatory Regulator"

4) Histamine

Derived from Mast Cells in damaged tissues and from basophils in the blood
Released due to : tissue damage, tissues inflammation, allergic reaction
Powerful VD
Increases capillary permeability

5) Prostaglandins: local tissue hormones
Found in every tissue of the body in small to moderate amounts.
Some are VC's
Most are VD's
Deemed "true local tissue hormones"
Released by the tissues to VD their area

3) Nervous Regulation of the Circulation

Nervous control mainly affects "Global" functions
Redistribution of blood flow to different areas of the body, increase pumping of heart, rapid control of arterial BP

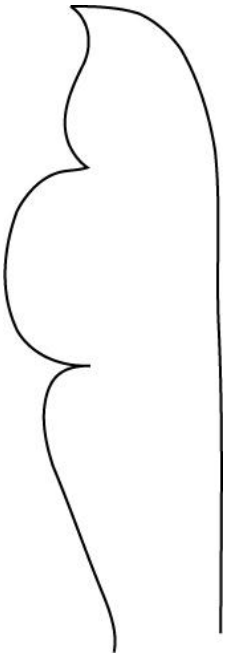
Autonomic Nervous System

Nervous control of circulation is almost entirely ANS
Mostly Sympathetic Nervous System - PSNS - can affect cardiac tissue function

1) Sympathetic Nervous System

Increase SNS Stimulation
↓
Increased Vasoconstriction (VC) Nor-epinephrine
↓
Increased Total Peripheral Resistance (TPR)
↓
Decreased Flow (Q, Increase P)

Also, SNS innervates the all vasculature EXCEPT - capillaries, pre-cap. sphincters & metarterioles

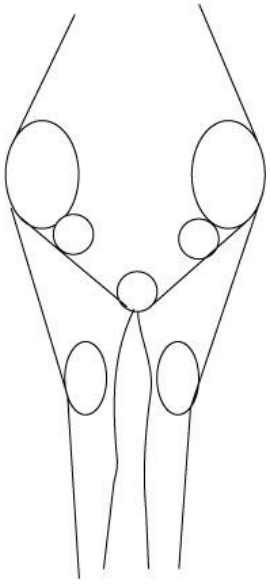


a) Vasomotor Center: coordinates regulation of circulation; is composed of 3 parts

b) Reticular Activating Center: Coordinates brainstem, thalamus & hypothalamus activities
(Reticular: web-like)

Nervous System Regulation of Blood Flow

Vasomotor Center - Primary function is to maintain vascular tone
- has 3 parts:



1) Vasoconstrictor area (C-1) -secrete Nor-Epinephrine →VC (excites SNS →VC)

2) Vasodilator area (A-1) -inhibits VC area

3) Sensory area - take in information from the periphery and use it to coordinate the efforts of l and 2

Vasovagal syncope
Fainting (loss of consciousness) Due to a powerful emotional stimulus
Mechanism unknown? Possibly limbic system input - occurs due to stimulation of Vasodilating centers

Cardioinhibitory Center slows heart rate

Regulation of Blood Pressure (Arterial)
The nervous system is capable of producing a rapid increase in arterial pressure
Short term control = rapid response

Mechanism of rapid response involves:
a) Vasoconstriction center } Vasomotor center stim. as a unit
b) Cardio-accelerator system }

1) Almost all arterioles of the body are constricted Increase total peripheral resistance = an increase in arterial pressure.

2) Veins & large vessels strongly constrict increasing blood volume to the heart = Increased force contraction.

3) SNS stimulation of heart to increase HR & increase force of contraction. All 3 help to increase arterial pressure

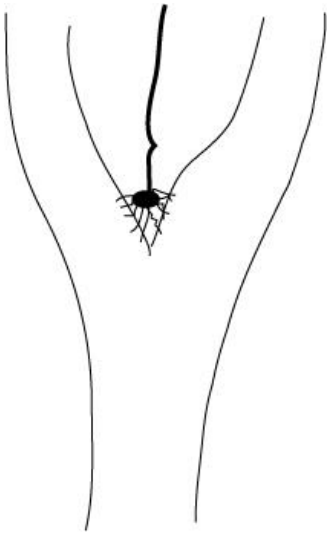
Sympathetic Nervous System
Transmits impulses to the adrenal medulla to release epinephrine and norepinephrine to all parts of the body. This stimulates vasoconstriction and vasodilation of vessels depending on the area involved.

Short Term Control Systems (arterial BP)
Controlled by the cardiac center of the brain (Medulla Oblongata)

Baroreceptor Reflexes
A reflex initiated by stretch receptors
Baroreceptor: have specialized nerve endings ("spray-like") that lie in arterial walls and are stimulated when stretched.

2 important locations where baroreceptors are extremely abundant

1) Carotid Sinus - function to prevent arterial rupture in brain
   a) not stimulated @ 0 -60mmHG
   b) > 60mmHG = stimulus (max @ 180 mmHG)
   c) respond better to rapidly changing pressure (as opposed to prolonged increase P's)
   d) not as functional with long term change's



2) Aortic Baroreceptors > 90 mmHg = stimulus

2nd Impact Syndrome
Condition in which an athlete has not fully recovered from a concussion LOOSES function of the carotid sinus baroreceptor allowing pressure increase and produce brainstem herniation!

Rapid Control of Arterial Pressure
Maintained through Vasoconstrictor and Cardioaccelerator Centers

1) Almost all arterioles are constricted to increase total peripheral resistance.
2) Veins strongly constrict.
3) Heart is directly stimulated by SNS

Responses From an ***Increase in Blood Volume***

A) Atrial Reflexes to the Kidney (Increase Art BP)

"The Volume Reflex"
Atria are OVERSTRETCHED

1) sends signal to hypothalamus to decrease ADH
2) decrease reabsorbtion of H20 in the tubules
3) reflexive dilation of afferent arterioles of kidneys -increase flow to kidneys → increase urine =decrease blood volume and decrease pressure.

B) An Atrial Reflex to control HR

"The Bainbridge Reflex"
Stretched atria increase HR by 75%

Bainbridge Reflex due to atrial stretch receptors stimulated
↓

Afferent Signal via vagus nerves sent to medulla oblongata

Efferent signals travel through vagal & SNS to cause:

1) increase HR
2) increase strength of contraction

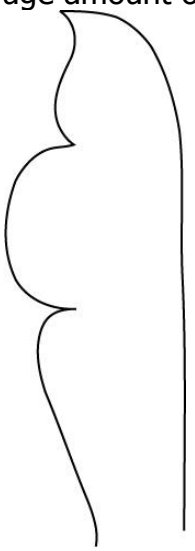
Responses from decreased blood flow

1) CNS Ischemic Response - very powerful

Decrease flow (02) to the vasomotor center

↓

Huge amount of VC (can elevate MAP for 10 min. @ 250mm)

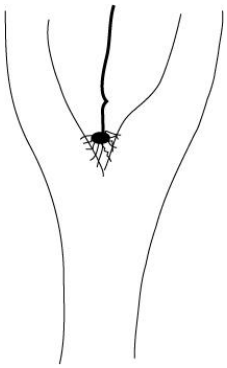


2) Cushing's Reflex: triggered by increase CSF pressure > arterial pressure cutting off arterial flow to brain.

This reflex increase arterial pressure to > CSF pressure in order to restore flow to brain

Chemoreceptor Control of Arterial BP
Chemoreceptor cells are sensitive to decrease [02], increase [C02], or increase [H+]

Location:



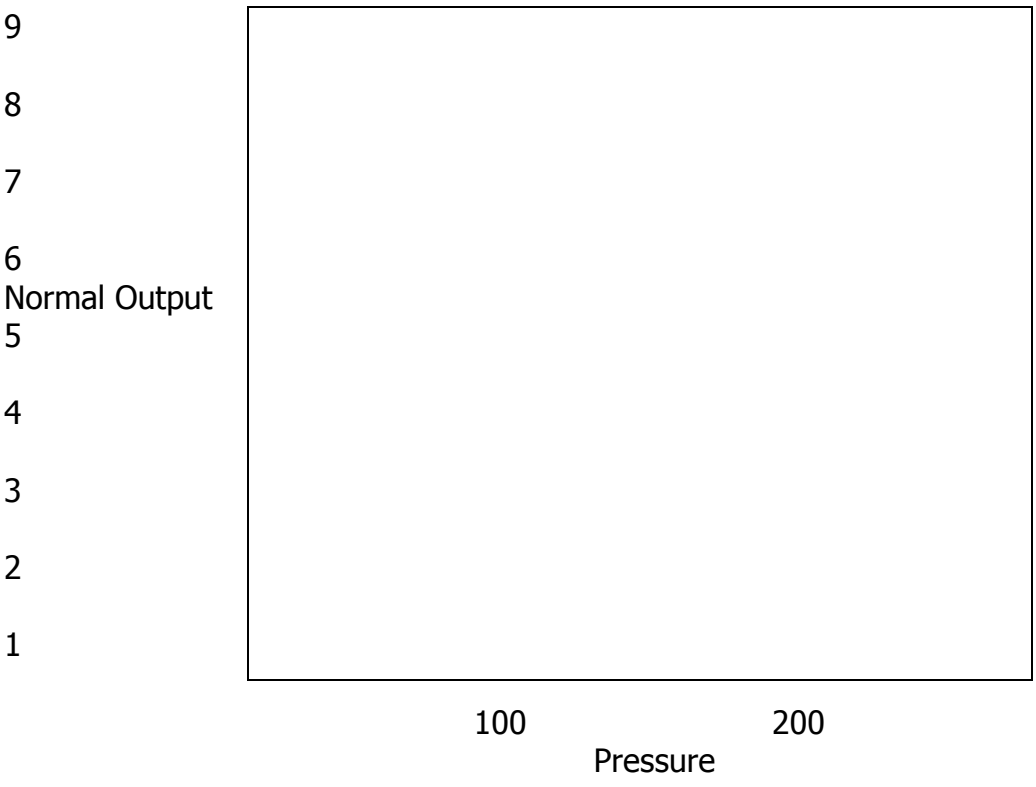
1) carotid bodies @ bifurcation of each carotid artery

2) Aortic bodies - adjacent to the aorta (aortic arch)

Transmit signal to the vasomotor center to increase arterial pressure.
A decrease in 02 increases stimulation of chemoreceptors.

Pressure Diuresis
An increase in arterial blood pressure of only a few mmHg can double renal output.

Pressure Natriuresis
Na+ is also excreted



Hypertension: "High Blood Pressure"

MAP > 110mHg ; normal - 90
DIA > 90
SYS > 135 –140

C.O. must = venous return

Arterial Pressure = C.O. x TPR

Increased TPR = increased total vasomotor tone → long term hypertension

Increased Vasomotor Tone over long time = hypertension

Increased Na+ will cause increased thirst

So... take in more H20

Increased H20 = decrease [Na+] in solution → increase pressure

Increase Na+ → increase ADH to retain H20
*Na+ is an important factor in renal - body fluid scheme

Essential Hypertension
hereditary (unknown cause)

Toxemia
Autoimmune disease increase thickening of the glomerular membranes which decrease filtration rate.

If MAP raises 50% or more above normal (100 mmHg)→ Increase to 150mmHg and goes untreated, patient has 3 years to live.

Why?
1) early CHF/coronary disease = increase risk heart attack
2) increase pressure = increase chance CVA or aneurysm
3) kidney failure
4) less distensible CV Tree = arteriosclerosis (vasculature cannot adjust to changes in pressure

Renin - Angiotensin II - Aldosterone System

Renin
A hormone produced by the Juxtaglomerular cells (JG cells).
Renin is released into the blood stream.

MECHANISM FOR RELEASE:
Decreased Arterial Pressure
↓

Renin Release (Kidney)
↓

Acts on Angiotensinogen → Angiotensin I
↓

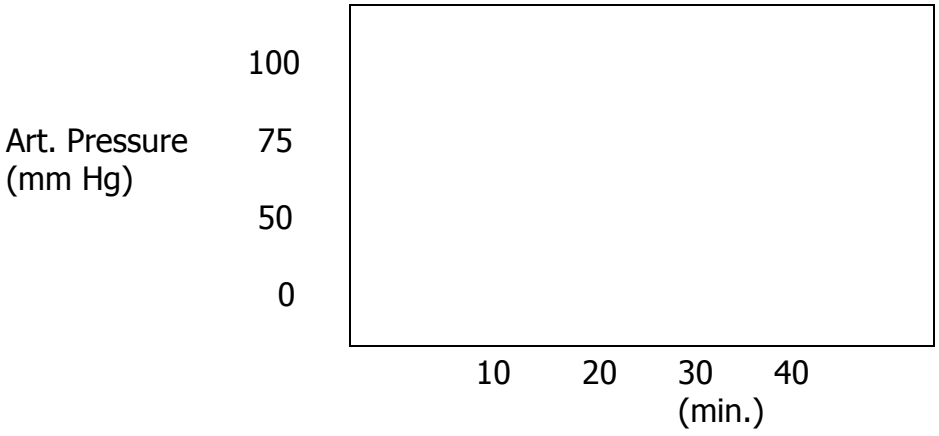
"ACE" (Angiotensin Converting Enzyme) located in lungs
↓

Angiotensin II (powerful V.C.) (has 2 effects)
↓ ↓

1) Renal Retention (Na/H20)
long Term

2) Vasoconstriction
short term

Increased Arterial Pressure (back to normal)



Angiotensinase
Angiotensin II ---------- inactivation

Angiotensin ----------increased TPR (VC) & increase C.O. (increased venous return)

*Angiotensin II is ~ 4 - 6 x's more powerful than Nor-Epi; but is not as strong as vasopressin/ADH

Long Term Effects of Angiotensin II

1) Acts directly on kidneys to retain H20 & Na+

- via constriction of renal vessels decrease flow to the kidneys = decrease filtrate production
- decrease peritubular cap. Flow = increase osmotic reabsorbtion through tubules
- Angiotensin II also stimulates tubules to reabsorb H20 & salt (Na+)

2) Angiotensin II → increase aldosterone secretion

- aldosterone: hormone that stimulates the reabsorption of Na+ in the distal convoluted tubules from the filtrate (increase Na+ in blood)
- stimulates adrenal glands to produce aldosterone

Na+ Effect:

Increase Na+ intake
↓
Increase Extra-cellular Fluid Volume
↓
Increase arterial Pressure (thirst & ADH)
↓
Decrease Renin/Angiotensin Production
↓
Decreasse Na+ & H2O Retension
↓
Increase Arterial Pressure back to normal

Hypertension Cycle

Abnormally High B.P.
↓

Increase MAP in the Kidneys
↓

Vasoconstriction of renal vessels
↓

Decrease in renal blood flow
↓

BUT Glomerular Filtrate Rate near normal due to increase art. Pressure
↓

C.O. near normal
↓

Total peripheral resistance increase 40- 60% (VC = increase TPR)
↓

Kidneys do not excrete normal amount of H20 & Na

Why decrease renal function?

Hypertension→ increased cardiac work→ L V hypertrophy
↓ ↓

aneurysm & stroke increased cardiac O2 demand
↓

ischemia

Intermediate Pressure Control Mechanisms
(30 min. to days)

1) Renin- Angiotensin System V.C. mechanism (already discussed)
V.C. → increase arterial pressure

2) Stress Relaxation Mechanism
- high pressures in the vessels → stretch (seconds)
- STRETCH (MINUTES) ----------STRETCH (HRS)

Due to stretch the pressure w/in the vessels approaches normal *remember V.D. → increase C.O.

VD of the peripheral tree can trigger volume release/increase flow in liver, spleen etc.

3) Capillary Shift Mechanism
-If low cap. Pressure, fluid comes in from tissues increase blood volume → increase pressure
-If cap. Pressure HIGH, forces fluid of arterial blood into tissues decrease blood volume

CARDIAC OUTPUT

C.O. = Arterial Pressure
Total Peripheral Pressure

= quantity of blood pumped into aorta/min

C.O. increases proportionally to the surface area of the body

Venous Return blood flowing back from vena cava to right atrium each minute.

Remember OHM'S Law:

Increase Arterial Pressure = increase C.O.

Decrease TPR = increase C.O.

Factors that increase heart effectiveness (Hypereffectivity)

1) Frank Starling Law - increase cardiac wall stretch = increase contraction force

2) Nervous Stimulation (also increase BP)
@ increase SNS → increase HR,
increase force of contraction can double C.O. increase PSNS (inhibit HR)

3) Heart muscle Hypertrophy
@ increase mass * contractility
can increase C.O. 50 - 100%

4) AV Fistula: Arterio-venous shunt Greatly decrease TPR → Increase venous return = increase C.O.
A shunt between a major artery and vein.

Factors that decrease heart effectiveness (Hypoeffectivity)

1) Inhibition (decrease) SNS

2) Pathology ---abnormal rate/rhythm

3) Valve disease

4) Hypertension (increase art. Pressure the heart must pump against)

5) Congenital heart disease

6) Myocarditis

7) Cardiac anoxia

8) Diptheria or other myocardial damage/toxicity

High C.O. almost always caused by a decrease in total peripheral resistance.

1) Beriberi - decreased thiamine = decreased tissue nutrients = increased vasodilation
2) Hyperthyroidism - increased metabolic rates = increased 02 usage = increased vasodilation

VENOUS RETURN

Factors that affect venous return:

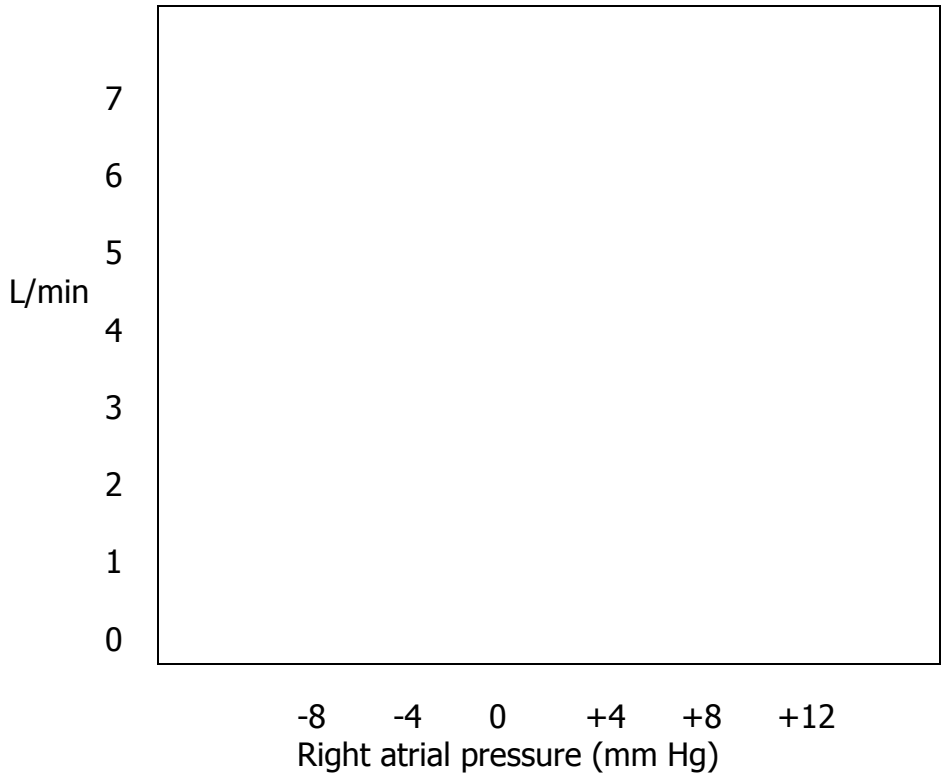
1) Right Atrial Pressure: exerts a backward force on the veins to impede flow of the blood into the R atrium
Increase Pressure makes it harder for blood to enter, so blood back-up on the venous side
Increase R atrial pressure → decrease venous return

2) Mean Systemic Filling Pressure (R AP = + 7mmHg)- forces the systemic blood toward the heart (when Q has stopped)

3) Resistance to blood flow between the peripheral vessels and the Right Atrium

4) Left Ventricular Failure - blood backs up in lungs

Venous Return Curve



As right atrial pressure rises, we eventually reach a point where the right atrial pressure is so great that the heart cannot pump hard enough to fill the right atrium.

Mean Systemic Filling Pressure

The arterial & venous pressures come to equilibrium when all flow in the systemic system has stopped (R atrial pressure of 7-8 mmHG).

This can be due to an increase R Atrial Pressure.

CARDIAC OUTPUT

FICK' S Principle - determines C.O in L/min.

C.O. (L/Min) = $\frac{\text{02 Absorbed per min. by lungs (ml/min)}}{\text{Arteriovenous 02 difference (ml/L of blood) (160ml } 0_2)}$

↓

(200 -160 = 40 ml 0_2)

Example: $\frac{\text{200 ml}}{\text{40 ml/L}}$ C.O. =5L/Min

C.O. = Stroke Volume x HR

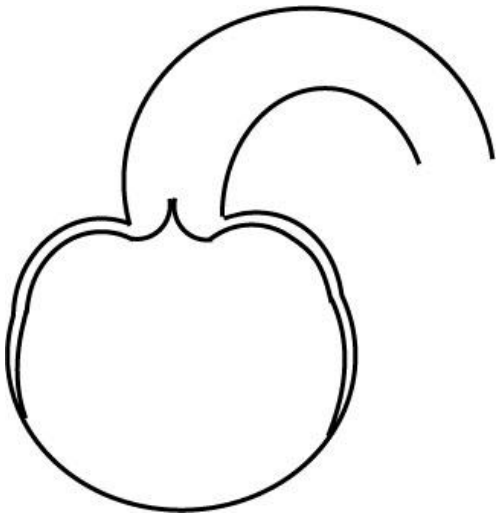
C.O. = 60 ml x 72 bpm = 5 L/min

Or an athlete C.O. = 100 ml x 55 - 5 L/min

CORONARY CIRCULATION

- The L & R Coronary arteries branch directly off of the ascending aorta.

- During ventricular diastole there is backflow of blood in the aorta which supplies the coronary circulation.



Pulmonary Edema

1) Increased Venous return increases the load on an already weakened L ventricle →blood damming in the lungs.

2) Increased blood in lungs → elevated pulmonary capillary pressure which allows fluid to leak out into the lungs tissues/alveoli.

3) Increased fluid in lung tissue/alveoli → decrease oxygenation

4) Decreased [02] further weakens heart → peripheral vasodilation

5) Peripheral V.D. → even more venous return

6) Further increase venous return → more damming!

HEART SOUNDS

The closure of valves causes heart sounds. "LUBB" "DUP"

1) LUBB - (S1) closure of A-V (chordae tendinae) valves @ beginning of systole (first sound).

2) DUP - (S2) closure of semi-lunar (aortic/pulmonary) @ the end of systole (second sound).

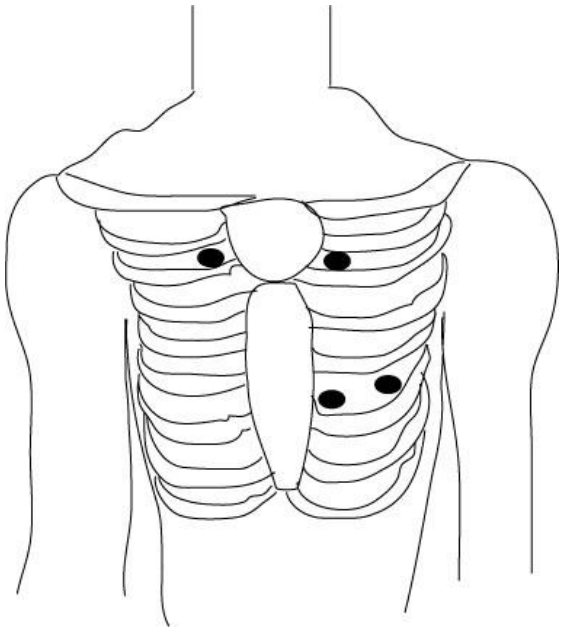
The second sound is the more audible of the 2, it is "crisper" due to > tautness of SL valves vs. AV valves and the arteries "vibrate" more.

3) Third Heart Sound - a weak rumbling - mid diastolic from blood filling ventricles.

4) Forth Heart Sound - not heard by the unaided ear, frequency too low, from atrial contraction, causing the rush of blood into the ventricles.

Areas for Auscultation

Aortic area = upward along aorta -	R 2nd intercostals space
Pulm. area = upward along the pulmonary art –	L 2nd intercostals space
Tricuspid = over R ventricle -	L 5th intercostals space
Mitral = apex (L vent) -	2" more lateral than tricuspid



Valvular Lesions

1) Rheumatic Fever –

2) Aortic Stenosis and Regurgitation –

3) Mitral Valve Disease –

Tetralogy of Fallout

A Right to Left Shunt - most of the blood fails to flow through the lungs. (unoxygenated aortic blood)

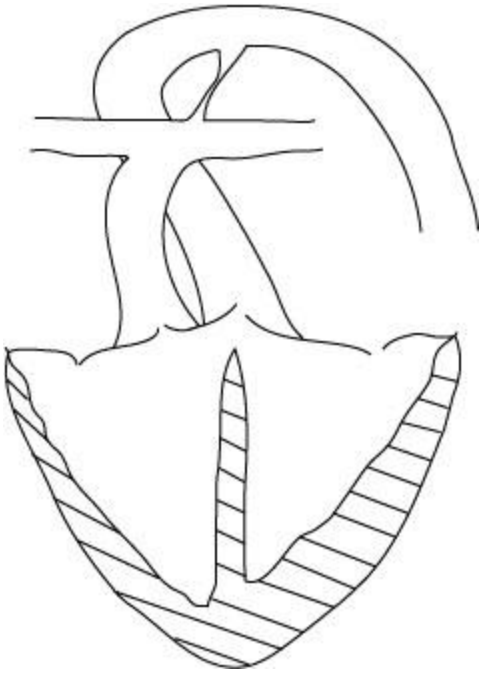
The Four Abnormalities

1) Overridding of the Aorta - Originates from the right ventricle rather than the left, or it overrides a hole in the septum and receives blood from both ventricles.

2) Pulmonary Artery Stenosis - Much less blood goes from R vent. --> lungs, instead blood passes directly to aorta

3) Ventricular Septal Defect - Blood from L vent. Flows through a whole to R vent., then aorta on durect to the aorta

4) R ventricular Hypertrophy - The R vent. must pump against aortic pressure → enlarged musculature



Production of Red Blood Cells
Embryonic Life

a) 1st trimester: RBC's are formed in the Yolk Sac
These cells are primitive & nucleated

b) 2nd trimester: RBC's are produced in the liver
(also spleen & lymph nodes)

c) Last month of gestation & for life
RBC's are produced exclusively by the Bone Marrow

Genesis of Blood Cells
Pluripotent Hemopoietic Stem Cell (PHSC) (aka Hemocytoblast)
All cells of the circulating blood are derived from this cell line; found in bone marrow.

1) A portion of these cells remains in bone marrow in its exact form to continue the line

2) The larger portion of reproduced stem cells become committed stem cells

(PHSC)

CFU-S and LSC
Colony Forming Unit Spleen Lymphoid Stem Cell

CFU-E CFU-GM CFU-M B-Lymphs T-Lymphs
Megakaryocytes
Platelets

Erthrocytes

Granulocytes: Neut.; Eosin; Baso
Monocytes: Macrophages

PHSC's make 3 cell lines:
1) More PHSC's
2) LSC
3) CFU-S

Red Blood Cells, Anemia & Polycythemia

Red Blood Cells = erythrocytes
- Shape & size
- Biconcave Disc
- Shape can change remarkably as they pass through capillaries
- Deformation of a normal RBC does not rupture
- 7.8 - 8.0 micrometers in diameter
- *RBC's live - 120 days

RBC Functions

1) The #1 function of the RBC is to transport Hemoglobin - which in turn transport 02. There are - 280 million molecules of HGB/RBC

2) Carbonic Anhydrase: RBC's contain a Large Quantity Carbonic Anhydrase catalyzes the rxn: C02 + H20 → H2C03

3) Acid/Base Buffer: RBC's/HGB are responsible for most of the buffering power of whole blood HGB + H+ → HHGB HGB looses/ binds H+ to increase blood pH

RBC concentration in the Blood

Males have 4.5 → 6.3 million RBC's/mm3 Females have 4.2 to 5.5 million RBC's/mm3
*Altitude can affect this #

HCT - Hematocrit: the % of blood that is cells (formed elements) male = 46%; female = 42%

Genesis of the RBC

Proerythroblast
↓

Basophil Erythroblast ("Stain with Basic Dyes")
↓

Polychromatophil Eryth.
↓

Orthochromatic Eryth.
↓

Reticulocyte
↓

Erythrocytes (Mature) (No Nuclei!)

During reticulocyte stage, cells leave bone marrow via diapedesis (squeezing through the pores of the capillary membrane).

*Reticulocytes are seen in higher than normal concentration when:
1) trauma has occurred

2) subject resides at altitude

PHSC's
*In leukemia's - these are the cells transplanted in bone marrow transplants.

1) CFU-S cells: Colony forming unit Spleen
   A) CFU-B: Colony forming unit Blast
      a)CFU-E: Colony forming unit Erythrocytes -produce Erythrocytes (RBC's)

   B) CFU-GM: Colony forming unit Granulocytes, Monocytes
      a) Granulocytes: Neutrophilis, Eosinophilis, Basophils
      b) Monocytes
         ↓
         macrophages

   C) CFU-M - Megakaryocytes = large nucleus Slough off membrane → Platelets
   *Should you ever see a megakaryocytes in circ. blood?

2) LSC = Lymphoid Stem Cell

   A) T-Lymphocytes
   B) B-Lymphocytes

Erythropoietin - hormone which regulates red blood cell production
   90% produced in the kidneys (where in kidney - unknown)
   10% produced in liver

Red Blood Cell production increases under any condition of Hypoxia: (also - destruction of large portions of bone marrow)
High altitudes, cardiac failure, lung disease

Factors that decrease oxygenation
1) Low Blood volume
2) Anemia
3) Low Hemoglobin (HGb)
4) Poor Blood flow
5) Pulmonary Disease
6) Altitude

Decreased 02
↓
Decrease Tissue Oxygenation
↓
Increase Erythropoietin
↓
Hemopoietic stem cells
↓
Proerythroblasts
↓
RBC's

Formation of Hemoglobin

I. 2 succ - CoA + 2 Glycine = 4pyrrole

II. 4 pyrole = 4 protoporphyrin IX

III. Protoporphyrin IX + Fe++ = HEME

IV. Heme + polypeptide = Hemoglobin chain α or β

V. 2 α chain + 2 β chain = HGb-A

Hemoglobin: 0_2 carrier w/in the RBC
- Binds loosely/reversibly to 0_2 so it can p/u or give 0_2
- Quaternary Protein
- Composed of 2a + 2 β chains
- 4 Fe++ molecules/HGB

Iron Metabolism - transportation/storage Iron (Fe++) is absorbed in the Small Intestine.

Once absorbed in plasma:

1) Apotransferrin + Fe → Transferrin "transport iron"(In plasma)
2) Apoferritin + Fe → Ferritin = "storage iron" (In cells) delivered to mitochondria where heme is made

Hemosiderin: Fe++ stored in an extremely insoluble form in tissues

Excretion of Fe++: some Fe++ is excreted in menses and feces

Degradation of Hemoglobin releases free iron

HGb →degraded by Macrophages →Heme (Free iron) + bilirubin (goes to liver) or excreted in feces

1) Spleen macrophages destroy old RBC's (they rupture) Or
2) Kupffer cells: macrophages of liver that destroy RBC's

RBC + Macrophage → Heme (break down RBC to release heme)

Porphyrin ring

Heme converted in liver → Bilirubin → Bile (a percent is excreted in feces, much is reabsorbed by small intestine)
→Free Iron → Recycled

Anemia
Deficiency of red blood cells (decrease RBC count)

1) Blood Loss Anemia: due to rapid hemorrhage or chronic blood loss Microcytic Hypochromic Anemia: RBC's produced w/ too little HGb due to chronic blood loss where the body can not absorb Fe++ as fast as it loses it.

2) Aplastic Anemia: Bone marrow aplasia lack of functioning bone marrow due to cancer or drugs

3) Megaloblastic Anemia: due to loss of function of Vit B12, Folic Acid, Intrinsic Factor

Slow reproduction of RBC's in bone marrow → Large RBC's called "Megaloblasts"

Pernicious Anemia: due to atrophy of stomach mucosa causes decreased Intrinsic Factor absorption.

4) Hemolytic Anemia: Abnormalities of the RBC's fragile, easily ruptured cells

5) Spherocytosis - sphere shaped cells

6) Sickle Cell - have HGb-S; when exposed to decrease [02], the HGb-S "crystalizes", these crystals elongate the cell causing the "sickle shape"

Hemolytic Disease of the Newborn (Erythroblastosis Fetalis)
Rh + RBC's of fetus are attacked by the mothers (RH-) Antibodies
These fragile cells rupture.

Polycythemia
Increased red blood cell count Secondary

1) Polycythemia can be due to to high altitudes or cardiac failure.

2) Physiologic Polycythemia: seen @ > 14,000 -17,000 ft.

Polycythemia Vera
- HCT increase 60 - 70%
- Caused by a gene aberration
- Excess production of RBC's
- Decrease rate of venous return
- Increase blood volume ---- increase venous return
- Increase blood viscosity --- increase arterial P

"rudy" complexion w/ bluish skin tint
- increased clotting

IMMUNOLOGY

White Blood Cells (WBC's aka Leukocytes)

Primary function is to fight infections from infectious/toxic agents: bacteria, viruses, fungi, parasites

Work by:
1) Actually destroying invading agents via phagocytosis
2) Forming antibodies/sensitized lymphocytes which destroy or inactivate an invader
3) Life cycle: depends on the individual cell = hours to years

Concentration of Different WBC's

Neutrophils (polymophonuclear) 62%
Lymphocytes 30%
Monocytes 8%
Eosinophils (polymorphonuclear) 3%
Basophils 0%

Defensive Properties/Characteristics of WBC's

1) Diapedesis: the cell slides through a pore much smaller than the cell itself by constricting a portion at a time. The cells ability to pass through the capillary membrane pores and enter the tissue

2) Ameboid Motion: cell movement by extension of cell membrane/cytoplasm

3) Chemotaxis
   WBC's migrate toward chemicals emitted by inflamed tissues/toxins

4) Phagocytosis: Cellular ingestion/eating of the offending agent - most important function of neutrophilis/macrophages

Factors affecting Phagocytosis:
Surface texture: smooth decrease chance; rough - gets eaten!

5) Opsonization: Antibodies adhere to the bacterial membranes "marking" them for phagocytosis.

The C-3 molecules also attach to the phagocyte!
This gives the WBC the ability to selectively bind a foreign material.
Proteins that bind to antibodies act as enzymes to catalyze a series of reactions that activate the compliment system.

Tissue Macrophages: Once monocytes have entered the tissue, they enlarge to become:

1) Kupffer cells: macrophages of the liver sinuses; destroy bacteria which enter through GI tract.

2) Lymph Node Macrophages: destroy bacteria in the lymphatics.

3) Spleen Macrophages: macrophages reside in the meshwork and destroy bacteria.

<u>Inflamation</u>
(redness, swelling, heat, pain) - complex of tissue changes caused by any damage

5 Characteristics:

1) Vasodilation of local vessels --- excess blood flow = redness

2) Increase capillary permeability --- leakage of fluid into tissue = swelling

3) Clotting of fluid in interstitial spaces due to excessive amounts of Protein (Fibrinogen)

4) Migration of large amounts of granulocytes & monocytes

5) Swelling of tissue cells = increase temp. = pain

<u>Lines of Defense</u>
Macrophage/Neutrophil response: Lines of Defense

1) Tissue Macrophage is 1st line of defense
   - immediate phagocytic action
   previously sessile phages --- mobile

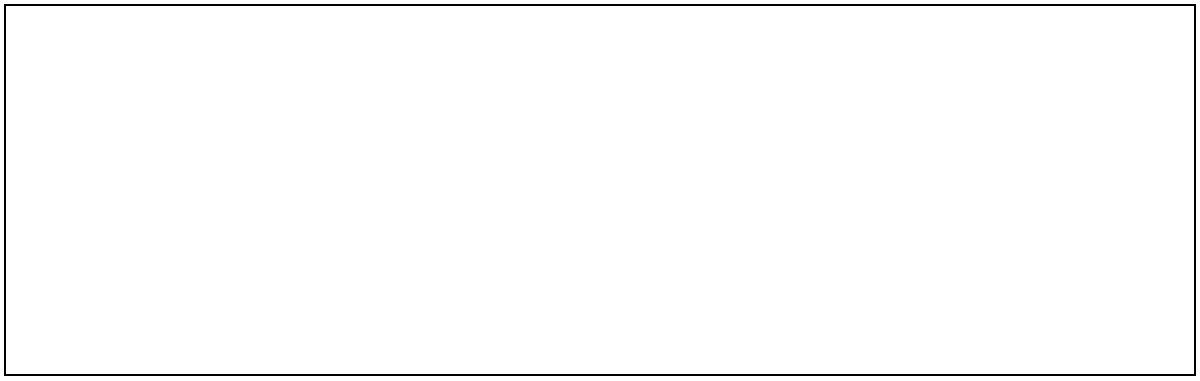
2) Neutrophil Invasion
   a) Margination: neutrophils stick to capillary walls in the inflamed area

   b) Then neutrophils enter tissues by diapedesis

   c) Chemotaxis attracts more!
   Neutrophils migrate and phagocytize

3) 2nd Macrophage Invasion:
   Monocytes from the blood enter the inflamed tissue & enlarge to become macrophages

4) Increased production of Granulocytes & monocytes by the bone marrow.



Time

Feedback Control of Macrophages

Inflamation induces WBC's production
1) TNF: Tumor Necrosis Factor
2) Interleukin -1 (IL-1)
3) GM-CSF: Granulocyte-Monocyte Colony Stimulating Factor

Macrophages/T-cells produce/release these and stimulate the bone marrow to increase WBC production (granulocytes/monocytes)

Eosinophils: 2% of WBC's
- produced in large numbers in people with parasitic infections. The Eosin's attach to parasites and...
1) They release hydrolytic enzymes from their granules
2) They release reactive forms of 02
3) Major basic protein

Basophils: 0.5%
- release Heparin, Histamine, Bradykinin, serotonin } cell ruptures - releasing granules
- play role in ALLERGIES
- Ig E binds the basophil and mast cell causing rupture, releasing histamine, bradykinin, and heparin

Mast Cells
Connective tissue cells located outside the capillaries and inside the tissue.
They are immunocompetent tissue cells similar to basophils in form and function.

Leukopenia: (aka) Agranulocytosis
Decrease WBC's due to bone marrow not producing WBC's

Caused By:
irradiation by gamma rays

Immunity & Allergy
Immunity: the body's ability to resist almost all types of organisms/toxins that tend to damage tissue/organs.

2 Types of Immunity
1) Innate immunity: general processes not directed @ a specific disease.

2) Acquired immunity: does not develop until after the body is 1st attacked by a disease or toxin - takes weeks/months to develop

Innate Immunity Examples:

1) Phagocytosis by WBC's already present

2) GI defense: HCl secretions & digestive enzymes

3) Skin resistance to invaders

4) Blood compounds that attach and destroy
lysozyme, basic polypeptides, complement complex, natural killer lymphocytes, hydrolytic enzymes: (H202 = peroxisomes)

5) Interferons

Acquired Immunity:
Develops after the first attack (2 Types)

1) Humoral Immunity or B-Cell Immunity.
The body develops circulating anti-bodies (globulin molecules) which are capable of attacking invading agents.

2) Cell mediated or T-Cell Immunity
Involves large amounts of "activated lymphocytes" specifically designed to destroy "the foreign agent".

Antigens(BIG): proteins or large polysaccharides that initiate an acquired immune response -must have MW = > 8000

Haptens(Little): Substance w/MW < 8000 which act as antigens

1) The Hapten 1st combines w/a substance that is antigenic (like a protein)
2) The combination elicits the immune response

B-Lymphocytes: Humoral: Responsible for forming the Antibodies which destroy antigens (directly and indirectly).

T-Lymphocytes: cell mediated: responsible for forming the "activated lymphocytes". Cells directly destroy the antigen.

<u>Lymphocyte Locations: "Lymphoid Tissues"</u>

- Lymph nodes
- Spleen
- GI Tract
- Bone Marrow
- Peyer's patches in the ileocecal area - prevents "backflow" of bacteria

Appendix
Thymus
Tonsils
Adenoids (back of soft pallet)

Lymphocyte Production:

PHSC: Pleuripotent Hemopoietic Stem Cell
↓ ↓

T-Cells B-Cells
↓ develop in
↓
Thymus Bone Marrow/ Fetal Liver(Late Fetal & after)
↓ ↓

Lymphatic Tissue
↓ ↓

T cells B cell → plasma cell → antibodies
↓

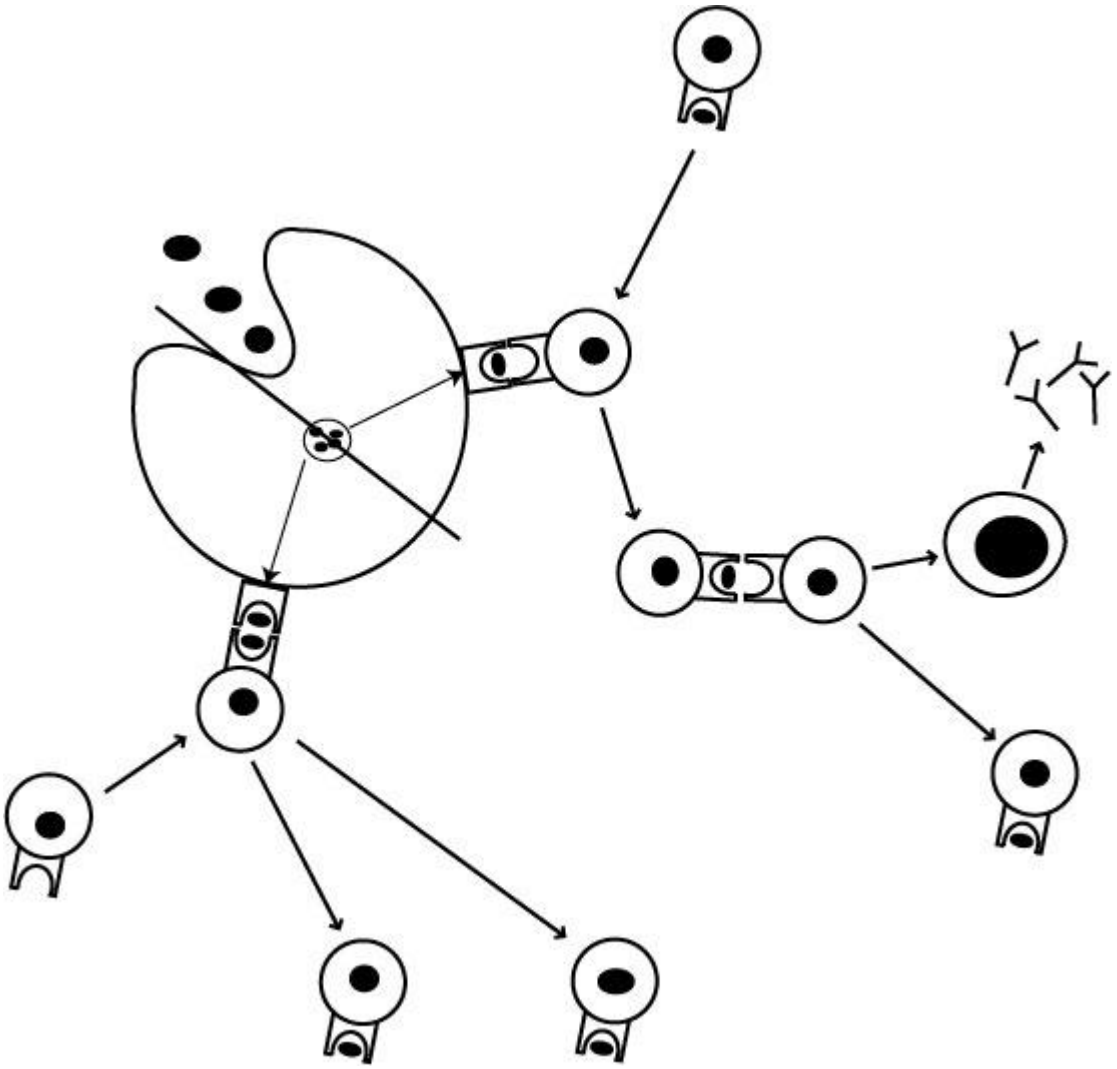
Activated T cells (Shortly before birth & few months after)

Thymus: Location of T-cells Differentiation/Maturation
Makes certain that T-cells produced against self are not circulated (Eliminates them via phagocytosis) via Thymus Epithelial Cells
*any T cells that develop against self are destroyed by thymus epithelial cells.

*Once the cells are in the lymphoid tissue, they await activation: Stimulus → Activation = Wild Division

Role of Macrophages in Activation Process

Most invaders are 1st phagocytized & partially digested by macrophages.
Then antigenic products are passed by cell to cell contact.
The macrophage presents the antigen to the B & T lymphocytes.



Formation of Antibodies
Produced by B-lymphocytes: specific for a particular antigen

Once activated enlarge → lymphoblasts Lymphoblasts → plasmablasts

Plasmablasts are precursors to:
Plasma Cells: produces gamma globulin antibodies to a specific antigen

Typical "IGD Antibody"

Antibodies:
Gamma Globulins "immunoglobulins"

- 2 light chains
- 2 heavy chains

Classes of Antibodies
1) IgG = 75% of antibodies
   Specialize in neutralizing bacteria, viruses & toxins

2) IgM = few
   Large "star shaped" w/10 binding sites
   Common in blood reactions (agglutination)

3) IgE = Small
   Especially involved in Allergy

4) IgD = helps activate B-lymphocytes 5) IgA = 1St line of defense; common in tears
   Mucous membranes

Actions of Antibodies
Act by 2 methods against invaders

1) Direct Attack
2) Activation of the Complement System

Direct Action
1) Agglutination: Multiple particles w/ antigens on their surfaces such as Bacteria or RBC's (foreign) are bound together in a clump.

2) Precipitation: The molecular complex of a soluble antigen (tetanus toxin) + the antigen --- very large so that it becomes Insoluble and precipitates.

3) Neutralization: antibodies cover the binding sites of the antigenic agent.

4) Lysis: some antibodies directly attack the membranes of antigens → Rupture

Complement System for Antibody Action
Complement: a system of - 20 proteins
11 principal proteins = C 1 --> C9, B & D

Activation of the Complement = 2 Pathways
1) Classical Pathway = activated by an antigen & antibody reaction.

2) Alternate Pathway = large polysaccharide molecules of a micro-organism react w/ Factors B & D which activates C3 → entire cascade.

The "Cascade"
A series of reactions occurring after formation of an antigen/antibody complex.

Compliment System Effects

1) Opsonization and Phagocytosis - C3b activates phagocytosis and make it easier for neutrophils and monocytes to engulf.

2) Lysis – C5b6789 causes rupturing of the cell

3) Agglutination - causes the clumping and precipitation of antigen

4) Neutralization of the virus - attacks viral structure

5) Chemotaxis – C5a factor attacks neutrophils and macrophages

Mediated Immunity (T cell)- special attributes

There are as many as 100,000 cells receptors sites/T-cell

Types of T-Cells: (4)

1) T-Lymphocyte Memory Cell: Formed @ 1st exposure, circulate and remain dormant until 2nd exposure.

2) Helper T-Cells - Most numerous of the T's.
Regulate all immune functions: coordinates B & T Lymp activity.
Produce Lymphokines - all stimulate immune system function
Interleukin 2 → 6
Granulocyte/Monocyte Colony Stimulating Factor
δ Interferon - stimulates and attracks NK cells
Affected by AIDS which cripples immunity

3) Cytotoxic T-Cells - direct attack cells aka "Killer Cells"
stimulates by interleukin-δ from Helpers
secrete Perforins: proteins which punch holes in the antigens membrane
destroys: cancer, virus infected cells, transplant cells

4) Suppressor T-Cells:
Suppress the function of Cytotoxic & Helper T's
prevent excessive immune reactions that may damage the body
"Self Tolerance": blocks/counteracts autoimmune reactions
Failure of Tolerance Mechanism" → Autoimmune Diseases.

Autoimmune Diseases

1) Rheumatic Fever: body becomes immunized against the tissues of the joints & Heart Valves

2) Myasthenia Gravis: immunity against ACH (Droopy eyelids) Receptors = Paralysis

3) Lupus Erythematosis: Immunity against multiple body tissues at once Extra: Glomerulonephritis - reaction against the basement membrane of glomeruli

4) Multiple Sclerosis

Vaccination

Utilized to produce an acquired immune response to specific diseases using dead organisms that are no longer capable of causing disease, but still have their chemical ANTIGENS.

Passive Immunity

Acquired secondarily, i.e. breast milk

Attenuated

Live organisms that have mutated or rendered, so they cannot cause disease but still carry specific antigens.

Allergies

Excess IgE Antibodies (oversensitization to antigen)
inherited
large quantities of IgE = reagins or sensitizing antibodies
Reagin + Allergen = Allergic Reaction
IgE binds with Mast Cells and Basophils → Rupture
Ruptured cells release: histamine, slow reacting substance of anaphylaxis, heparin, and eosinophilic chemotactic factor

Types of Allergic Reactions

1) Anaphylaxis:
A widespread reaction throughout the vascular system and associated tissues.

Histamine released into circulation→ body wide vasodilation → increased capillary permeability decreased plasma levels → circulatory shock.

Loss of plasma to interstitium
This can produce: Circulatory shock
Tx with Epinephrine
Slow Reacting Substance of Anaphylaxis causes spasm of smooth muscle bronchioles→ Asthma-like attack can cause suffocation.

2) Urticaria - Hives Antigens contact skin areas --- local histamine release

1. V.D. 4redness
2. Increase Cap. Perm. 4 swollen patches Tx: Anti-histamine

3) Hay Fever - Histamine release in the nose

4) Asthma - slow releasing anaphylaxis substance

Blood Groups
Specific antigens on the surface of RBC's: OAB + Rh
O - 47% No A or B antigens = universal donor = o neg
A - 41%
B - 9%
A/B - 3% Has both A & B = universal recipient

Erthroblastosis Fetalis
"Hemolytic Disease of the Newborn"
-Agglutination/phagocytosis of RBC's
Mom =Rh-
Dad =Rh+

Mom has produced Rh + agglutinins which pass to baby via placenta
During 1st pregnancy only a few anti-Rh agglutinins

3% of 2nd births
10% of 3rd births etc...

Kernicterus
Destruction of infant neuronal cells due to precipitation of Bilirubin can lead to permanent brain damage.

Transplantation
Autograft: transplant of a tissue or whole organ from one part of the same animal to another
Isograft: one identical twin to another
Allograft: same species; i.e. human ↔ human, dog ↔ dog
Xenograft: lower animal → human (pig → human)

HEMOSTASIS/BLOOD COAGULATION
Hemostasis: prevention of blood loss; several mechanisms (4)

1) Vascular Spasm = damage to vascular wall in smaller vessels → thromboxane A2 (produced by platelets) → V.C.

2) Platelet Plug Formation

3) Blood Clot Formation (by blood coagulation)

4) Fibrous Tissue Growth

Platelets: aka Thrombocytes
Produced by Megakaryocytes in bone marrow

Cytoplasm has:
• Actin, Myosin, Thrombosthenin -These cause platelet contraction
• Enzymes that can produced: ATP & ADP (energy for contraction)
• Synthesize Prostaglandins
• Fibrin-stabilizing factor
• Growth factor
• Coated by glycoproteins which avoid normal endothelium, but attach to injured areas
• Membrane has lots of phospholipids

* contractile proteins contract to cause release of granules that have multiple active factors residing within them (ADP, thromboxane which also activate nearby platelets to form the platelet plug.

Mechanism of the Platelet Plug

When platelets contact a damaged vascular surface, multiple changes occur:

1) They swell

2) Pseudopods

3) Contract releasing active factors

4) They get sticky & stick to collagen fibers (know)

5) Secrete ADP & thromboxane AZ

6) Platelets attach to other platelets = Platelet Plug + Fibrin thread → SCAB

Blood Clot Formation

General mechanism has 3 main steps

1) Prothrombin Activator: a complex of activated substances

2) Conversion:

Prothrombin Activator

Prothrombin ---------- > Thrombin

3) Fibrinogen ----------> Fibrin Fibers

Prothrombin: plasma protein formed continually by the liver

- Vit K is required
- Prothrombin is unstable & easily split
- Thrombin - smaller than prothrombin ------ split

Prothrombin

↓

Prothrombin activator ↓Ca++

↓

Thrombin

↓

Fibrinogen ----------> Fibrinogen Monomer

↓Ca++

↓

↓

Fibrin Fibers

Cross-linked fibrin fibers = Clot

↓

Clot Retract

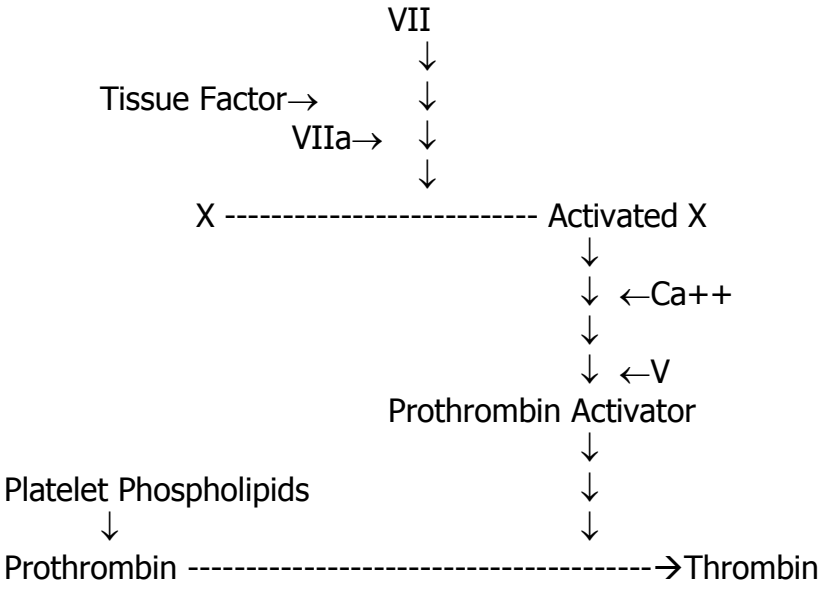
Blood Clotting

Formation of Prothrombin activator has 2 pathways:

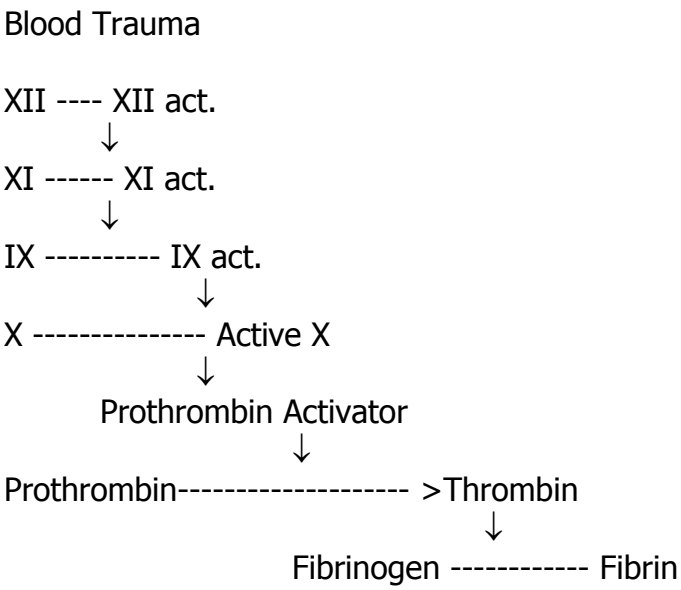
1) Extrinsic Pathway: begins by trauma to the vascular wall & surrounding tissues

2) Intrinsic Pathway: begins in the blood itself by damage to platelets

Extrinsic Pathway



Intrinsic Pathway

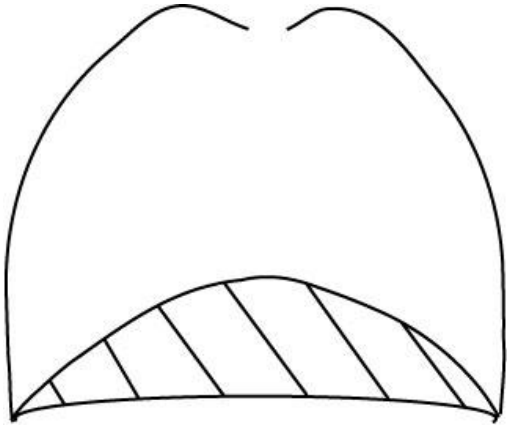


THE RESPIRATORY SYSTEM

Pulmonary Ventilation

Pulmonary Ventilation: The inflow and outflow of air between the atmosphere and the lung alveoli; "Breathing"

1) Inspiration: breathing inward
Contraction of the diaphragm pulls the lower surface of the lungs downward.



2) Forceful Inspiration:

a) External Intercostals
Pull the rib cage upward, moving the sternum away from the spine & increase anteroposterior thickness of the chest by 20%.

b) Scaleni - lift the 1st 2 ribs upward

c) Others that help: sternocleidomastoid (lift sternum upward), anterior serratus (lift rib upward)

3) Expiration: (Exhaling); mostly passive

a) Diaphragm relaxes

b) "Elastic Recoil": The lungs, chest wall, & abdomen structures compress the lungs
Elastic Connective Tissue Fibers surround each alveoli
Smooth muscle and skeletal muscle recoil too.

4) Rapid Expiration: achieved w/ abdomen muscle contraction

a) Rectus abdominus
b) internal intercostals

Asthma
Smooth muscles constrict, and expiration must be forced -"Reactive Airway Disease".

Smooth muscle lines the terminal and respiratory bronchioles.

Internal Respiration: The exchange of gases between the tissues & the blood.

External Respiration: The exchange of gases between the blood and the air in the lungs.
"A Respiration" = 1 inspiration + 1 expiration= 1 cycle

Avg. RR = 12; RR > 20 tachypnic; RR < 6 = Bradypnic

Anatomy of Respiration

General Passageway of Air

Nostril/Mouth
↓
Nasal cavity
↓
Pharynx
↓
Larynx
↓
Trachea: hyaline cartilage to prevent collapse of tube
↓
Primary (main) Bronchi (L & R): conducts air to bronchioles
↓
Secondary Bronchi
↓
Tertiary Bronchi
↓
Small Bronchi
↓
Bronchioles: Large → small → no longer have cartilage; encased in smooth muscle that can expand/contract the lumen
↓
Terminal Bronchioles

↓

Respiratory Bronchioles - thinnest, most delicate

↓

Alveolar Ducts

↓

Alveolar Sac - "grapelike" clusters

↓

Alveoli - site of gas exchange w/ blood Each has extensive capillary network Surrounded by elastic fibers (can expand/contract)

β-receptors of smooth muscle in Bronchioles are responsive to EPI / NorEpi
→Bronchodilation

Functions of Respiratory System

1) provide gas exchange between blood and air
2) regulation of ions (Bicarb/C02)
3) fight infection (foreign particles inhaled) - macrophages
4) vocalization - sound production
5) olfactory sensation

Respiratory Mechanics

1) Pleural Membranes & Potential Space
   Secrete a serous fluid into the pleural space.

The lung "Floats" in the thoracic cavity surrounded by a thin layer of Pleural Fluid: lubricates the movement of lungs w/in cavity.

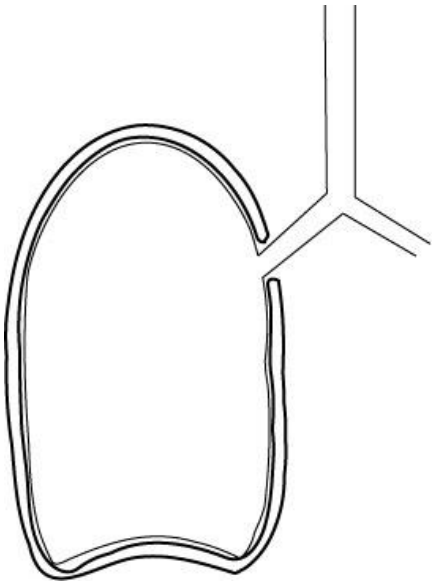
Lymphatics: continual secretion of excess fluids into the lymphatic ~ secretion between the visceral surface and parietal pleural

"Fist-in-the-Balloon Theory"

Visceral Pleura

Parietal Pleura

Potential Space



2) Negative Pleural Pressure

The pleural space has a negative pressure between the two membranes.

Function: helps hold the inner and outer membranes together.

Pleural Pressure: pressure of the fluid within the pleural cavity is slightly negative ~ -5 cm H_20

Expansion w/ inspiration

-develop -7.5 cm H_20 (lung V increase 0.5 L) $\rightarrow$ pulls air in.

<u>Alveolar Pressure</u>
Pressure inside the lung alveoli

a. At rest - not breathing = 0 cm H_20

b. For inspiration to occur alveolar P must be more negative than atmospheric pressure

c. During inspiration, alveolar pressure decrease to -1 cm which is enough to bring in .5 L air into lungs

d. Expiration: alveolar P = + 1, forcing .5 L out in 2 - 3 s

Pleural Effusion
Excess fluid in the potential space.

Transudate: interstital fluid that leaks into the potential space composed of mucopolysaccharides & proteins.

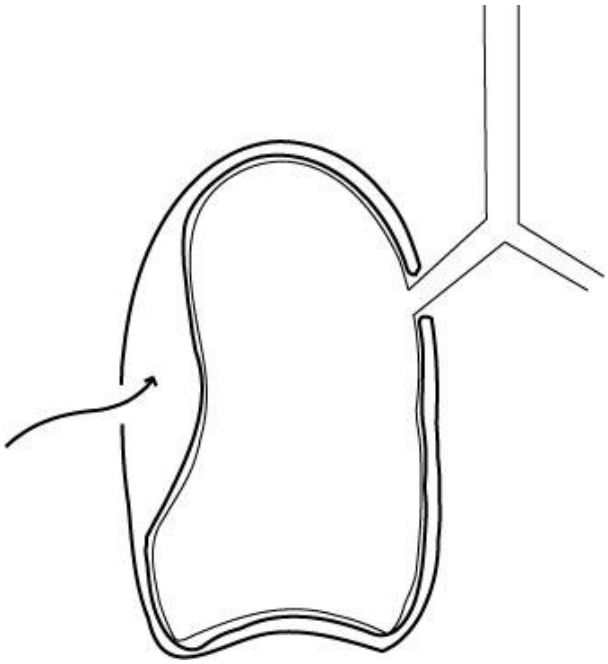
Causes of Pleural Effusion:
1) Blockage of lymphatic drainage

2) Cardiac Failure -- increase high peripheral & pulmonary cap- pressures →"edema" in the potential space (transudate fluid).

3) Decrease plasma colloid osmotic pressure → "edema"

4) Infection/inflammation of pleural surfaces

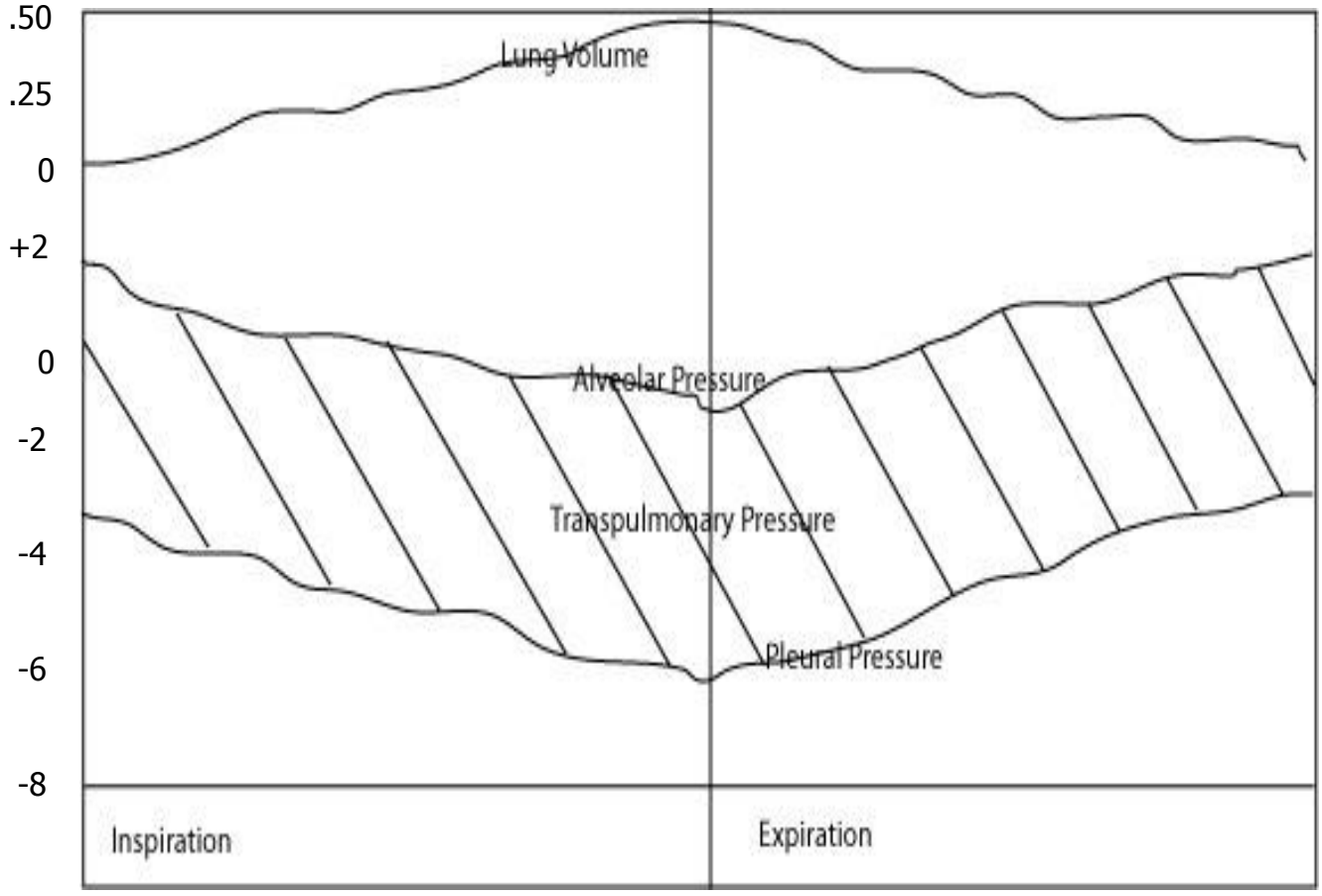
Pneumothorax: Air in the lungs
Lung Collapse



Creating Negative Pressure for Inspiration
1) Expand the cage
2) Diaphragm down

Transpulmonary Pressure
The pressure difference between the alveolar pressure & the pleural pressure.
A measure of the elastic forces in the lungs that tend to collapse the lungs = AKA. Recoil Pressure.
The pressure across the lungs from outside to inside.

Amount of Pressure needed to overcome the elastic recoil of the lung tissue "The measure of elastic recoil".



Surface Tension & Surfactant

Surface Tension:
When H20 contacts air, the water molecules on the surface are strongly attracted to each other causing the water surface to contract and hold together; like raindrops.

Surface Elastic Force:
On the inner surface of the alveoli the H20 surface attempts to contract, which would decrease the diameter of the alveoli;
*The net effect of this is an elastic contractive force over the entire lungs - H20 makes it harder for the alveoli to expand.

Surfactant: a "surface active agent" which spreads over the H20 on the inner surface of the alveoli $\rightarrow$ decrease in surface tension.

Type II Alveolar Epithelial Cells:
Cells produce surfactant - a mixture of phospholipids, proteins & ions; the phospholipid structure (hydrophobic/hydrophilic) is key to decrease surface tension.

Premature Babies
Type II cells are not mature $\rightarrow$ decrease surfactant decrease alveolar diameter (alveoli collapse).
Collapsing pressure of occluded alveoli caused by surface tension.

$$\text{Collapsing Pressure} = \frac{2 \times \text{surface tension}}{\text{Alveolar Radius}}$$

Decrease radius = increase collapsing pressure

Increase radius = decrease collapsing pressure

Premies have dual problems $\rightarrow$ decrease surfactant + decrease alveoli radius/size

Interdependence Between Adjacent Alveoli
The large alveoli that share adjacent septal walls w/ smaller alveoli help hold open the small alveoli. The large alveoli "splint" the small ones.

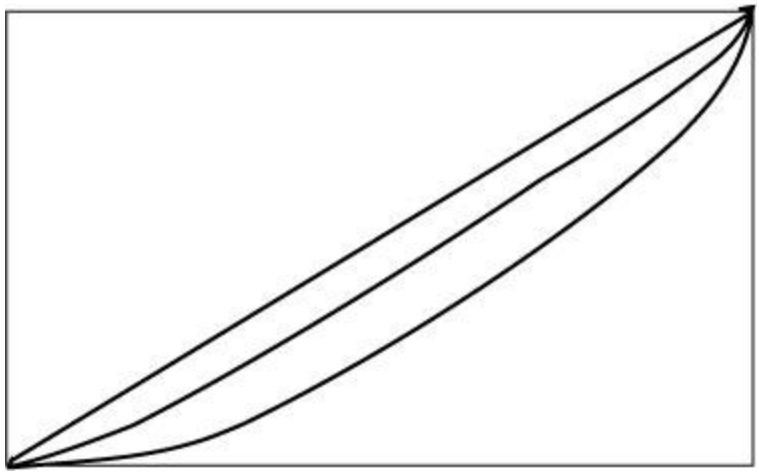
Forces to overcome during breathing; "Work of Breathing"

The work of Inspiration (expiration is passive)

1) Compliance Work (elastic work) = The force required to expand the lungs against the lung & chest elastic forces; The work required to overcome the recoil forces of the lung tissue.

2) Tissue Resistance Work: Work required to expand the "thoracic cage" (tissue, lung, chest wall structures); required to overcome the viscosity of the lung & chest wall structures.

3) Airway Resistance Work: Work required to overcome the airway resistance during the movement of air into the lungs; overcome the "airflow" through the passageways.



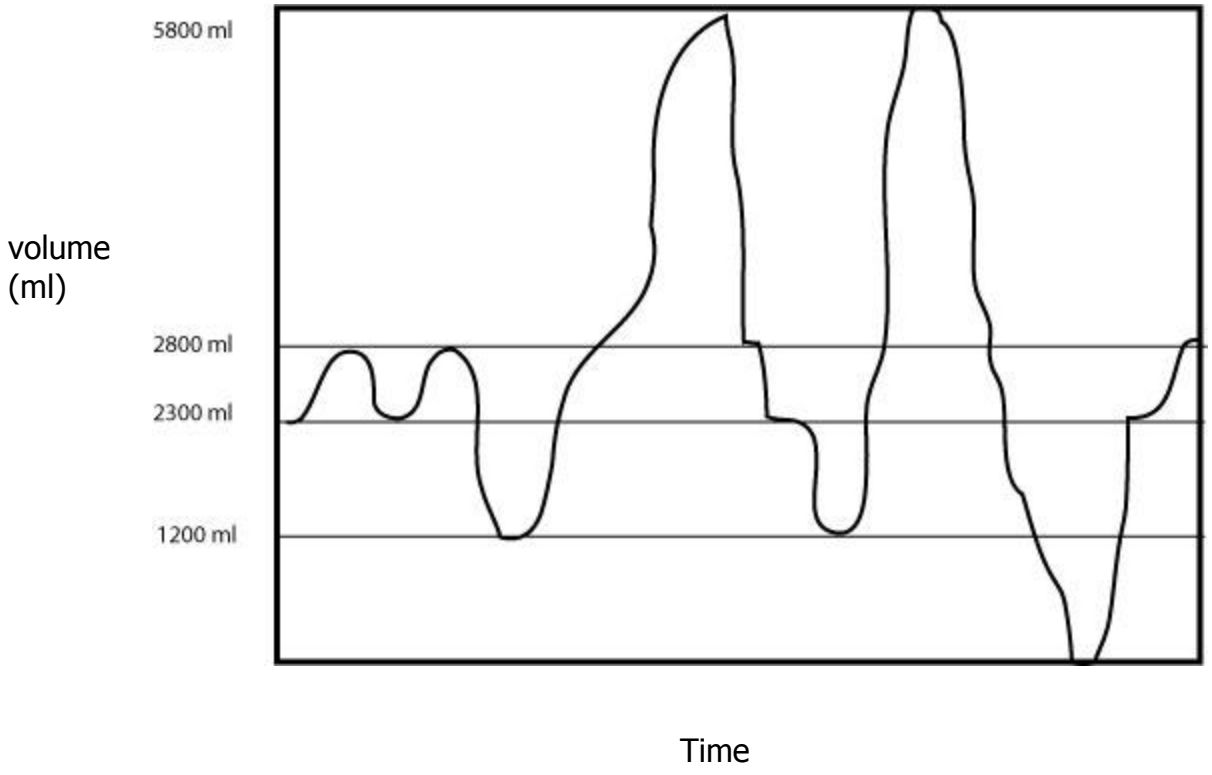
Pulmonary Volumes:

1) Tidal Volume (TV):Tthe volume of air inspired or expired w/ each normal breath; "Normal respiration" - 500ML (.5 L)

2) Inspiratory Reserve Volume (IRV): The extra volume of air that can be inspired over and above the normal TV - 3000 mL (3L)

3) Expiratory Reserve Volume (ERV): Extra amount of air that can be expired by forceful expiration @ the end of TV; - 1100 mL

4) Residual Volume (RV): The amount of air left in the lungs after forceful expiration - 1200 mL



<u>Pulmonary Capacities:</u>
Combinations of Pulmonary Volumes

1) Inspiratory Capacity
Tidal Volume + Insp. Reserve Volume
500mL +3000mL = 3500mL

2) Functional Residual Capacity
Exp. Reserve Volume + Residual Volume
1100mL + 1200mL = 2300mL

3) Vital Capacity
Insp. Reserve Volume + TV + Exp. Res. Volume
3000 + 500 + 1100 = 4600mL
This is the Max a person can expel from the lungs after first filling the lung to their maximum.

4) Total Lung Capacity
Vital Capacity + Residual Volume
4600mL + 1200mL = 5800mL
The max volume to which the lungs can be expanded w/ greatest possible inspiratory effort.

Capacity Equation

VC = IRV + TV + ERV & VC = IC + ERV
TLC = VC + RV & TLC = IC + FRC
FRC = ERV + RV

Minute Respiratory Volume

TV x RPM = the amount of new air moved into the respiratory passages/minute.
500 x 12 = 6000mL/Min

Alveolar Ventilation: the rate at which new air reaches the alveoli.
How does "new air" move from the terminal branches to the alveoli?

Diffusion: Gas exchange occurs via diffusion through the spaces between term. bronchioles & alveoli.

$[0_2]$ alveoli < $[0_2]$ bronchioles

Dead Space
The respiratory passages where no gas exhange occurs (150mL).

Rate of Alveolar Respiration:
The total volume of new air entering the alveoli/minute.

Va = (Freq) x (TV - VD)
(12) x (500 -150) = 4200 mL/Min

Va = Volume Alveolar Vent/Min
Freq = RPM
VD = Volume Dead Space

Pulmonary Circulation

Pulmonary Arteries
R side of heart→ Lungs = unoxygenated blood
Thin & distensible
The pulmonary tree is very compliant - can serve as a blood reservoir.

Pulmonary Edema L Heart failure → damming of blood → Pulmonary edema

Pulmonary Arterial Pressure:
Much less than that of aorta
1) compliant vessel (thin & distensible)
2) R ventricle does not contract as hard
a. short distance
b. little resistance

Systolic BP - 25 mmHg Diastolic BP – 8 mmHg

Effect of Decrease 0_2 on Alveolar Blood Flow
The effect is opposite the systemic circulation (decrease 0_2 → VD)
Decrease 0_2 in alveoli → V.C. This maximizes gas exchange efficiency because blood flow is shifted away from decrease aeration to areas w/ good/better aeration.

Effects of Hydrostatic Pressure Gradients in the Lungs

Hydrostatic Pressure
The weight of the blood itself.
Height is inversely proportional to Hydrostatic Pressure.

Cm = 1/P

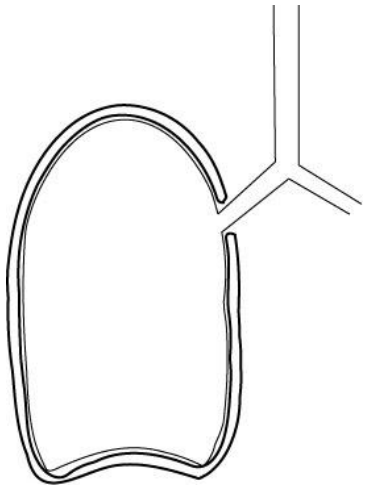
Increase Ht (cm) ----- decrease Hydrostatic P

Regional Pulmonary Blood Flow

Lowest point of lung is 30 cm below the highest point.

The pressure difference is 23 mmHg.

Lower lung fields have increased pressure.



The capillaries inside the alveolar walls are distended by BP, but they are also compressed by alveolar pressure.

ZONES

Zone 1	No blood flow during any part of the cardiac cycle. CAP Press < Alveolar P
Zone 2	Intermittent blood flow Flow when Systolic BP peaks so Capillay P > Alveolar P 10 cm above heart to top of lungs
Zone 3	Continuous Blood Flow Capillary P > Alveolar P

Zone 1

Zone 2

Zone 3

Pulmonary Pressures

Capillary exchange of fluid in the lungs, & pulmonary interstitial fluid

1) Pulmonary Capillary (Hydrostatic) Pressure
   +7mmHg (cause fluid flow out of capillaries into interstitial tissue)

2) Interstitial Hydrostatic Pressure
   -8mmHg (fluid moves out of capillaries into interstitial tissue)

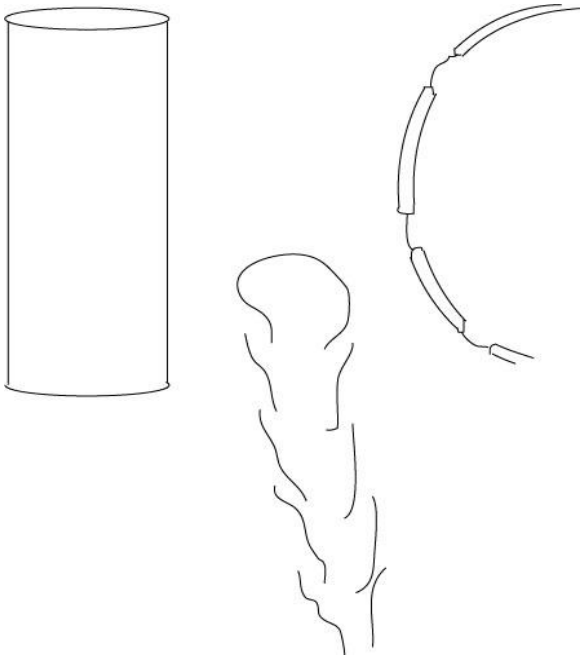
3) Interstitial Colloid Osmotic Pressure
   -14mmHg (out of capillaries and into interstitial tissue)

4) Plasma Colloid Osmotic Pressure (CAP)
   -28 (Fluid into Capillaries)

Pressure Outward = 29

7
8
14
+29

Pressure Inward = -28



Net Mean Filtration Pressure = (+29) + (-28) = +1

(+1) +(-5) = -4 = Neg. Interstitial Fluid Pressure (Keeps alveoli "DRY")

Pulmonary Edema: Any factor that cause Pulmonary Interstital Fluid Pressure to be + will cause sudden filling of alveoli w/ free fluid

Pulmonary Edema
Common cause: L sided heart failure
-fluid backs up in the pulmonary capillary system
-increase pulmonary hydrostatic capillary pressure

30 min. to death

Gas Exchange Through Respiratory Membrane

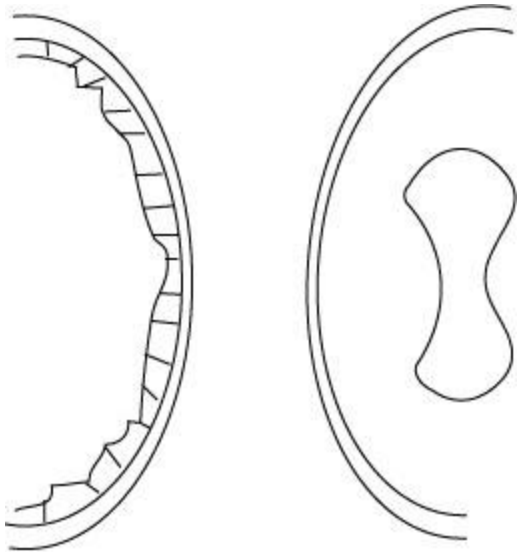
Alveolus

Capillary

Basement Membrane

Simple Squamous Epithelium

Surfactant



Basement Membrane

Endothelium

Interstitial Tissue Space

Gas Pressures

Diffusion Capacity - Volume of gas that diffuses through a membrane each minute for a pressure difference of 1 mm Hg.

760 mmHg = 1 ATM @ Sea Level
Composition of air = 79% N, 21 % O

Dalton's Law – each gas in a mixture of many gases exerts it's own pressure as if the other gases were not present. This is called partial pressure.

Partial Pressure of 0_2

.21 x 760 mmHg = 160 mmHg = partial pressure 0_2
$p0_2$ = 160 mmHg

0_2 Diffusion Capacity -
21m1/min/mm Hg @ resting conditions

CO_2 Diffusion Capacity -

Solubility Coefficient
A measure of how well a gas dissolves in H_20.

A specific gas pressure is determined by it's solubility coefficient and it's concentration.

Henry's Law:

$$\text{Partial Pressure} = \frac{[\text{Gas}]}{\text{Solubility Coefficient}}$$

Increase solubility = decrease pressure

$C0_2$ is very soluble in H_20 (20 x's more than 0_2), so @ any given concentration ([$C0_2$]), $C0_2$ will diffuse quicker through H_20.

Slow Replacement of Alveolar Air

- Important because it prevents sudden changes in [0_2/$C0_2$] in the blood
- Keeps [0_2] constant

Factors That Affect the Rate of Gas Diffusion

1) Membrane Thickness: The distance a gas has to travel.

2) Surface area of the membrane = can be decrease by diseases (emphysema)

3) Diffusion Coefficient of the gas = $C0_2$ diffuses 20 x's faster than 0_2

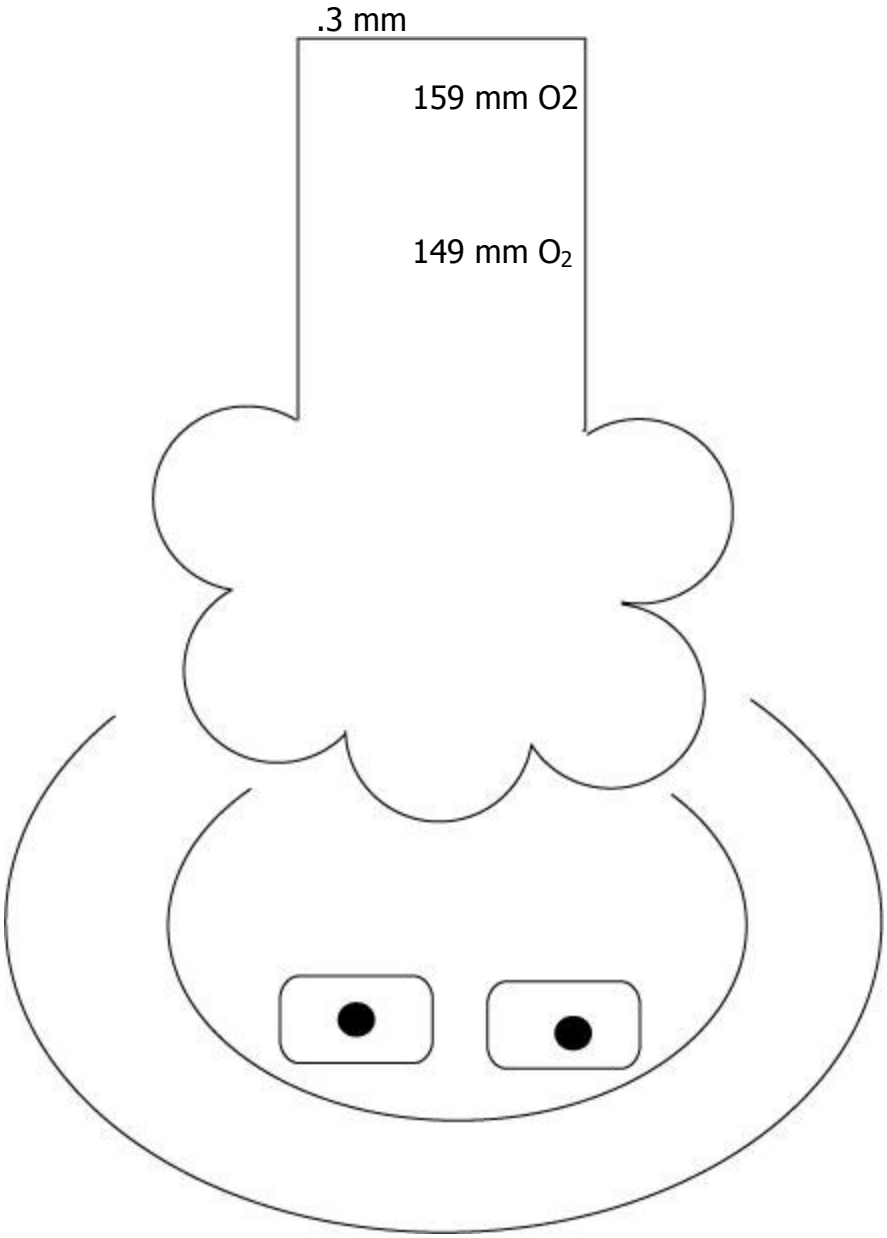
4) Concentration (partial Pressure) Difference: Gases diffuse via concentration gradients across the membrane

5) Molecular Weight

6) Temperature

O_2 and CO_2 Partial Pressures During Respiration

$[O_2]$		$[CO_2]$
1)Inspired Air = 159 mm		1)Inspired Air= .3 mm
2)Humidified Air = 149 mm		2)Arterial = 45 mm
3)Alveolar Air = 104 mm		3)Cellular = 46 mmHg
4)Arterial Bld = 95 mm	Dead	4)Venous = 45 mHg
5) Interstitium = 40 mm	Space	5)Alveolar = 40 mmHg



*CO_2 doesn't need a large concentration gradient because it is very soluble!!!

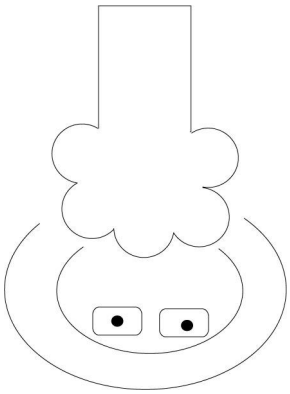
Ventilation Perfusion Ratio

Determines if there is an imbalance between:
The alveolar rate of ventilation and alveolar blood flow.

Vent. Perfusion Ratio = $\frac{Va}{Q}$ = $\frac{\text{Alveolar Vent. Rate}}{\text{Alveolar Blood Flow}}$

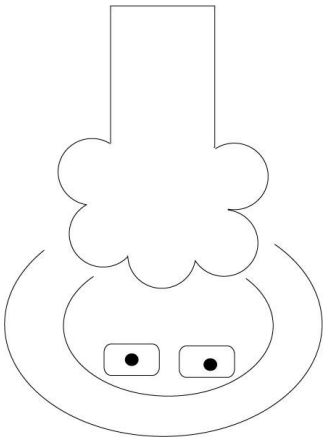
1) Va = 0 then Va/Q = 0

Without alveolar ventilation (blocked), but plenty of blood flow $\rightarrow$ the air in the alveolus will come to equilibrium with the [$C0_2$ & 0_2] in the blood. $P0_2$ = 40, $PC0_2$ = 45 (same as venous blood)



2) Q = 0 then Va/Q = ∞

There is no capillary flow to transport gases.
Alveolar air losses no 0_2 or gains no $C0_2$ so it's [gas] will = humidified inspired air.
[0_2] = 159 mmHg = max. amount



Summary:
Physiological Shunt = Va/Q < 1 If Va/Q < 1, no ventilation/aeration
A certain fraction of capillary blood is not oxygenated.

Physiologic Dead Space = If Va/Q > 1, no blood flow

Hemoglobin:
Transports 0_2 in blood

-Avg adult: has 25 billion RBC's
-Each RBC: has 280 million molecules Hgb
-RBC's are huge 0_2 reservoirs
-0_2 binds to "HEME" units in RBC's
-4 Heme units/Hgb
-Over a billion 0_2 molecules carried /RBC

Oxyhemoglobin: oxygenated Hgb = Bright Red
0_2 depleted Hgb - bluish $C0_2$ binds to globulin portion of Hgb

Effect of Metabolism (tissues) on [Gases]

Increase Metabolic Rate = increase $pC0_2$, decrease $p0_2$
Decrease Metabolic Rate = decrease $pC0_2$, increase $p0_2$

Decrease Blood flow = Increase $pC0_2$, decrease $p0_2$

Transport of 0_2 in the Blood
97% 0_2 is transported as 0_2 - Hgb
3% 0_2 is free in the plasma
%Saturation of Hgb leaving the alveoli = 97%
%Saturation of Hgb leaving the tissues = 75%
0_2 "Dumped" in tissues = 22%
*RBC's are a O_2 reservoir - they will give up their [0_2] to maintain a [3%] in the plasma

Effect of Hgb to "Buffer" Tissue $p0_2$
Hgb stabilized the $p0_2$ in tissues

1) If there is a large concentration gradient of 0_2 between the blood and the tissues HGB will quickly release 0_2 to maintain tissue levels.

2) If the [ ] gradient is small Hgb releases 0_2 slowly.

The BOHR Effect

Addresses factors involved in determining partial pressure of O2 relative to %Hb saturation in blood

1) Increase $CO_2 \rightarrow$ Hgb to release 0_2 @ a faster rate.
This is a right shift in the normal 0_2-Hgb dissociation curve.

Other causes of right shift:

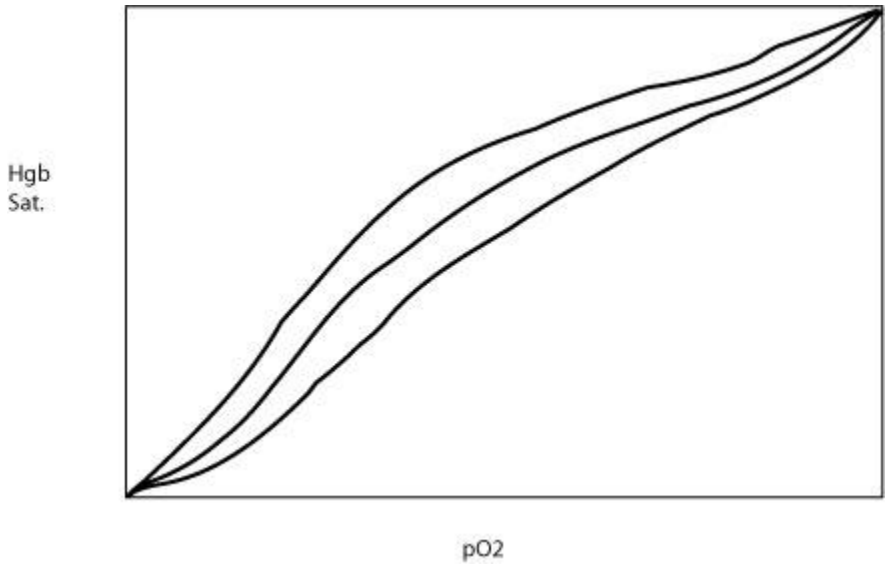
2) Increase H+ ion
3) Increase Temp.
4) Increase DPG (DPG - 2.3 diphosphoglycerate)

A by-product of glycolysis/anaerobic respiration. Increased levels DPG mean decreased 0_2 - so HGB will release 0_2 faster

pH Relationships

Decrease pH (7.4 $\rightarrow$ 7.2) mean increase H+ and increase $pC0_2$ HgB will release 0_2

100%



Normal pH = 7.4
pH = 7.2
pH = 7.6

$C0_2$ Transport in the Blood

1) 23% $C0_2$ is transported as Hgb - $C0_2$- carbaminohemoglobin
2) 7% $C0_2$ is free in plasma
3) 70% $C0_2$ is transported as $HC0_3^-$

The $HC0_3^-$ diffuses into the plasma

Chloride Shift

For every HC03- exported from an RBC, 1 Cl- is pumped into the RBC via = Bicarbonate-Chloride Carrier Protein
[Chloride] venous blood > [CI-] arterial

Carbaminohemoglobin

Hgb - C02

C02 + Hgb ---------- C02 - Hgb

The Haldane Effect

1) When [C02] in blood increase causes 02 to be displaced (kicked off) Hgb.

2) When [02] in blood increase causes C02 to be kicked of Hgb.

SO .... C02 is displaced in the alveolar capillaries and 02 is displaced in the tissues.

Regulation of Respiration
2 Primary Mechanisms:

1) Local
2) Neurogenic

Local Control
With increased activity - P02 decrease PC02 increase
• smooth muscle walls of arterials relax (V.D.) of capillaries to increase local blood flow

Neural Control of Respiration
a) Respiratory Center
Rhythmicity area - dorsal respiratory group -chemosensitive area

b) Peripheral areas affecting respiratory center -chemoreceptor reflexes

Respiratory Center:
composed of several groups of nuclei located bilaterally in the medulla oblongata and pons

Function: Adjusts frequency and depth of respiration by stimulation or inhibition of the respiratory muscles.

Reticular Center = consists of widely dispersed group of neurons, connect resp. centers

Three Areas of the Respiratory Center (3 pair of nuclei)
1) Dorsal respiratory group
2) Ventral Respiratory Group
3) Pneumotaxic Center
4) Apneustic Center

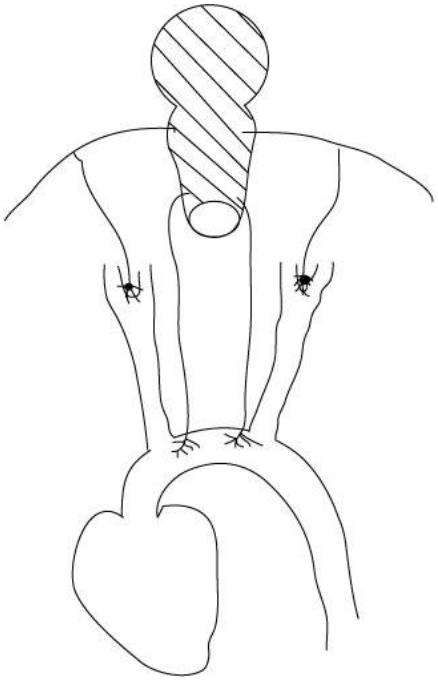
1) Dorsal Respiratory Group
Located in dorsal portion of medulla extending through medulla mainly causes inspiration plays the most fundamental role in respiratory control.

a) Controls Rhythmicity basic rhythm of respiration 12/min
usual inspiration = 2 seconds
usual expiration = 3 seconds
1 breath = 5 seconds
contains both inspiratory & expiratory neurons

b) Tractus Solitarius
location of most of the Dorsal Groups neurons; located in brain stem

1) Connects/terminates in the Vagal and Glossopharyngeal nerves
2) These nerves transmit chemosensory and baroreceptor info.

Herring's Nerve = Transmit signals from the carotid body to glossopharyngeal nerve to tractus solitarius; transmits afferent (sensory) nerve impulses from the chemo. & baroreceptors of the cardiovascular system.



Dorsal Respiratory Center (continued)

Mechanism of Action Potentials
This region emits a burst of inspiratory action potentials.

The Pyramid Effect

Excite 1 neuron → excites 2nd set etc ....

Action Potentials trigger Motor neurons → contraction of diaphragm via the Phrenic Nerve:

"C3, 4 & 5 keeps the diaphragm alive"

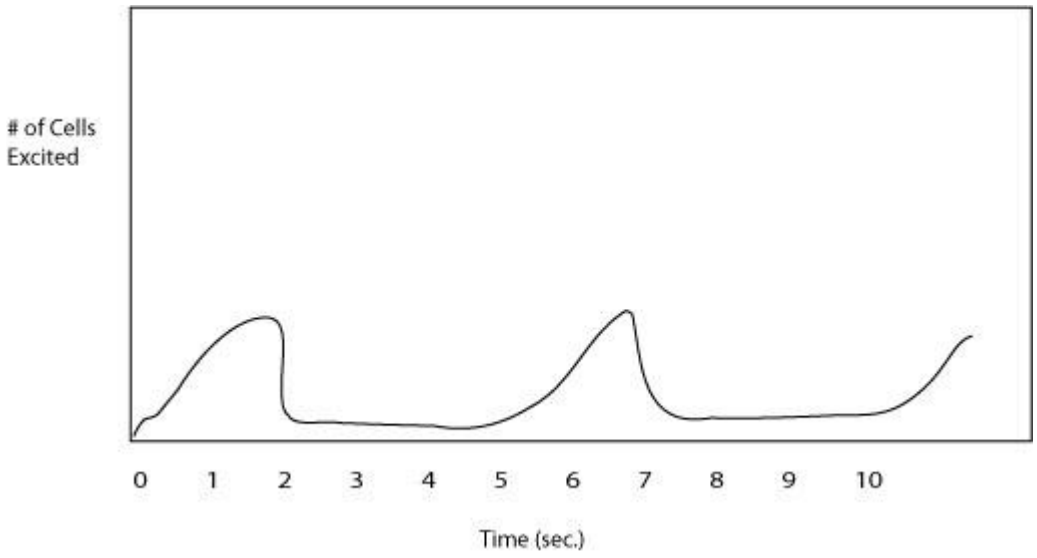
Inspiratory Ramp Signal

- Signal to the inspiratory muscle begins weakly & increase over ~ 2 sec.
- The excitement of one neuron cell initiates the pyramid effect of exciting more & more nerve cells including the motor neurons of the diaphragm
- After 2 sec. the signal stops for 3 sec.

2 ways ramps signal is controlled
1) control of the rate of increase - normal = 2 s (rate lungs fill)

2) control of point @ which the ramp ceases (begin expiration)

Inspiratory Ramp



2) Ventral Respiratory Group

* located in the ventrolateral part of the medulla
-functions in both inspiration & expiration
-operates as an overdrive mechanism, when high levels of pulmonary respiration are required

Mechanism of Action
With increase need for pulmonary ventilation, the electrical impulses from the Dorsal Respiratory Group "Spill over" into the Ventral Group.

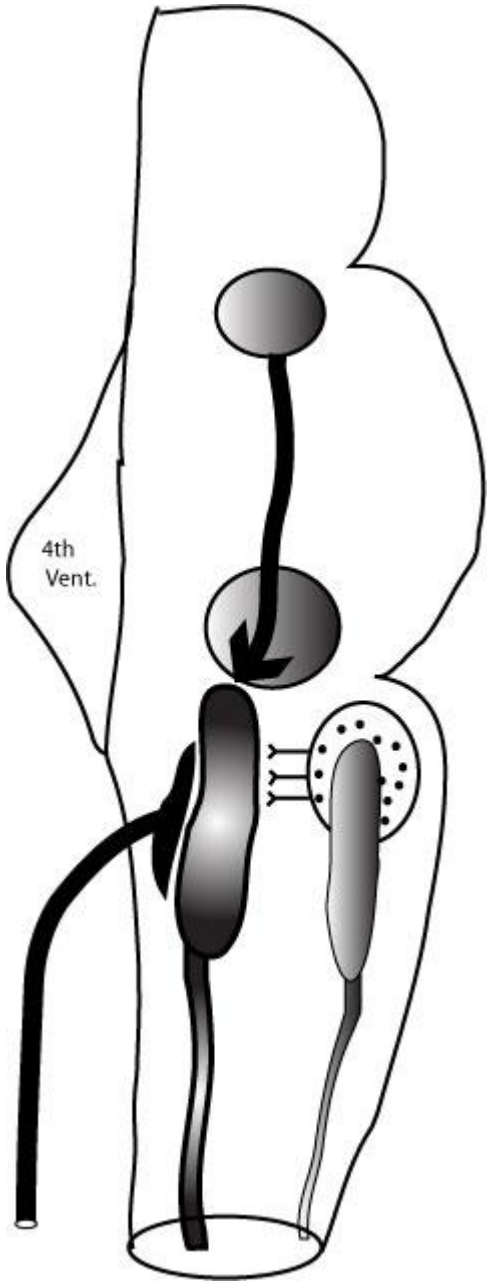
Primary Function
Providing the powerful expiratory signals to the abdominal muscles producing forceful expiration.

3) Apneustic Center
located in the lower pons
muscles controls depth of respiration

Mechanism of Action
Send signals to the dorsal respiratory center that retard/block the "Switch off' of the insp. ramp signal $\rightarrow$ lung almost completely fill with air.

What prevents overfilling: stretch receptors in lungs

Respiratory Centers



Stretch Receptors ---- Hering-Breuer Inflation Reflex

When lungs are over-filled, stretch receptors send signals through the VAGI to the Dorsal Group.
This causes the inspiratory ramp to switch off.

4) Pneumotaxic Center
- -Located dorsally in the superior portion of the pons
- -helps control the rate & pattern of breathing
- -functions primarily to limit respiration (decrease fm 5 s)
- -causes increase RR due to limited inspiration from sending signals to dorsal center to "switch off' resp. ramp.
- *The Dorsal Center & Pneumotaxic center work together to control volume & frequency of respiration.

Chemosensory Neurons of the Respiratory Center
-located ventral to the ventral respiratory group
-Sensitive to changes in blood [$C0_2$] or [H+]
-when stimulated excites other respiratory centers

Stimulus by H+ Ions
- -primary stimulus for this area
- -H+ ions do not easily pass through BBB (Blood Brain Barrier)
- -Proteins do not easily pass through BBB -very little proteins for buffering
- -$C0_2$ does pass the BBB
- -H+ produced from $C0_2$ + H_2O stimulate the chemoreceptive area (Increase $pC0_2$ ----- Increase H+)
- -changes in [H+] in CSF ---- Wild swings in CSF pH
- -increase $pC0_2$ ---- increase RR

Chemosensory response to increase [$C0_2$] is short term (blow off $C0_2$)
Long term: Kidneys will increase $HC0_3$- neutralizing increase [H+]

The effect of increase [$C0_2$] on the chemosensory area is acute (not long term)

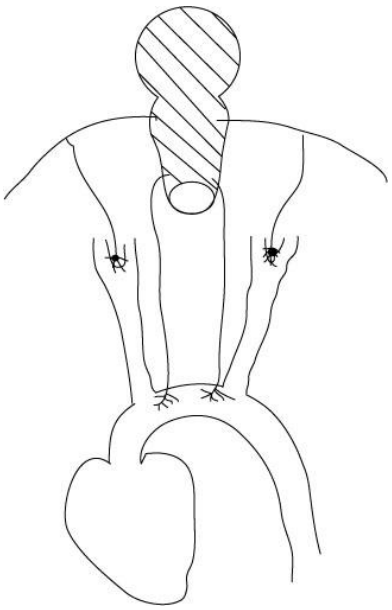
Peripheral Chemoreceptor Reflexes

1) Carotid Bodies: group of chemoreceptors located in the bifurcation of the common carotid artery to int. & ext. Carotids.

2) Aortic Bodies: located in the aortic arch and stimulated by decrease p02 in the arterial blood.

Mechanism - mostly unknown
Glomus Cells - grandular like cells found in the aortic & carotid bodies
-possible chemoreceptors that mediate nerve firing

Carotid Bodies
↓
Herings Nerves
↓
Glossopharyngeal
↓
Dorsal Resp. Center



Aortic Bodies
↓
VAGI
↓
Dorsal Resp. Center

The blood flow through the special blood supply of these chemoreceptors is extremely fast (20 x's the weight of each body /min.)
Why is this important?

Voluntary Control

- Irritant Receptors: ---- coughing/sneezing
  Keep unwanted substances out of bronchioles: H_20, gas, dust

- "J-Receptors": sensory nerve endings of the alveolar walls in "Juxtaposition" to the capillaries.

  Stimulated by increase blood in pulmonary caps.
  Stimulated by pulmonary edema
  Provide a sensation of dyspnea

Signal travels directly from cerebral cortex and other higher centers down through corticospinal tract to spinal neurons of the respiratory muscles.

Effects of Low $p0_2$ on Alveolar Ventilation

Breath air with decrease $0_2 \rightarrow$ decrease $p0_2$

Decrease 0_2 stimulates Peripheral (aortic/carotid) Chemoreceptors $\rightarrow$ increase RR

Decrease 0_2 = Increase $C0_2$ stimulate Central chemoreceptor $\rightarrow$ increase RR

$P0_2$ must decrease < 100mmHg to increase RR (normal 159 mmHG)

COPD's
Pneumonia/Emphysema - high levels of supplemental 0_2 depresses the respiratory drive

- poor gas exchange @ alveolar membrane
- too little 0_2 absorbed
- normal or increase $pC0_2$ due to poor diffusion of $C0_2$

- Decrease $p0_2$ Increase RR

Do Not give high [0_2]
Because supplemental 0_2 causes:

Decrease RR, Increase $C0_2$ retention, Increase H+

Effects of Altitude on the Respiratory System

Changes in barometric pressures are the basic cause of Hypoxia @ high altitudes
Alveolar ventilation increase as much as 5 x's in the acclimatized person
• @ > 10,000 ft. p02 falls

Acclimatization

A) Increased pulmonary ventilation
-immediate response to decrease $p0_2$ is increase pulmonary vent. by up to 70%
several days - pulmonary vent. increase 400% above normal

Decrease P02
↓
Increase Pulmonary Vent. (70%) (Increase RR)
↓
Increase $C0_2$ Blow Off→ Decrease H+, Increase pH
This step opposes the peripheral chemoreceptors reaction to decrease $P0_2$ - thus inhibiting increase RR
↓

3 - 5 days . ... .. Inhibition wears off
↓

Pulmonary Vent. increase by 5 x's normal

High altitude over a period of 2 -3 days decrease the sensitivity of the respiratory center in the brain stem to increased C02 levels.

1) Initial increase $C0_2$ = increase RR = decrease $C0_2$

2) 2 - 3 days . . ... decrease $C0_2$ does not inhibit resp. drive (decrease RR)

3) Controlling factor becomes $[0_2]$

4) decrease $p0_2$, resp. drive is increase 400-500%

B) Increase in RBC's & HGB during Acclimatization
- HCT rises from - 40 to average = 60
- HGB increase from 15 gm/dl to 20 gm/dl
- Blood volume increase 20 - 30% ---- total increase HGB = 50%
- Begin @ 2 weeks
- Completed @ several months

C) Increase Diffusion capacity after acclimatization
- Increase in pulmonary capillary blood volume
- Increase in lung volume (Increase S.A.)
- Increase Pulmonary Art. Pressure
- Forces upper lobe to be perfused

D) Increased Capillary Number
- Increase in the number of capillaries in the tissues
- Higher in those born @ high Alt.
- Increase capillaries to R ventricle due to pulmonary hypertension

E) Cellular Acclimatization
- Increase number of mitochondria = increase efficiency to utilize 02

<u>Mountain Sickness</u>
1) Increase HCT
2) Increase pulmonary art. pressure
3) R heart enlarges
4) Decrease peripheral arterial pressure
5) CHF
6) Death Tx by decreasing altitude & supp. 02

<u>Respiration During Exercise</u>

1) The brain excites the respiratory center via impulses to the brain stem when impulses to contracting muscles are sent

2) Proprioceptors: receptors that detect movement of the extremities send excitatory signals to the respiratory centers

Cheyne-Stokes Breathing

Periodic breathing - a slow waxing and waning breathing that occurs every 40 - 60 seconds.

Mexhanism:

1) Person overbreathes → decrease $C0_2$ (blow off $C0_2$) = ↑ blood 0_2 causing the brain to
↓
2) Inhibit ventilation
↓
3) Extreme depression of respiratory drive y
↓
4) $C0_2$ increases, 0_2 decreases
↓
5) New cycle of over breathing

Common Causes:

1) Because of a long delay of blood flow to the brain from L heart failure.
Slow blood flow; thus, delaying transport of blood gases between lungs and brain

2) Brain Damage: Respiratory drive is "turned off" 2 - 3 s until extreme increase in blood $C0_2$ turns it back on with great force.
Chemoreceptors are less sensitive.
This condition commonly precedes death.

Chronic Pulmonary Emphysema

"Excess air in the lungs"

Common cause: long term smoking

2 Major Pathophysiological Pathways

1) Chronic infection
- Due to inhalation of substances that irritate the bronchioles
- Partial paralysis of cilia due to nicotine
- Stimulation of excess mucus secretion
- Inhibition of alveolar macrophages

2) Chronic obstruction of small airways (from the above effects)
Entrapped air in the alveoli.
Mucus in alveolar walls leads to further infections

Physiological Effects

1) Increase airway resistance
2) Decrease diffusing capacity
3) Abnormal vent./perfusion (VA/Q) ratios some physiological shunting = poor aeration of blood

Pneumonia

Any inflammatory condition of the lung in which alveoli are filled with fluid & blood cells.

1) reduction in available S.A.

2) decrease Va/Q → decrease diffusion capacity

Asthma

Spastic contraction of smooth muscle in bronchioles.

Common Cause:
Hypersensitivity of bronchioles to foreign substances of the air.
histamine, slow reacting anaphylaxis substance, eosinophilic chemotactic factor, bradykinin

Obstructive	vs.	Constrictive Pathology
Asthma		TB
Emphysema		Silicosis, Kyphosis
		Scoliosis, Fibrotic Pleurisy
High Lung Volumes		Decrease Lung Volumes
Cannot Expire		Lung Cannot Expand (inspire)

FEV = forced expiratory volume

FVC = forced exp. vital capacity

THE AUTONOMIC NERVOUS SYSTEM AND NEUROTRANSMITTERS

Characteristic comparisons between SNS and ANS

Somatic Nervous System

1. conscious control of skeletal muscles

2. mixed nerves; motor and sensory. (sensory is proprioception)

Autonomic Nervous System

1. subconscious control of visceral activities (organs, glands, smooth and cardiac muscle)

2. predominantly motor. (When it fires, it will cause an action of some type (secretion of a gland or contraction of a muscle. Do not typically need proprioception for this)

3. predominantly controlled by the hypothalamus

The Two Divisions of the ANS

A) sympathetic nervous system;

A) parasympathetic nervous system;

Effects of the ANS

	Parasympathetic	Sympathetic
1. pupils	*-constriction*	*-dilation*
2. digestion/ glands	*-increase in secretion*	*-decrease in secretion*
3. smooth muscle	*-increase in activity*	*-decrease in activity*

4. digestion	*- increase in activity*	*-decrease in activity*
5. respiratory passages	*-constriction*	*-dilation*
6. heart	*-decrease in HR*	*-increase in HR*
7. skin vessels	*-no innervation*	*-constriction at skin vessel*
8. skeletal muscle vessels	***-****no innervation*	*-dilation (more O2)*
9. adrenal glands	*-no NT*	*-release epinephrine and norepinephrine*

<u>Autonomic Pathways</u>

A) Sympathetic (T1-L2)

White rami communicans: from spinal nerve to sympathetic cell body
Gray rami communicans: from ganglia posteriorly

Autonomic Ganglia

1. Autonomic ganglia has a cell body and a synapse
2. Autonomic ganglia is a motor, not a sensory cell body

B) Parasympathetic; aka craniosacral division either S234 or brainstem

Can be a plexus or a ganglion

<u>The Sympathetic Nerve Network</u>

A) The Sympathetic Chain Ganglia; series of ganglia lying in a vertical row on either side of the vertebral column.

Function;

- to receive preganglionic fibers from the lateral horn/ sympathetic division (T1-L2)

∗fibers terminate in the skin to innervate (connect with nerves)

(If they synapse in the chain ganglia, those terminal fibers will innervate the skin; Sweat glands of the skin, the vessels of the skin (general vasoconstriction), and the erector pili muscles.)

B) The Collateral Ganglia; preganglionic fibers; 'splanchnic nerves' that pass through the sympathetic ganglia to synapse in one of the three collateral ganglia. These collateral ganglia are located anterior to the vertebral column. (named after the arteries that they are near or around)

Function; ∗innervate organs of the abdominopelvic cavity.

<u>The Three Collateral Ganglia</u>

1. **celiac ganglion**

2. **superior mesenteric ganglia**

3. **inferior mesenteric ganglia**

C) The Adrenal Medulla (located on top of the kidneys)

Preganglionic fibers pass through the sympathetic chain. They also pass through the collateral ganglia (the celiac ganglion) without synapsing, to eventually synapse in the adrenal medulla on specialized cells that release epinepherine and norepinepherine that are then carried to the bloodstream.

The Parasympathetic Nerve Network; aka the craniosacral division

A) The 4 Cranial Ganglia

1. sphenopalatine ganglion (pterygopalatine ganglion); travels with cranial nerve VII to innervate the lacrimal gland

2. ciliary ganglion; comes off the pons and lies along the cranial nerve III.

3. submandibular ganglion; goes to the submandibular gland and is associated with cranial nerve VII.

4. Otic ganglion; associated with cranial nerve IX, and innervated the parotid gland

B) The Intramural Ganglia; intramural means within the walls- parasympathetic ganglia located within the walls of the effector organ.

1. Vagus Nerve; arises off brainstem and innervates chest and abdomen.

a) cardiac and pulmonary plexus

b) celiac plexus; innervates the

c) hypogastric plexus; innervates the

*plexus; nerve network

2. Pelvic Nerves; arise off of cord levels S234 to synapse in the walls of the

Autonomic Neurotransmitters

1. **Cholinergic fibers**- release ACH
    a) ACH is released from all preganglionic ANS fibers
        - including parasympathetic and sympathetic fibers

    b) ACH is released from all postganglionic parasympathetic fibers
        ∗effects are short-lived and local due to the presence of Acetylcholinesterase

    ACH "Postsynaptic" Receptor sites- effects on target organ dependent on the receptors on that organ

    a) Nicotinic- receptors for ACH on the postganglionic synapse (dendrites + cell body)
        -causes firing of all para and sympathetic postganglionic fibers

    b) Muscarinic- receptor sites on all parasympathetic target organs and some sympathetic target organs
        - results are variable- causes exitation or inhibition, depending on the organ

2. **Adrenergic Fibers**- release epinephrine and norepinephrine

    a) released from most postganglionic sympathetic fibers

    b) effects are longer lasting and more widespread

"Postsynaptic Receptors"- Alpha and Beta receptors- have variable effects depending on the specific target organs involved

Control of ANS

-controlled through higher centers in the cerebral cortex and the hypothalamus

NEUROTRANSMITTERS

I. Cholinergic Receptors – post-synaptic receptors that bind to ACH.

Two Types

A) Nicotinic- initial work done with nicotine which will bind to all nicotinic receptors.

Location:
1) motor endplates of skeletal muscles
2) all postganglionic ANS neurons
3) located on hormone producing cells of the adrenal gland

Mode of Action: opens chemically regulated sodium channels to initiate EPSP's.

B) Muscarinic – initial work done with toadstools. Muscarine activates only muscarinic receptors.

Location: On all PNS target organs and a few SNS target organs.

Mode of Action: ACH binding to muscarinic receptors causes changes in potassium membrane permeability. Mostly causing excitation, but inhibits cardiac muscle.

Overview

PNS	ACH	ACH	Muscarinic Receptors
		Nicotinic	
SNS	ACH	Epi/Norepi	Alpha/Beta

PNS- General Effects: Increased lacrimal/salivary gland secretions
Papillary constriction
Increased gastric motility and vessel dilation

ACH binding to muscarinic receptors has varied effects.
EPSPs in intestinal smooth muscle and IPSPs in cardiac muscle.

Drugs

1) Pilocarpine/metacholine: activates only muscarinic receptors

2) Atropine/Scopolamine: block PNS effects.
Suppress salivation and respiratory secretions during surgery.
Opthalmologists use it to dilate pupils.
Blocking ACH at muscarinic receptors, not nicotine.
3) Neostigmine: block acetylcholinesterase. An anticholinesterase drug: inhibits acetylcholinesterase preventing it's breakdown. Serves to increase ACH at the synapse. Treatment for myasthenia gravis.

II. Adrenergic Receptors- receptors that bind to epinephrine and norepinephrine(NE).

A) Alpha Receptors NE/epi. binding to alpha receptors generally produce a stimulatory effect. Alpha receptors generally have a greater affinity for NE

1) Alpha1 Receptor – generally stimulatory bound to NE.

Location: found in most tissue, increases metabolism, pupillary dilation, salivary gland – viscous secretion (cottonmouth), skin – increase sweating, piloerection, constriction of skin vessels, increase heart rate and force of contraction, GI sphincter constriction, GI vasoconstriction, decreased urine output. No heart vessel constriction. Alpha 1 stimulation- smooth muscle constriction.

Mechanism of Action:

Alpha1 Receptor broken down by MAO

Constriction of Smooth muscle- constriction of peripheral blood vessels/GI spchinters.

Drugs:

1) Reserpine: blocks synthesis and storage of NE
2) Prazosin: alpha adrenergic blocking agent treats hypertension. Binds to alpha receptors in smooth muscle wall of vessels to block NE effects. Vessels relax
3) Sympathomimetics- stimulates Adrenergic receptors or increases the release of NE.
    a. Methoxamine
    b. Phenylephrine- found in chlortrimetron or Dimetapp- stimulates alpha1 receptors to dilate bronchioles

4) Alpha Blockers – Phentolamine – decrease vasomotor tone to decrease blood pressure. Treatment for hypertension.
5) Sympatholytics: decrease SNS action- inhibit NE release or bind to adrenergic receptors to prevent activation.
6) Tricyclic Antidepressants – allow prolonged activity of NE. NE is a feel good neurotransmitter. Relieves depression- Elavil, Simequan
7) SSRIs- Selective Seratonin Reuptake Inhibitors.
    Imiramine- blocks reuptake of serotonin and NE. Prozac(fluoxetine)- blocks serotonin reuptake

8) MAO Inhibitors- block MAO destruction of monoamines NE/EPI to increase good mood.

B) Alpha 2 Receptors – with binding of NE/EPI – generally create an inhibitory effect.

Location: found on cell membranes located at a distance from axon terminals releasing NE. They respond to NE released from blood (adrenal glands). Longer lasting effects (5x's as long) Broken down by COMT (catechol-O-methyl transferase). Found on Neuromuscluar and neuroglandular junctions to cause general inhibition.
Alpha2 stimulation: decrease urine output, decrease insulin secretion, decrease GI motility, decrease GI secretions, increase blood coagulation.

Mechanism of Action:

C) Beta Receptors – NE or EPI binding to B receptors is generally inhibitory, but can be stimulated too. Stimulation of a Beta receptor increases cAMP levels to activate or inactivate enzymes.

1) B1 Receptors – equal affinity for NE and EPI

a. Location: heart- Increase HR and FOC.
Skeletal Muscles – increase skeletal muscle metabolism and vasodilation
Lipolysis- increase fat breakdown
Kidneys- increase rennin released by the kidneys. NE – bind to B1 receptors – strong peripheral vasoconstriction to vessels other than cardiac and skeletal to increase TPR and increase BP.

Mechanism of Action:

2) B2 Receptors – greater affinity for epi. Activation of B2 receptor – inhibitory response in many tissues.

a. locations: lungs – NE binding- dilates blood vessels and bronchioles. Causing inhibition- dilation of lung vessels and bronchioles. Heart- increase FOC and vasodilation of vessels. Kidneys – increase urine output. GI tract- decrease GI motility and vasodilation. Skeletal Muscles- increase force of contraction and increase glycogen breakdown.
b. Also found on cell membranes not nears axon terminals that release NE. Respond to NE released by adrenal glands into blood. NE binds to B2 receptors to increase skeletal muscle vasodilation.

3) B3 Receptors – found in adipose tissue. NE binding – stimulates lipolysis in fat cells.

Drugs: Beta Blockers: Block NE attachment to B1 receptor (Sectral/Acebutolol) to reduce HR and prevent arrhythmias (metoprolol-Lopressor)

Neurohormonal Control of the Brain Activity

The release of the excitatory or inhibitory NT agents into the brain

1) Locus Ceruleus: Norepinephrine
   -Located in the posterior portion of the pons
   -Produces Norepi. → excites/increase brain activity

2) Substantia Nigra: dopamine
   -Anterior and superior to mesencephalon
   -Dopamine - is generally inhibitory NT in basal ganglia
   -Absence of Dopa → Parkinson's

3) Nuclei of Raphe: Serotonin
   -Raphe= midline of the body
   -Located in the midline of the pons/medulla
   -Seratonin - inhibitory to cause sleep

4) Gigantocellular Nucleus of the Reticular Formation: Acetylcholine
   - excitatory NT
   -stimulates the brain/mind to be "acutely awake"/excited (antagonistic to serotonin)

Epinephrine & Norepinephrine
-derived from the amino acid tyrosine

Tyrosine→ hydroxylated
↓
Dopa → decarboxylated
↓
Dopamine → hydroxylated
↓
Noreprnephrine → Methylation in the adrenal Medulla (80%) epinephrine (20%)

Degradation of Norepinephrine

1) Monoamine Oxidase – degrades at the synapse

2) Catechol-o-methyl Transferase – degrades in the liver and tissues

ENDOCRINOLOGY

Homeostasis of the body is maintained by 2 systems.

1) Nervous System - fast acting, short term

2) Endocrine System - slow acting, long term –
"Hormonal System"
Some hormonal effects occurs in seconds, others require days to start, but last for weeks → months

Hormone: A chemical substance that is secreted into the internal body fluids by one cell or group of cells and has a physiological effect on other cells of the body.

Hormone Chemistry - chemically there are 3 types of hormones

1) Steroid Hormones - consist of a 4-ring carbon structure based on or derived from Cholesterol

Adrenal Cortex:	Cortisol, Aldosterone
Ovaries:	Estrogen, Progesterone
Testes:	Testosterone
Placenta:	Estrogen, Progesterone

2) Tyrosine Derivatives: 2 groups derived from this A.A.

a) Thyroid Hormones: Thyroxine, Triiodothyronine (T-3)

b) Adrenal Medulla: Catecholamines, Epinephrine, Nor-epinephrine

3) Proteins or Peptides
Ant. Pituitary
Post Pituitary: ADH, Oxytocin
Insulin, Glucagons & Parathormone are all large Polypeptides

Storage and Secretion of Hormones

All protein hormones are formed by the granular endoplasmic reticulum

(ER); this product is not the final hormone, but is larger and is called the:

Preprohormone 1st product of ER = large

Cleaved in the periphery of the ER
Prohormone – 2nd product of ER = smaller

Transport to Golgi for last cleavage

Hormone

Packaged by Golgi into Secretory Vesicles/Granules

Mechanisms of Hormonal Action

1) Change in membrane permeability: When the hormone binds to the cell membrane receptor, it causes a conformational change in the receptor protein and usually initiates the opening or closing of ion channels; Ex: ACH

2) Activation of An Intracellular Enzyme: When a hormone combines with a membrane receptor Ex. Adenyl Cyclase Ex. Calmodulin

3) Activation of Genes by binding with Intracellular Receptors
Steroid Hormone passes through cell membrane

Example: Aldosterone

Binds w/proteins receptor (Intracellular)
-found within the cytoplasm and called a
Receptor Protein Hormone Complex

Passes into the cell nucleus

Activates Transcription of mRNA for protein synthesis

Increases production of a Protein

4) Direct Activation of a Gene

'Note: T3 & T4 are gene activators that do not require a cytoplasmic receptor. They go directly into the nucleus.

Measurement of Hormone concentrations in the blood

Radioimmunoassay:

1) Inject purified hormone into a lower animal (mouse) in order to produce large quantities of an antibody specific to that hormone. (Antibodies made in lower animal)

2) Take a sample of antibody and mix with: a)sample of body fluid with unknown amount (my blood sample) and b)mix with known amount of purified standard hormone that has been radioactively tagged

   There must be too little antibody to bind completely with both samples

3) Mix a & b and let them Compete for Binding Sites

4) Equilibrium

5) Count the # of radioactive antibody/hormone complexes with an isotope counter

Results:

a) If a large amount of radioactive complex is measured, then only a small amount of hormone was present in the unknown

b) If a small amount of radioactive complex is measured then the amount of hormone in unknown sample is large

Measurement of Metabolic Clearance Rates of Hormones

Metabolic Clearance Rate (MCR): the rate of removal of the hormone from the blood

1) Infuse a known amount of standard purified tagged sample (Hormone) into the blood until Steady State reached (rate infused = rate of disappearance)

2) Measure radioactive concentration in the plasma (lml)

MCR = Rate of Disappearance of a Hormone from Plasma (#1)
Concentration of Hormone per ml. Plasma (#2)

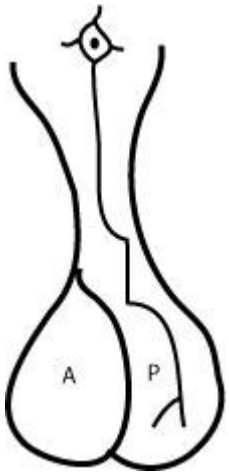
Pituitary Hormones

Pituitary Gland: (aka: hypophysis) located in the Sella Turcica: a bony cavity @ the base of the brain.

Composed of 3 parts:
1) Anterior Pituitary: (Adenohypophysis) Embryonic origination: Rathke's Pouch: Invagination of pharyngeal epithelium

2) Posterior Pituitary (Neurohypophysis) Embryonic origination: Outgrowth of hypothalamus = neural tissue has a large number of glial type cells (=support cells)

3) Pars Intermedia: avascular zone between Ant. & Post Pituitary Gland



Hypothalamic Control of Pituitary

Posterior Pituitary secretion is controlled by nervous signals that originates in the hypothalamus
Median Eminence: location of the axon terminals

Hypothalamic - Hypophyseal Portal System
-Blood supply from the hypothalamus to the anterior pituitary
-is a venous portal system.
-Releasing /Inhibiting hormones carried here

Hormones Acting on the Anterior Pituitary Gland

Produced by the hypothalamic neurons and are released into the median eminence and dumped into the hypothalamic-hypophyseal portal system and travel to the pituitary gland.

1) Hypothalamic Releasing hormones

TRH: Thyrotropin - causes release of Thyroid Stimulating Hormone (TSH)
GHRH: Growth hormone - causes release of growth hormone
CRH: Corticotropin - causes release of Adrenocorticotropin
GNRH: Gonadotropin - causes release of Luteinizing Hormone & Follicle Stimulating Hormone

2) Hypothalamic Inhibitory Hormones

GHIH: Growth hormone inhibitory Hormone= SOMATOSTATIN
PIH: Prolactin Inhibitory hormone

Posterior Pituitary and the Hypothalamus

2 Nuclei in the hypothalamus travel down to the Posterior Pituitary Gland

1) Supraoptic: secretes ADH

2) Paraventricular: secretes Oxytocin

These substances are produced in the cell bodies
They travel down the nuclei via axoplasmic transport on the carrier protein neurophysin

Growth Hormone

- secreted by Anteror Pituitary Gland
  Exerts it's effect on all or almost all tissues of the body.
  AKA: Somatotropic hormone or Somatotropin (produced by somatotropes)

Metabolic effects of growth hormone

1) Protein synthesis:
a) Increased rate of protein synthesis (Transcription/Translation)
b) Increases transport of proteins to the cells of the body
c) Increases transcription of DNA to from RNA

2) Fatty Acids:
a) Increased mobilization of F.A.'s from storage ---- blood
b) Increased use of F.A.'s for energy
-Fats converted to proteins
-Fats converted to sugars

Beta Oxidation of Fatty Acids

2 acetyl CoA
↓
Acetoacetic Acid

Ketone Bodies: Beta Hydroxybutyric Acid Acetone

Acetyl-CoA

*Ketone Bodies TCA Cycle
Metabolic Acidosis

3) Glucose:
Decreases rate of glucose utilization
Increases Blood glucose levels (converts F.A. into acetyl COA->ATP)
Increases Glycogen storage

Summary: Enhance protein storage, use up fat, conserve CHO's

Clinical Note: Pituitary Diabetes: (β cells burn out; GH causes diminished uptake of glucose by cells and increase blood sugar; tx: insulin)

Growth Hormone
Stimulation of Cartilage & Bone Growth

1) Increased deposition of protein by chondrocytic & ostegenic cells
2) Increased reproduction of chondrocytes & osteogenic cells
3) Bone $\rightarrow$ cartilage and then increase bone
4) Increased conversion of stem cells into osteoblasts

Somatomedins
Small proteins formed in the liver which have a potent effect on increasing bone growth; produced in response to GH
IGF-1: Insulin-like Growth Factor (Somatomedian C)

Regulation of GH Secretion

1) Protein deficiency (Kwashshiorkor)
2) Exercise
3) Trauma } Stimulate GH Secretion
4) Excitement

Mechanism of GH Secretion

1) Ventromedial Nucleus of hypothalamus is stimulated by decrease blood supply of GH or glucose

2) GHRH is released by V.M. nucleus and travels via Hypothalamic - Hypophysial Portal System to the Ant. Pit. Gland

3) Ant. Pit. Releases GH

Mechanisms of GHRH
GHRH activated adenyl cyclase

Increase level c-AMP in cell

Increase Ca++ into the cell

GH secretory vesicles fuse with cell membrane

Exocytosis of GH = release of GH

Abnormalities of GH Secretion

1) Decrease GH in childhood → Dwarfism
2) Increase GH in childhood → Gigantism
3) Increase GH after childhood → Acromegaly

Thickening of the flat bones
Increased Brow size, Increase Jaw
Spaces between teeth
Increased Hand & Foot size

Hormones of the Posterior Pituitary

1) ADH - antidiuretic hormone = Vasopressin produced by Supraoptic Nuclei

Neurophysins bind with ADH and they travel down the axon via axoplasmic flow. Released with the neurophysins by secretory vesicles of the posterior pituitary, but because these two molecules are loosely bound together they split after release into the blood stream. No further functions known regarding neurophysins after they enter the blood stream.

Why is ADH produced? Osmoreceptors in the wall of the 3rd ventricle, the Organum Vasculosum - detect the osmolarity of plasma. They stimulate the supraoptic nuclei to produce ADH.

How ADH Works:

Affects Distal Convoluted Tubules of nephron & collecting ducts causing the tubules to conserve H20.

Specialized Lumen Cells

2) Oxytocin - causes contraction of pregnant uterus and smooth muscle tissue of breast
-produced by Paraventricular Nucleus

Stimulated by:
1) Increase size of uterine wall during pregnancy
2) Stimulation of the cervix during pregnancy
3) Crying Baby } "Let Down
4) Sucking on the nipple } Reflex"

Thyroid Hormones (Metabolic Hormones)
Stimulation of Thyroid Hormone Secretion

1) Thyrotropin Releasing Hormone (TRH) is secreted by the Hypothalamus

2) TRH binds with receptors in the Pituitary Cell membrane

3) This stimulates the activation of Phospholipase - C = 2nd Messenger

4) Release of TSH from Ant. Pit. (thyrotropes)

5) TSH travels to Thyroid gland and binds receptors

6) This activates Adenyl Cyclase 4 Increase CAMP

7) Camp activates Protein Kinase which phosphorylates the thyroid cells

Thyroid Gland produces 3 Hormones

1) T4 – Thyroxine represents 93% of glandular production
2) T3 – Triiodothyronine represents 7% of glandular production

Note: T3 is 4 times as potent as potent as T4

3) Calcitonin - important to Ca++ metabolism

Anatomy of Thyroid Gland:

-Consists of many closed follicles lined with cuboidal epithelium that secrete colloid composed of thyroglobulin which is a large glycoprotein containing thyroid hormone.

The Follicle

Colloid: Secretory substance consists of Thyroglobulin (a large glycoprotein)

Chemistry of Thyroid Hormone Formation

1) Iodide Trapping - "iodide pump" actively transports iodide from the blood into the thyroid epithelial cells

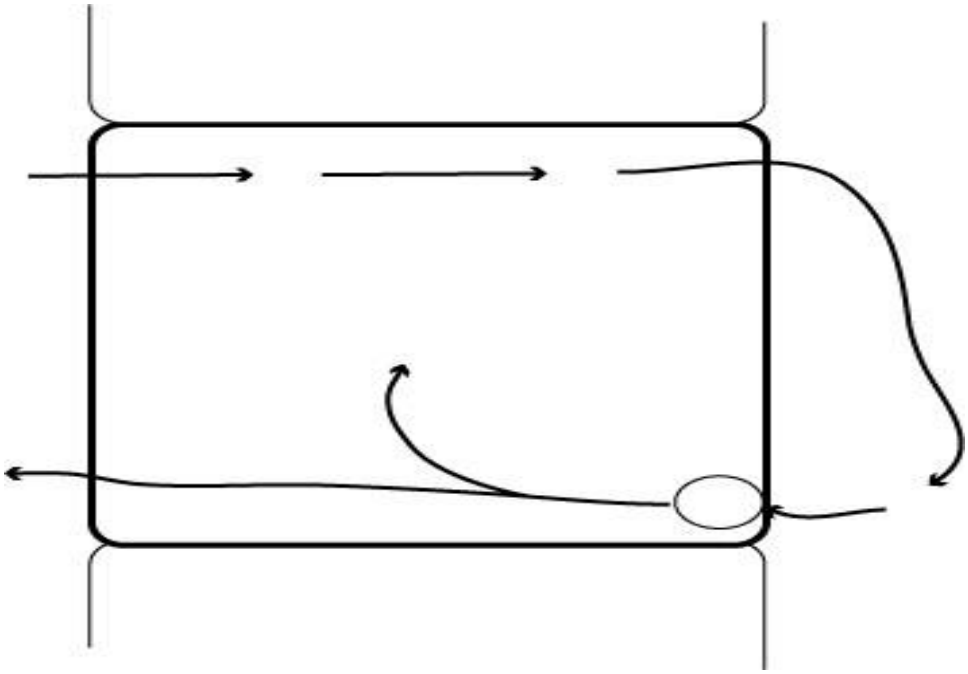
2) Peroxidase oxidizes iodide $\rightarrow$iodine (I)

3) Iodination of Tyrosine in the presence of iodinase in the endoplasmic reticulum

Tyrosine + I
Iodinase $\rightarrow$ $\downarrow$
Monoidotyrosine
$\downarrow$ + I

Diiodotyrosine
$\downarrow$+ I
T3 = Triiodothyronine
D + DP
T4 = Thyroxine

4) T3 & T4 are



exocytosed to the follicle in the form of thyroglobulin molecules

5) In the presence of TSH, colloid containing T3/T4 is pinocytosed back into the epithelial cells where Proteinases cleave the hormones from thyroglobulin

Lysosomes fuse with vesicles to allow proteinase to release thyroxin from thyroglobulin

6) T3/T4 are sent into the blood and thyroglobulin is recycled

7) T4 binds with Thyroxine Binding Globulin (plasma protein) and travels to the cells with receptors for T3/T4 (T4 is released to the cells slowly and T3 is released quickly).

8) T3/T4 are brought into the cell where T4 is deiodinated $\rightarrow$ T3

T3 is the metabolically active agent; it goes directly to the DNA & institutes transcription/translation, thus, increasing protein synthesis.

Functions of Thyroid Hormones

1) T3 increases the number and size of mitochondria =TATP
2) T3 increases Gluconeogenesis & CHO metabolism
3) T3 increases fatty acid metabolism
4) T3 increases cholesterol secretion in Bile
5) Increase BMR (Basal Metabolic Rate)

Effects on the cardiovascular system

1) Increase HR due to direct effect of T3 making heart excitable
2) V.D. $\rightarrow$ Increase blood flow
3) Increase blood flow $\rightarrow$ Increase C.O. (cardiac output)

All $\downarrow$

Due to increase metabolic activity

Thyroid Diseases

Hyperthyroidism = Increase or Decrease TSH depending on

cause

Increased size & secretion of thyroid gland

1) Thyrotoxicosis (Toxic Goider) or Grave's Disease

    a) At one time thyroid cells were "shed off' to the blood stream producing an Auto-immune response in the form of TSI: Thyroid Stimulating Immunoglobin

    b) TSI binds to receptor sites on thyroid cells causes continuous activation of the c-AMP system
    Increase the thyroid production which increases size of the thyroid gland

2) Thyroid Adenoma (Adenoma = tumor)
    Tumor in the thyroid tissue secretes large quantities of thyroid hormone

Hyperthyroidism (Signs and Symptoms)
-Exophthalmos: "Bulging " of the eyeballs due to retro-orbital edema
-Increase (BMR) Basal Metabolic Rate increases due to excess stimulus from T3

Hypothyroidism

1) Thyroiditis: Secondary autoimmune response in which the body destroys its own thyroid after prolonged inflammation; resulting in fibrosis

2) Endemic Goider: Greatly enlarged thyroid -lack of iodine prevents the production of T3/T4; however, thyroglobulin is formed in excess $\rightarrow$ large, but non-productive gland (iodized table salt) -because no T3/T4, TSH levels increase

Hypothyroidism (Signs and Symptoms)

Fatigue, sleeping 12 -14 hrs/day, muscular sluggishness, decrease HR, decrease C.O., decrease blood volume
Myxedema -swelling of the face due to increased production of hyaluronic acid & chondroitin sulfate which form "tissue gel" -"non-pitting" edema
Atheriosclerosis -increase blood cholesterol due to decrease liver excretion of cholesterol in bile -Decrease BMR - decreased metabolism due to lack of T3/T4

Cretinism - caused by extreme hypothyroidism during development in fetal life, infancy & childhood -Failure to grow -Mental Retardation

Adrenocortical Hormones
produced in the adrenal cortex in response to ACTH (Adrenocorticotropic hormone)
Adrenal Cortex

-secretes corticosteroids
-consists of 3 layers

1) Zona Glomerulosa - secretes aldosterone
2) Zona Fasciculata - secretes glucocorticoids & some androgens
   -cortisol (hydrocortisone)
3) Zona Reticularis - secretes adrenal androgens & some glucocorticoids

Chemistry of the Adrenocortical Hormones
All are chemically similar; derived from cholesterol in the blood.

Principle steps in the formation of adrenocorticotropics:

Acetate

Cholesterol

Pregnenolone

Progesterone 17-OH-Pregnenolone

Aldosterone 17-OH-Progesterone Androgen

Cortisol

Adrenocortical Hormones

1. Mineralocorticoids:

-effect the electrolytes (Na+/K+)
-Aldosterone is the principal mineral corticoid of the body
-secreted by the Zona Glomerulosa of the adrenal cortex

Transport of Aldosterone
-50% combines loosely with plasma proteins -50% is free

Function of Aldosterone

-promotes Na+ reabsorption from collecting tubules in kidney (and distal tubules/collecting ducts) -promotes the excretion of K+ into the urine primarily in the distal convoluted tubule

Aldosterone Escape
In the presence of excess aldosterone, initially Na & H20 are retained and the excess fluid initiates Pressure Diuresis which causes the excretion of Na+ & H20 even in the presence of aldosterone, thus "escape" from its effects are achieved.

Excess Aldosterone
Hypokalemia causes muscle weakness
Hypokalemia causes an alteration in the nerve membrane potential which prevents the transmission of normal action potentials

Aldosterone Deficiency
Causes Hyperkalemia = Severe Cardiac Toxicity
Hyperkalemia leads to weak cardiac muscle contraction due to membrane hypopolarization (difficult to reach threshold)

Effects on GI tract & Salivary Glands
Aldosterone increase Na+ reabsorption & increase K+ secretion in the GI tract

Cellular Mechanism of Aldosterone

1) Aldosterone diffuses into the cell (lipid soluble)

2) Aldosterone binds with its receptor protein in the cytoplasm

3) Aldosterone/receptor complex travels into the nucleus

4) Initiation of Transcription/Translation to produce Na+/K+/H+ membrane transport proteins & Na+ - K+ ATPases

Regulation of Aldosterone Secretion

1) Increase K+ = Increase Aldosterone

} Most Potent

2) Increase Renin/Angiotensin (Decrease BP)

(Decrease flow to kidneys) = Increase Aldosterone

3) Increase ACTH (Adrenocorticotropic hormone) = aldosterone production

2. Glucocorticoids

Exhibit important effects on blood glucose concentrations
-produced in the Zona Fasciculata of the adrenal cortex

Cortisol (aka Hydrocortisone)
The principal glucocorticoid of the body
Control of ACTH secretion by Corticotropin - Releasing Factor (CRF) by the hypothalamus

CRF
↓
Release of ACTH
↓
(Control of Cortical Secretions by ACTH:
-Secreted by Ant. Pit.)
↓

Activates adenyl cyclase c-AMP
↓
(activates intracellular enzymes that form ACTHs)
which activates
↓
Protein Kinase A: causes conversion of cholesterol --> pregnenolone

Effects of Cortisol (Glucocorticoids)

A) Carbohydrate Metabolism

1) Stimulates Gluconeogenesis by
a)Increase enzymes required for conversion of A.A. -j Glucose
b)Mobilizes A.A.'s from muscle tissue for conversion to glucose

2) Decreases glucose utilization by the cells

3) Increases blood glucose levels and can cause adrenal diabetes

B) Effects on Protein Metabolism

1) Decrease cellular protein by:
   a)Decrease protein synthesis
   b)Increase protein catabolism

2) Increase mobilization of proteins into the plasma and to the liver for conversion to glucose via deamination

C) Effects on Fat Metabolism

1) Mobilizes F.A.'s from Adipose tissue

2) Increases F.A. concentration in the plasma
   *Excess cortisol secretion causes excess fat deposition in the chest & head region
   a) "Buffalo Hump Torso"
   b) "Moon Face"

D) Effects on Stress and Inflammation

1) Physical/Mental stress---- increase secretion of ACTH
2) Mobilization of F.A.'s & A.A.'s to convert 4 Glucose for energy
3) Cortisol decreases inflammation

<u>Cortisol decreases inflammation</u>

1) Stabilizes lysosomal membranes
   -prevents/decreases the release of proteolytic enzymes and other chemicals (histamine) which contribute to inflammation

2) Decreases capillary membrane permeability
-decrease swelling in tissues

3) Decrease VVB (Migration by diminishing the formation of prostaglandins & Leukotrines

4) Suppresses the immune system
-Decrease T-Cell production

5) Lowers fever by decrease release of interleukin-1 from WBC's

6) Block allergic response by characteristics listed and by decreasing lymphocyte & eosinophil count

ACTH Association with MSH
ACTH is part of a Preprohormone that has as part of its subunits:

1) MSH: Melanocyte Stimulating Hormone
-stimulates the production of melanin by melanocytes

2) Endorphins (internal morphines)

3. Adrenal Androgens
Secreted by Zona Reticularis of the Adrenal Cortex
DHEA: Dehydroepiandrosterone is primary adrenal androgen
-mildly androgenic
-2 steps removed from testosterone

DHEA

Androstenedione

Testosterone

Diseases of the Adrenal Cortex

Addison's Disease = Hypoadrenalism
-due to atrophy of the adrenal cortices most commonly from an autoimmune attack

Effects:
1) Decrease Aldosterone = decrease Na+ retention ---- decrease Fluid volume

2) Decrease cortisol -Decrease blood sugar due to decrease in synthesis of glucose from A.A.'s & F.A.'s between meals

3) Increase melanin = increase pigmentation
-due to increase ACTH secretion from decreased cortisol levels (neg. Feedback)

TX: exogenous quantities of the adrenal cortex hormones

Cushings Syndrome = HyperAdrenalism

-caused by tumor or general hyperplasia

Effects:
1) Mobilization of Fat from lower body and deposition of fat to upper body
-Buffalo Hump
-Moon Face

2) Hypertension due to mineralocorticoid (aldosterone) effects

3) Increase gluconeogenesis

4) Decrease protein in muscles 4 severe muscular weakness
TX: Surgery

1 ° Aldosteronism

-caused by tumor in Zona Glomerulosa
-Increase Aldosterone

1) Hypertension due to Na+ retention
2) Muscle Paralysis from Hypokalemia

Insulin, Glucagon, & Diabetes Mellitus

Physiologic Anatomy of the Pancreas

2 Types of Tissue:

1) Acini cells: secrete digestive juices into the duodenum

2) Islets of Langerhans: secrete insulin and glucagons directly into the blood 1 - 2 million islets of langerhans/human pancreas

4 types of islets cells

a) Beta cells: secrete insulin 60%
b) Alpha cells: secrete glucagons 25%
c) Delta cells: secrete somatostatin 10%
d) PP cells: secrete pancreatic polypeptide (Function Unknown)

Feedback: Because the various islet cell are in such close relation, their secretions have direct effects on each other

-insulin inhibits glucagons secretion
-somatostatin inhibits both insulin & glucagons

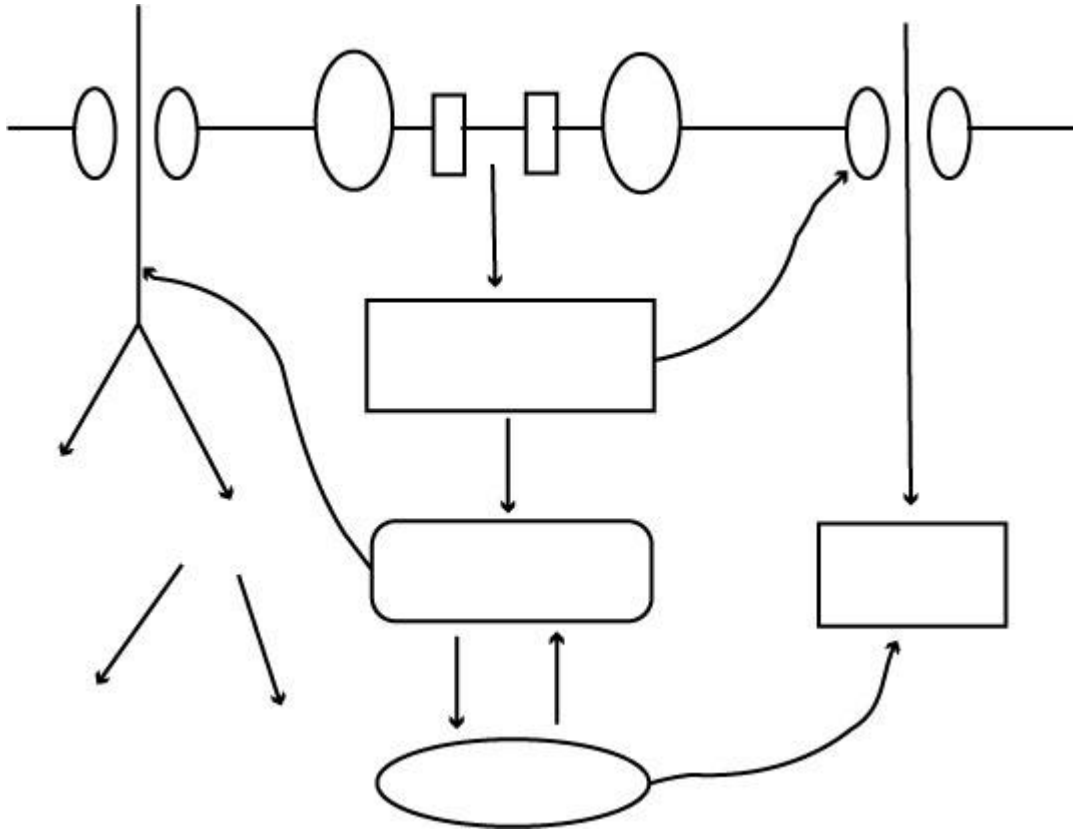
Activation of Target Cell Receptors by Insulin

1) Insulin binds with and activates a membrane receptor; the insulin receptor is composed of 4 subunits:
    2 - Alpha subunits outside the cell
    2 - Beta subunits protruding into the cell cytoplasm.

2) Portions of the Beta subunits become phosphorylated.

3) This "activation" causes a cascade of phosphorylations by protein kinase within the cell which results in direction of the cells metabolic machinery.

Insulin Intracellular Pathway



End Effects of Insulin Stimulation:

1) Seconds after insulin binds, 80% of the body's cells become highly permeable to glucose (The exception is neurons in the brain) via a glucose transport protein produced by the cell.

2) Membrane permeability increases for all of the following: Amino acids, K+ ions, P04 ions

3) The activity of many intracellular enzymes is changed (phosphorylation cascade).

4) Over hours to days insulin affects transcription/translation rates controlling protein production & cellular metabolism.

Effects of Insulin in promoting Glucose Metabolism in Muscle

The resting muscle depends on Fatty Acids for energy.

Muscles use glucose for energy:

1) During moderate or heavy exercise

(With exercise muscles have increase glucose permeability)

2) After meals, in the presence of insulin there is rapid transport of glucose into the cells causing the muscle to prefer using glucose over F.A.'s for energy

-Excess glucose in the muscles is stored in the form of Glycogen

Effects of Insulin on Liver Uptake of Glucose

-Insulin promotes the storage of most of the glucose absorbed after a meal in the liver as Glycogen

Mechanism of Insulin & Glucose storage in the Liver

1) Insulin inactivates liver phosphorylase: The enzyme which facilitates breakdown of Glycogen → Glucose

2) Insulin causes enhanced uptake of Glucose from the blood by the liver cells and increased activity of glucokinase which "traps" glucose in the cells via phosphorylation

3) Insulin increases the activity of Glycogen Synthase which promotes the formation of glucose ---- glycogen for storage

Insulin increase the amount of glycogen stored in the liver

Mechanism for Release of Glucose from the Liver

1) Decrease blood sugar causes the pancreas to decrease insulin secretion

2) Lack of insulin reverses the process of glucose storage/glycogen formation; also prevents further uptake of glucose from the blood

3) Lack of insulin/presence of glucagons causes activation of phosphorylase which breaks
down glycogen to units of G-6-P

4) Lack of insulin activates glucose phosphatase which dephosphorylate G-6-P thus releasing glucose to the blood.

*The liver stores 60% of the glucose from a meal.
If glucose is in excess (more than can be used or stored as glycogen) insulin will promote the conversion of excess glucose → Fatty Acids

Hypoglycemic Shock: results from blood sugar levels in the range of 20 - 50 mg/dL

Effects of Insulin on Protein Metabolism:

1) Insulin increases the uptake of amino acids into the cells

2) Insulin "turns on" the ribosomal machinery thus increasing the translation of messenger RNA

3) Insulin increases the rate of transcription of selected DNA genetic sequences

4) Insulin inhibits the catabolism of proteins

5) Insulin depresses the rate of gluconeogenesis in the liver

Role of Insulin in "switching" between Carbohydrate and Lipid Metabolism

When blood glucose is Low, insulin secretion is suppressed & Fat is used.
When blood glucose is High, insulin secretion is stimulated and CHO is used for energy.

Epinephrine: enhances the utilization of Fats during stressful states such as exercise, circulatory shock & anxiety

Glucagon and its Functions
-secreted by alpha cells of Islets of Langerhans when blood sugar falls
-opposes insulin, increase blood sugar
-"Hyperglycemic Hormone"

Effects on Glucose Metabolism
1) Breakdown of liver glycogen
2) Increase Gluconeogenesis in the liver

Mechanism of Glycogenolysis in the liver

1) Glucagon activates adenyl cyclase in the hepatic cell membrane

2) Formation of CAMP

3) Protein Kinase regulator - activated

4) Protein Kinase - activated

5) Phosphorylase B Kinase - activated

6) Phosphorylase B → Phosphorylase A

7) Glycogen breakdown into units of G-1-P

8) G-1-P is dephosphorylated liberating glucose

Regulation of Glucagon Secretion

Increase blood glucose inhibits glucagon secretion.

Increase concentrations of amino acids after a protein meal stimulate the secretion of glucagons which then promotes rapid conversion of A.A.'s 4 glucose

Exercise increase blood concentration of glucagons by 4 - 5 times

Glucagon prevents blood sugar levels from decreasing -Autonomic stimulation of islets

Somatostatin

Secreted by the delta-cells of islets of Langerhans

Ingestion of food stimulated the release of somatostatin:
1) Increase blood sugar
2) Increase A.A.'s
3) Increase F.A.'s
4) Increase concentrations of Gastrointestinal hormones

Inhibitory Functions of Somatostatin

1) Acts on the islet cells to depress the secretion of insulin & glucagons

2) Decrease GI motility

3) Decrease secretion & absorption in the GI tract

Functions to prevent rapid exhaustion of nutrient sources.

Pathological Physiology of Diabetes Mellitus

Insulin lack causes:
1) Decrease utilization of glucose by cells

2) Marked increase in mobilization of Fats 4 atherosclerosis

3) Depletion of protein in the tissues of the body

Loss of Glucose in Urine
Occurs when blood glucose concentrations are > 180 mg/dL

Dehydrating Effect of Increase Blood Glucose
Elevated blood glucose causes dehydration of the tissue cells due to osmotic pressure transferring H20 out of cells into blood

Elevated blood glucose → decrease tubular reabsorption of fluids, which equals a massive loss of fluid in the urine. This causes dehydration of extracellular fluid.

Both intra & extra cellular dehydration occur

Acidosis in Diabetes
Due to increase fat metabolism, blood ketone bodies can increase by 10 fold → acidosis

Ketoacids must be combined with sodium for excretion, therefore increase ketones → decrease Na+ and increase H+

Signs and Symptons
1) Polyuria - excessive urination
2) Polydipsia - excessive drinking of H20
3) Weight loss
4) Polyphagia - excessive eating
5) Asthenia - lack of energy

Parathyroid Hormone, Calcitonin, Calcium, & P04 Metabolism, Vit D, Bone, & Teeth

Calcium intake:	1 gm.day	Absorbed	Excreted
GI absorption	*350 mg*		
GI Juices secreted			*250 mg*
Net Absorption	*100 mg*		
Net Loss in Feces			*900 mg*
Further loss in urine up to			*100 mg*

The most important factor controlling calcium reabsorption from the urine in the distal tubules is Parathyroid Hormone

Phosphate intake
Almost all phosphate is absorbed through the gut into the blood, excess is secreted in the urine and this is regulated by Parathyroid Hormone.

Vitamin D & its role in Ca+/P04 absorption -Vit. D has a potent effect on increasing Ca++ absorption in the GI tract, but it must first undergo 2 steps to be ACTIVE.

1) Cholecalciferol (Vit. D3) } this step is controlled by feedback, increase levels
} of 25-hydroxycholecalciferol will inhibit further
in the Liver } conversion

2) 2,5-Hydroxycholecalciferol } regulated by Parathyroid Hormone

in the Kidneys
(proximal tubules)

1,25 - Dihydroxycholecalciferol

Calcium's Effect on the Formation of 1,25- Dihydroxycholecalciferol

1) Calcium ion itself has a slight inhibitory effect on this conversion

2) Increase plasma Ca++ concentrations = decrease parathyroid hormone so = decrease conversion of Vit. D to active which decrease intestinal absorption of Ca++

"Hormonal" effects of 1,25 Dihydroxycholecalciferol on Ca++ absorption

1) Active Vit. D promotes formation of calcium - binding protein in the intestinal epithelium which will transport Ca++ into the cells. This is a long term effect - several weeks once formed.

2) Active Vit. D promotes the formation of Ca++ stimulated ATPases

Calcium in the Plasma/Interstitial Fluid -concentration of calcium = 9.4 mg/dL = 2.4 mmol/L -calcium is present in the body in 3 forms

1) Calcium + Plasma Proteins = 40%
   (Not diffusible)
2) Calcium + X (Citrate, Phosphate) = 10%
   (Not diffusible)
3) Ca++ = 50%
   Diffusible & Ionized

The Calcium Ion (Ca ++) concentration in the plasma/interstitial fluids = 1.2 mmol/L -Ionized calcium is the form of active calcium in the body (heart, nervous system, & bone formation)

Precipitation & Absorption of Ca++ & P04 in Bone

Supersaturated State of Ca++/P04 in the Extracellular Fluids
+Concentrations are much higher than necessary to form hydroxyappetite in the tissues.
+The presence of INHIBITORS in the tissues prevents precipitation.

Mechanism of Bone Calcification
1) Secretion of collagen & ground substance by osteoblasts

2) Formation of Osteoid
   -Collagen form fibers
   -Osteoblasts "trapped" → Osteocytes

3) Calcium salts begin to precipitate in 2 - 3 days to form Hydroxyapatite crystals

Abnormal Precipitation in non-osseous tissues
-loss of inhibitory factors allow precipitation

1) Arteriosclerosis
2) Degenerative Tissues
3) Blood clots

Parathyroid Hormone
Increase Parathyroid activity → rapid absorption of Ca salts from bones

Hypercalcimia in extracellular fluid =

Decrease Parathyroid activity → Hypocalcemia
↓
Tetany

Anatomy of Parathyroid Glands
4 glands in humans
Located behind the thyroid glands

2 cell types:
1) Oxyphil cells = function unknown
2) Chief cells = secrete parathyroid hormone

Chemistry of PTH:
Preprohormone - ER
↓
Prohormone
↓ ER/Golgi
Hormone
↓
Fragments
↓
Fragments of PTH are active!

Effects of PTH on Ca++ & P04 concentrations in the Extracellular Fluid
Increased PTH causes:

1) Calcium and Phosphate are mobilized from the bones

2) Decrease excretion of Ca++ by kidneys

3) Increase excretion of P04 by kidneys

Osteolysis
Osteocytic pumps, which pump Ca ions from the bone fluid to the extracellular fluid, are excessively activated causing calcium phosphate salts to be absorbed (removed from the bone) and transported to the extra-cellular fluid.

Activation of Osteoclasts

1) Immediate activation of existing osteoclast

2) Formation of new osteoclast

-Stimulation is believed to be a signal sent by activated osteoblasts & osteocytes

Effect of PTH on P04 & Ca Excretion in the Kidneys
PTH increase P04 excretion by decreasing proximal tube reabsorption.
PTH decrease Ca++ excretion by increasing tubular reabsorption in the late distal tubules & collecting ducts.

Effect of PTH on Intestinal Absorption of P04/Ca++
PTH promotes increase absorption of both P04/Ca++ by increasing the formation of 1,25 - Dihydroxycholecalciferol (active Vit. D).

Effects of Vit D on bone and its relation to PTH
In small quantities Vit. D promotes bone calcification by increase absorption of Ca++/P04 in the intestines.

*PTH uses the cAMP 2nd messenger system in the bone cells!!

Calcitonin
Secreted by the "C-Cells" of the Thyroid gland
Calcitonin reduces blood calcium ion concentration

1) Decrease absorptive activities of osteoclasts and opposes osteolysis, thus promoting deposition of Ca++ in bone.

2) Decrease formation of new osteoclasts which leads to decrease numbers of osteoclasts.

Calcitonin's effect on plasma calcium concentration
Has only a weak effect of reducing calcium absorption from the bones.

The Kidney & Body Fluids

Daily Intake of H20

1) Ingestion: 2100 ml/day	2100 ml
2) Synthesized 2 metabolism	200 ml
Total Intake/day	2300 ml

Daily Loss of H20

1) Insensible H20		
a) Evaporation		300 - 400 ml/day
b) Evaporation		300 - 400 nil/day
2) Sweat ~		100 ml/day
3) Feces		100 ml/day
4) Kidneys	~	1400 ml/day
Total Out/day		2300 ml/day

Fluid Compartments

Total body fluid is distributed among 2 major compartments

1)

2)

Extra-cellular Fluid: All fluids outside the cells

- 20% of body weight
- 14 L in average adult

1) Interstitial Fluid = 11.0 L (3/4)
2) Plasma [Increase P's] = 3.0 L (1/4)

Blood Volume

Blood is a separate fluid compartment

- 5 L /person
- 60% plasma
- 40% HCT (36%)

• note: Blood contains both intra& extra cellular components

RENAL PYSIOLOGY

Blood flow through the kidneys

Renal Artery
↓
Segmental Arteries
↓
Interlobar Arteries
↓
Arcuate Arteries
↓
Interlobular Arteries
↓
Afferent Arterioles
↓
Glomerular Capillaries } Microcirculation of nephron
↓
Glomerulus
↓
Efferent arteriole
↓
Peritubular capillaries
↓
Venous System

Renal Circulation

Venous System
Peritubular capillaries empty into the venous system: interlobular vein arcuate vein 4interlobar vein 4 renal vein 4 exit kidney

REVIEW KIDNEY ANATOMY

Functions of Urinary system

1) regulate H20/electrolyte balance
2) regulate acid/base balance
3) excrete metabolic wastes & foreign chemicals
4) regulate arterial pressure - long term
5) erthropoeitin -increases BC production, produced by kidneys in response to hypoxia
6) also: secretion of hormones, body fluid osmolarity & [electrolyte]

Metabolic wastes excreted by kidneys:

Urea - amino acid metabolism
Uric acid - nucleic acid metabolism
Creatinine - muscle metabolism
Bilirubin - red blood cell breakdown

Kidneys regulate electrolytes:
Sodium, Cl-, K+, Ca++, H+, Mg ++, PO,4, HC03-

Control of Renal Blood Flow/Glomerular Filtration

1) SNS stimulation
   - Decrease glomerular filtration rate
   - Vasoconstriction of renal arterioles which decrease renal blood flow

2) Hormonal Effect on GFR

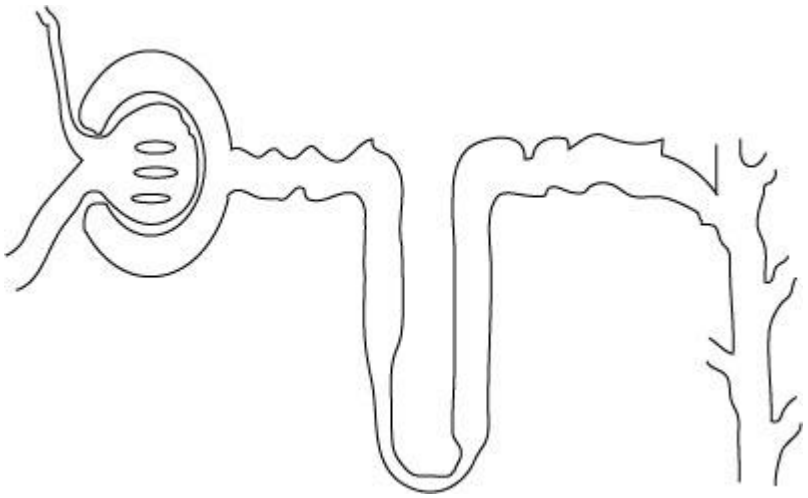
a) V.C. that decrease GFR
   i. noerepinephrine
   ii. epinephrine
   iii. endothelin

b) Angiotensin II
   V.C. arterioles
   - decrease renal blood flow

c) Prostaglandins cause vasodilation and increase renal blood flow serve to decrease the effects of vasoconstriction

Urine Formation: understand the steps in relation to the anatomy
- begins in the Nephron
functional unit of the kidney
1 million/kidney
180 L filtrate made/day
178.5 L reabsorbed/day
Urine output/day = 1.5 L or 1500 ml

The Nephron



Nephron - 2 major components

1) Glomerulus
   A network of capillaries encased in the Bowman's capsule site of filtration receives blood from renal arteries → arterioles → glomerulus
   The glomerulus is part of the circulatory system

2) Long Tubules - converts fluid to urine en route to renal pelvis
   a) Proximal tubule - lies in the cortex of the kidney aka. proximal convoluted tubule

      * has a brush border that increase surface area for increased H20 movement
      * many mitochondria → highly metabolic

   b) Loop of Henle - dips into the renal medulla
      *descending limb- very thin walls, thin segment

c) *ascending limb- lower wall thin
upper region = thick wall or "thick segment of the "Loop of Henle"
Thin segment; Loop of Henle

d) Macula Densa - located @ the end of the ascending limb

e) Distal Convoluted Tubule - lies in renal cortex

f) Connecting Tubule

g) Cortical Collecting Tubule

h) Cortical Collecting Duct

i) Medullary Collecting Duct

j) Renal Papillae

k) Renal Pelvis

Filtrate: composition similar to plasma

Tubuloglomerular Feedback Mechanism (regulates GFR)

Components to control GFR: (glomerular filtration rate)

1) Afferent arteriolar: feedback mechanism
a) The macula densa senses changes in volume delivery to the distal tubule

b) Decrease resistance in afferent arteriole

c) Increase glomerular hydrostatic pressure

d) GFR is increased

Bowman's Capsule: cup shaped initial portion of the renal tubule - surrounds glomerulus - receives filtrate from glomerulus - acts as a sieve

Renal Handling of 4 Substances

For each substance in the plasma, a particular combination of filtration, reabsorption & secretion occurs.

A. Freely filtered by the glomerulus
Neither reabsorbed or secreted
Creatinine - all that is filtered is excreted

B. Freely filtered by glomerulus
partially reabsorbed back into the blood
(electrolytes)

C. Freely filtered by glomerulus
All reabsorbed (none in urine)
(amino acids and glucose)

D. Freely filtered by glomerulus
Not reabsorbed BUT additional quantities
are secreted from peritubular capillaries

Structures of Nephrons:
2 types
1) Cortical nephrons
2) Juxtamedullary Nephrons

Cortical Nephron (85%): located in the renal cortex
1) glomerulus is located in the outer cortex

2) short loops of Henle- penetrate only a short distance into medulla

Juxtamedullary Nephrons (20 - 30%)
1) glomeruli deep in the renal cortex near medulla

2) have long loops of henle diving deep into the medulla

3) loops of henle tips near renal papilla

4) Have vasa recta- long efferent arterioles extending down into the medulla and run parallel to the loops of henle, they return to the cortex and empty into the cortical veins

Review: Urine Formation (4 parts)

1) Filtration (Glomerulus)-

2) Reabsorption -

3) Secretion -

4) Excretion -

Glomerular Capillary Membrane has 3 layers

1) Endothelium
Highly fenestrated, allows high filtration rate

2) Basement Membrane

- consists of collagen and proteoglycans
- allows : large amounts of H20 to pass through
- most restrictive portion
- prevents proteins from crossing

3) Podocytes
- long foot-like processes that encircle the outer surface of the capillaries
- separated by slit pores through which the glomerular filtrate flows

↓

Proximal Tubule

Net Filtration Pressure

Glomerular Hydrostatic Pressure	60
Bowmans Capsule Pressure	18
Glomerular Colloid Osmotic Pressure	32
Net Filtration Pressure	+10 mm

Proximal Convoluted Tubule
-has a Brush Border → increased surface area for increased movement of molecules

-relatively metabolic →many mitochondria for increased active transport

-reabsorbs → 65% of filtered Na,Cl, HC03, K, 100% of glucose

-high capacity for active and passive transport

Note: Kidney stones
Calcium oxalate
Uric acid crystal
Buildup in renal pelvis causing back pressure => pain

Tubular Reabsorption
Occurs through active transport and diffusion

-2 types of active transport

Primary active transport:
Moves solutes against an electrochemical gradient -gets energy from hydrolysis of ATP by way of membrane bound ATPase. ATP ase binds and moves solutes across the cell membrane (Na-K ATPase, H-K ATPase, Ca ATPase)

Transport Maximum:
-the amount of solute delivered to the transport system exceeds the capacity of the carrier proteins

-all of the transport proteins are full (saturation) -

Example: Diabetic & sugar in urine

1) level of sugar increases to saturation point

2) glucose is not reabsorbed into the blood, so it is excreted in the urine

Summary of Renal Function

1) Filtrate produced [300 mOSm/L]
    - BP forces plasma through pores in Bowman's Capsule
    - Filtrate produced is similar to plasma with less amino acids

2) Proximal Convoluted Tubule: PCT [300 m0sm/1]

- has Brush Border → increased surface area for rapid transport of Na and other ions

- cells are highly metabolic w/large number's of mitochondria to support lots of active transport

- 1^{st} ½ PCT is where Na is reabsorbed along with glucose and A.A.s

- 2^{nd} ½ PCT is where sodium and Cl is reabsorbed

- [Urea] increases in PCT

- PCT secretes: bile salts, oxalates, urate, catecholamines

3) PCT/Descending Loop of Henle
   - 300 → 600 → 900 → 1200 m0sm/1
   - filtrate = urea & salts
   - here the filtrate is highly concentrated

4) Ascending Loop of Henle (Thin)
   - decrease surface area, thin membrane
   - lots of fluids/solutes being drawn out
   - Na+/Cl- out → into medullas salty medulla
   - Urea stays in and is the primary solute in the tubule
   - [tubular fluid]

4 ½) Thick Ascending Loop of Henle
   - begins ascending limb
   - thicker membrane has increase mitochondria and is highly metabolic
   - lots of Active Transport
   - Reabsorbs: Na,C1,K (25% of load)

- Impermeable to : H20, so H20 stays in tubule

5) Distal Convoluted Tubule - uses active transport

- has some reabsorptive characteristics
- impermeable to H20/urea
- this is the diluting segment
- ions leave tubule to be reabsorbed while H20 and urea stay

Has 2 components:

A) Juxtaglomerular Apparatus
-location- where the distal convoluted tubule contacts the afferent arteriole

B) Late DCT
has 2 cell types:-

1) principal cells reabsorbs: Na/H20 secretes: K uses: Na/K ATPase pump

2) intercalated cells reabsorb: HC03, K and Na
secrete: H

<u>Aldosterone :</u> controls the rate of reabsorption for Na+ by : speeding up active transport in the DCT, also controls the rate of K secretion

<u>ADH (vasopressin)</u> effects in DCT & Collecting Duct

1) If high levels ADH → decrease urine output →
ADH makes DCT permeable to H20 so H20 is reabsorbed 3 an increase in blood volume secondarily to H20 conservation→ increase blood pressure

2) NO ADH
The tubules are impermeable to H20,
alcohol inhibits ADH secretion

Note: Diabetes Insipidus -
-causes up to 15 L urine/day to be excreted each day
-extreme thirst

<u>Reabsorption in the Peritubular Capillaries</u>

Reabsorption rate = Kf x Net Reabsorptive Force
Kf = coefficient filtration constant = permeability x surface area

The more permeable and greater surface area => increase filtration rate

<u>Forces that Govern Reabsorption Rate (4)</u>

Pc → 1) Hydrostatic Pressure of Peritubular Capillaries

PIF → 2) Hydrostatic Pressure of Interstitium outside the capillaries

C → 3) Colloid Osmotic pressure of Peritubular Capillary

F → 4) Colloid Osmotic Pressure of proteins in the Renal Interstitium

Remember: Increase arterial pressure 4 increase GFR which will
↓
Decrease Reabsorption Rate

6) Medullary Collecting Duct
(If ADH is working)
1) decrease urine

2) Some urea diffuses into medulla to keep this region concentrated

3) H_20 is pulled out here increasing urine concentration

7) Vasculature Surrounding Tubules

1) Vasa Recta

2) Peritubular capillaries

Their 1 ° function is to pull H20 and solutes into the vasculature by simple diffusion of these substances from interstitium into blood.

Secretion: Everything that ends up in the urine by way of secretion occurs from the tubular cells secreting them into urine.

Removes unwanted substances and wastes
(H20, urea, NH3, H+ drugs)

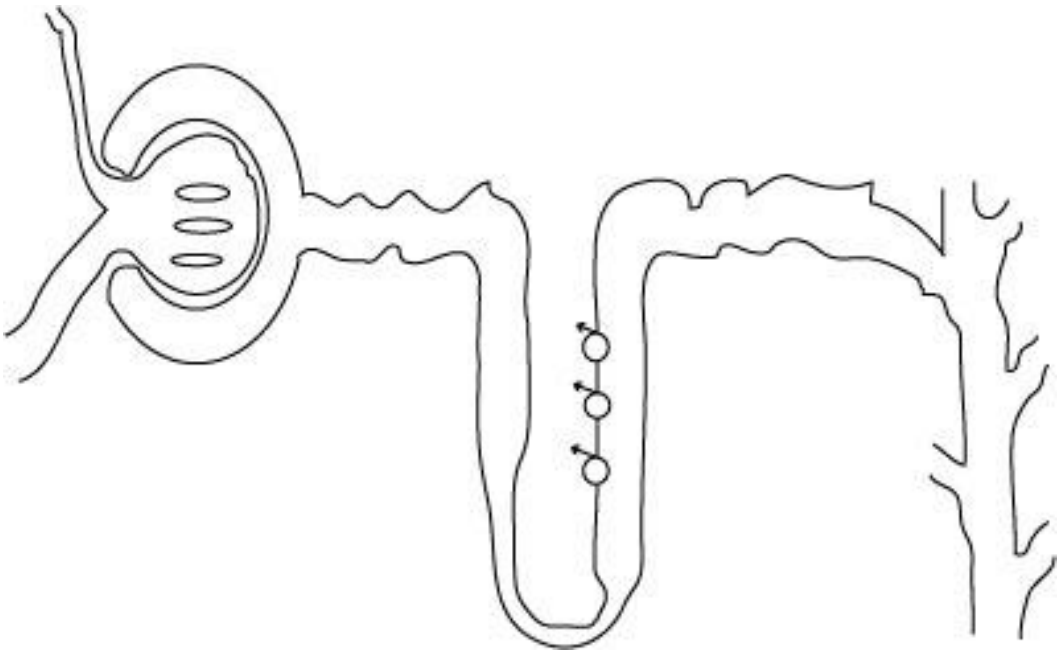
Tubular Secretion maintains pH:

If blood [H+] increase: then secrete H+ into urine

If blood [H+] decrease: then reabsorb H+ from urine back to body

Grand Summary

1) Solutes & H20 passively diffuse out of the PCT (descending limb) → Interstitial Tissue fluid
2) As descending limb dives into medulla, more H2O is pulled out
3) As filtrate moves up through Thick ascending limb, Na+/K+/2C1 Co-transporter move solute molecules out of the loop and DCT to the ITF
4) All the NaCl pumped out into the interstitial tissue fluid around the loop creates the gradient that causes H20 to move out in the PCT/descending limb
5) Na+ continues to be pumped out (actively) of DCT & the collecting ducts which further decrease [urine] (osmolarity)
6) In the presence of ADH (opens channels), remaining H20 in the DCT & collecting ducts is pulled out into the interstitial tissue fluid.



1) Hormonal Regulation

a) Renin = activated by decrease glomerular BP (decrease Q)
-initiates a cascade of hormones
-angiotensin II, aldosterone, ADH (increase GFR)

b) Angiotensin II
- stimulates thirst (increase H20 intake = increase BP)
- V.C. arterioles (afferent)
- Powerful Na+ retaining hormone stimulate Na+/K+ ion pumps
- Stimulates aldosterone production

c) Aldosterone: decrease U.O. & increase BP
- produced in the adrenal glands
- Reabsorbs Na+ by acting on the principal cells of the collecting ducts
- Excretes K+ } via stimulates Na/K pumps
- As Na+ (salt) leaves - H20 follows (into blood)

d) Angiotensin II stimulates ADH secretion
-ADH increase perm. of DCT/collecting ducts to H20, thus saving H20 from urine

e) Atrial Natriuretic Peptide/Hormone (ANP or ANH)

- opposes angiotensin II (inhibits renin release)
  + decrease renin, decrease aldosterone, decrease ADH
- natrium = salt; ouresis = urine production
- responds to increase blood volume: is released when the atria are stretched and the specialized cells in the atria sense this and they release ANP

Inhibit the reabsorption of Na+ & H20 by the renal tubules → increased U.O. → decrease blood volume

Increased GFR due to V.D. of afferent arteriole
(Also inhibits thirst)

2) Autonomic Regulation of Urine Formation
- activated by Vasomotor center

Stimulates the SNS
a) SNS : V.C. afferent arterioles decrease GFR
b) SNS : increase Na+ reabsorption and since . . .
H20 follows salt →U.O.
c) SNS : stimulates release of Renin → decrease U.O.

SNS stimulates Decrease U.O.

Renal Clearance
The volume of plasma that is completely cleared of a substance by the kidneys per unit time.

The rate at which a substance is "cleared" provides a useful way of quantifying the effectiveness of the kidneys.

Creatinine: used clinically because it is almost entirely excreted (0 reabsorption); so the rate of its excretion provides valuable information on renal function.

Inulin: polysaccharide molecule w/ MW = 5200 isn't reabsorbed so can be used.

GFR = urine excretion rate of substance = mL/min
Plasma concentration of substance

Example: 125 mg inulin excreted/min
1 mg/ml inulin in plasma

GFR = 125 ml/min

Filtration Fraction
The fraction of plasma that filters through the glomerular membrane.

FF = GFR = GFR = 125 = .19 - 20%
Renal Plasma Flow RPF = 650

Countercurrent Multiplier Mechanism

The repetitive reabsorption of solutes (Na+ & other ions) from:

1) The ascending limb of the loop of Henle into the interstitial tissue fluid of the medulla

2) The inflow of new Na+ & others from the PCT & the descending limb of the loop of Henle into the medulla creates a build up of solutes (deep) in the medulla which multiplies. It creates & maintains the solute concentration in the medulla.
The key is: Active Transport of solutes into the medulla

4) Passive diffusion of urea from the medullary collecting duct

5) H_20 restriction in the medullary ducts

Vasa Recta:
- The filtrate in the loop of Henle in the Juxtamedullary nephrons
- The [solutes] in the VASA RECTA «< [solutes] medulla because of this, solutes are reabsorbed into the circulation
- The Vasa Recta does not add to the hyperosmolarity of the medulla, but it doesn't prevent it either.
- A small amount of solute is pulled out.

Ion Regulation
Fluid & electrolyte regulation
- regulate urine formation (autoregulation, hormonal, autonomic)
- angiotensin II & ANP - ADH:
- 3 ways to activate:
  - 1) Angiotensin II activation
  - 2) Osmoreceptors
  - 3) Baroreceptors

Osmoreceptors:
Specialized cells located in the anterior hypothalamus that are sensitive to changes in osmolarity of plasma

Osmolarity - ADH Feedback Mechanism
↓
H20 Deficit
↓
Increase Extra-cellular OSM
↓ Osmoreceptors triggered (they shrink)
Increase ADH secretion by Posterior Pituitary
↓
Increase Plasma ADH
↓
Increase H20 Perm. Distal Tubules/Collecting Ducts = take back H20
↓
Increase H20 Reabsorption
↓
Decrease Urine output

*When Osmoreceptor cells shrink, they release ADH from the Magnocellular cells of the hypothalamus

Cardiovascular Baroreceptors:
- carotid & aortic sinuses
- increase in plasma blood volume → increase BP causing the baroreceptors to FIRE
- decrease in ADH production → increase U.O. → decrease blood volume

$3_{1/2}$) Nausea is a BIG stimulant of ADH production

Thirst Mechanism
The thirst center is located in the brain in the anterior wall of the 3rd ventricle (same as ADH origin)
Thirst - the conscious desire for H20

3 reasons for Thirst:

increase extra-cellular osmolarity is the stimulus for thirst (increase [solutes] outside the cells) because it causes intra-cellular dehydration of the cells of the thirst center

increase in extracellular fluid volume & decrease BP also → thirst

angiotensin II stimulates thirst

Maintenance of Body Na+ & Fluid Balance

2 important mechanisms:

1) Pressure Diuresis
   increase blood pressure → increase urine output
   (increase blood volume → increase BP → increase GFR → increase U.O.)
   so... because of increase GFR →Na+ reabsorption decrease

2) Pressure Natriuresis
   increase BP → increase Na+ excretion (2° increase GFR; decrease absorption time)

Sodium (Na+)

the major extra-cellular ion
Na+ intake via digestion
Na+ excretion via kidneys & perspiration

If increase or decrease Na+ intake, the [Na+] in plasma is unchanged because the body quickly adjusts to H20 levels via osmosis.

Increase [Na+] → stimulates Osmoreceptors → increase ADH → save H20, dilute [Na+]
Decrease [Na+] → decrease ADH production
Decrease [Na+] → increase aldosterone production → increase Na+ reabsorbed in DCT

Micturition

Micturition: process of urinary bladder emptying once full
- automatic reflex (primarily)

Detrusor Muscle: smooth muscle of the bladder Controlled by S2 & S3 of PSNS
- contraction ---- urination - bladder empties

Internal Urethral Sphincter: controlled by PSNS Is Involuntary

External Urethral Sphincter: is skeletal muscle and is under voluntary control

- relax ---- you micturate
- innervated by pudendal nerve

Trigone: area of bladder that is entirely smooth muscle so that there are no Rugae to retain urine (this would cause UTI)

The sympathetics regulate blood flow to the area via the hypogastric nerves

Micturition Reflex = is self regenerative; a single complete cycle of 1) Progressive & rapid increase of pressure (bladder) 2) Period of sustained pressure 3) Relaxation: return of the pressure to the basal tone of the bladder

GASTROINTESTINAL SYSTEM

GI - Tract (Alimentary Tract) 1 ° function is to provide the body with a continual supply of H20, electrolytes, nutrients (also rids the body of wastes & toxins)

Characteristics of the GI System
-a long tube from mouth to anus with organs and glands attached to it

The GI Wall from Outer to Inner
(x-section of intestine)

1) Serosa

2) Muscle layers
   a) Longitudinal
   b) Circular

3) Submucosa

4) Mucosa

Layers of the intestine

1) Serosa: is the peritoneum
   Peritoneum: the serious membrane that lines the peritoneal cavity
   -produces fluid for lubrication
   -lines the outside of the organs

2) Muscular Layers (smooth)
   a)Longitudinal - outer layer
   b)Circular - inner

3) Submucosa
   -composed of loose areolar connective tissue
   -site of vessel flow (blood, nerve, lymph)

4) Mucosal layer
   -composed of simple columnar epithelium

   & Goblet Cells -> Mucous

Enteroendocrine Cells: produce some type of secretion under the control of hormones

Smooth Muscle Physiology of GI Tract
-operates as a Functional Syncytium: a sheet of tissue working as one large contractile unit.

Example: a contraction starts in one place and travels through the syncytium as a "Wave"

-this muscle has GAP JUNCTIONS which allow the ions to flow from cell to cell

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Example: a contraction starts in one place and travels through the syncytium as a "Wave"

-this muscle has GAP JUNCTIONS which allow the ions to flow from cell to cell

Factors that depolarize the smooth muscle membrane

1) Parasympathetic NS Activation
ACH

2) Stretching (Distension) of the muscle

Factors that Hyperpolarize (decrease muscle excitability)

1) Stimulation of the sympathetic nerves
Nor-Epi/Epi

Smooth Muscle Contraction
1) Calmodulin binds with Ca++ which cause

2) Activation of Myosin Kinase - phosphorylates ADP on myosin

3) Myosin Head Activated (Cross Bridging)

4) Contraction

*Calmodulin parallels troponin in skeletal muscle contraction (the binding of Ca++)

Neural Control of GI function
Enteric Nervous System (has 2 components)

1) Myenteric Plexus: the "outer plexus" located between the longitudinal & circular muscle layers; aka. "Auerbach's Plexus"

-runs the entire length of "GUT" (pharynx -> anus)
-has sympathetic & Parasympathetic innervation the entire length

Neural Control of GI (cont.)

2) Meissner's Plexus (Submucosal)
-located in the submucosa

Functions in Local Regulation of

a) Endocrine cell secretion (enteroendocrine)

b) local absorption

c) lymphatic flow (absorb large P's & fats)

Contraction of the Muscularis Mucosa which causes various degrees infolding in the stomach mucosa

Functional Types of Movements in the GI tract

1) Propulsive Movements: Move food forward along the tract at the appropriate rate for digestion & absorption -Peristaltic Reflex: local distention initiates peristalsis

a) The contractile ring forms before the distention
b) The contraction pushes food toward the anus
c) The gut beyond the distention relaxes = "receptive relaxation"

* b and c occur at the same time

d) Contraction dies out in 5 -10 cm -Food travels in only one direction as long as there is a functioning myenteric plexus directing the contraction

2) Mixing Movements: keep the intestinal contents mixed at all times
-Local constrictive contractions occur every few cm. in the gut wall

-"Chopping" and "churning" occurs as different contractions occur in different areas

-uses the circular muscle fibers "1 ° function = mix & chop the food"

GI Blood Flow

Splanchnic Circulation - includes blood flow through the gut itself, plus the spleen, pancreas, & liver.

Hepatic Portal System: receives the blood from the gut, spleen & pancreas via the portal vein.
-takes unoxygenated nutrient rich blood returning from the GI tract and passes it through the liver (liver sinusoids) where reticuloendothelial cells - "Kupffer cells" phagocytize any bacteria that is passing through

ACINI Cells - the predominate liver cell
- handles secretory function
- modification/production of nutrients coming from the GI system

Lacteal: a blind end lymphatic sac that
absorbs fats and large proteins

Transport and Mixing of Food
Hunger: the desire for food
Appetite: the type of food desired

Mastication (Chewing)

1)Incisors:	generate 55 lbs. of force/sq. in =	cutting action
2)Molars:	generate 200 lbs. =	grinding

Chewing Reflex: a bolus of food triggers inhibition (relaxing) of the mastication muscles --- Jaw drops

Stretch Reflex of Jaw Muscles ------ rebound contraction (Jaw Reflex)
-repetitive cycle = chewing Innervated by Trigeminal nerve = CN #5

Swallowing (Deglutition)

1) **Voluntary Stage**: initiates the swallowing process -a bolus of food is push back against the pharyngeal arches; this initiates stage 2

2) **Pharyngeal Stage**
a) Soft palate is pulled up to close Posterior Nares
b) Glottis closes down tightly
c) Epiglottis covers the Glottis
d) Pharyngeal muscles pull the oropharynx/larynx up and forward
e) Upper esophageal sphincter closes above the bolus of food
f) First peristaltic wave is initiated which causes food bolus to travel down
g) a second wave is then initiated
h) Upper 1 /3 of the esophagus is voluntary skeletal muscle; lower 2/3 is involuntary smooth muscle

Gastroesophageal Sphincter (Cardiac Sphincter)

-relaxes ahead of the peristaltic wave allowing food into the stomach -functions to prevent reflux of stomach contents into the esophagus

Hiatal Hernia: stomach herniates into the esophagus -> excess reflux

Motor Functions of Stomach

1) Stores food
2) Mixes food
3) Empties food

STORAGE
Food in the stomach produces the VAGOVAGAL REFLEX, a reflex causing relaxation of the stomach wall (Decrease muscle tone) Stomach can hold 1.5 L of food before feeling full

MIXING
Slow waves: weak peristaltic waves occur every 15 - 20 sec.

Starts at Cardiac Region
Weak
Mod
Stronger

Antrum of stomach
Waves get stronger as they travel downward

EMPTYING
As waves progress to the pylorus (pyloric valve), food is propelled through the pyloric sphincter (small diameter) in Fluid Form

Degree of pyloric constriction is variable under the influence of neural/hormonal signals

Secretory Functions

Alimentary Tract Secretion
Four types of glands provide different secretions

1) Goblet cells: secrete mucus

-located throughout the canal -some are serous mucus producers (mucus is for lubrication) -some are viscous mucus producers (thick mucus) mucus is for protection

*Viscous mucus has more Glycoproteins

2) Crypts of Lieberkuhn

-"pits" that represent "invaginations" of the epithelium of the small intestine -contain specialized secretory cells

3) Tubular Glands

-stomach & upper duodenum -secrete pepsinogen: the precursor to pepsin -secrete acid (HCl)

[Pepsinogen + HCl 4 Pepsin]
Pepsin = digestive enzyme

4) Complex Glands (3 glands)

a) Salivary glands
b) Pancreas } dump into small intestine
c) Liver }
-the glands are located outside the alimentary canal walls
-the glands are lined with ACINI CELLS which feed into ducts which will dump secretions into the alimentary canal

Nervous Stimulation of Secretions

Activation of the Enteric Nervous System

1) Tactile stimulation (the presence of food)
2) Chemical Irritation
3) Distention of the Gut Wall

Autonomic Stimulation of Secretions

1) Parasympathetic stimulation
-increases the rate of glandular secretion

2) Sympathetic Stimulation -Decrease rate of secretions due to constriction of blood vessels supplying the glands

Peptic ulcers are common @ Gastric end of esophagus
Due to gastric reflux

Clinical Note: *Ulcers*

Duodenal ---- Peptic Ulcers: Symptoms occur 2 -4. hours after meals
Stomach ----- Gastric Ulcers: 1 - 2 hrs after meals
Small Intestine ------ Alkaline secretions that neutralize acids

Mechanism of Glandular Secretions

1) Organic Secretions

a) Produced in the Endoplasmic Reticulum and sent to the Golgi Complex (Golgi body)

b) Golgi packages as Zymogen granules (vesicles)

c) Presence of increase Ca++ causes vesicles to fuse with the cell membrane

d) Zymogen granules break open on the exterior of the cell releasing the secretion

2) H20 & Electrolyte Secretions

a) Nerve stimulation triggers Active Transport of Cl- into the cell
b) Increase negativity inside cell causes diffusion of cations into the cell
c) Net increase of solutes in the cells pulls H20 in via osmotic gradient
d) Cell swells and causes "Flushing" of H20 & electrolytes out of the secretory end of the cell

Secretion of Saliva

Principal glands of salivation
1) Parotid glands
2) Submandibular Glands
3) Sublingual Glands

Saliva contains two major types of *protein*
1) Ptyalin (Beta - amylase)
Serous secretion that digests starches

2) Mucin
Mucus secretion which protects and lubricates

Functions of Saliva

1) Breaks down starches in the mouth

2) Oral Hygiene -dilutes/washes away bacteria -Thiocyanate - destroys bacteria -Lysozyme - attack bacteria/help thiocyanate get in (1120) -Protein antibodies destroy bacteria that cause "dental caries" = cavities these are IgA Antibodies (tears and saliva)

Nervous Regulation of Salivary Secretion
Parasympathetic: Salivation is mainly controlled by PSNS in the brain stem

-Superior and inferior salivatory nuclei
motor nuclei that stimulates saliva secretion

-Signal travels down:
Facial Nerve = CN 7
Glossopharyngeal Nerve = CN 9

Esophageal Secretions
Lots of goblet cells secrete mucus for lubrication

Gastric Secretions
Located in the body and fundus of the stomach

2 important types of glands:
1) Oxyntic (Gastric) glands
HCI, Pepsinogen, Intrinsic Factor, Mucus

2) Pyloric glands
Mucus, pepsinogen, gastrin

Oxyntic Glands
A) Mucus Neck Cells
-secrete mainly mucus (viscous) which functions to coat/protect the stomach epithelium
-secretes some pepsinogen

B) Chief (Peptic) Cells
-secrete large quantities of pepsinogen

C) Oxyntic (Parietal) Cells
-Produce HCl (ph = 0.8 when secreted)
-Produced Intrinsic Factor:
+Vital to absorption of Vit B-12

Clinical Note: Lack of intrinsic factor results in Pernicious Anemia which is a form of Megoblastic anemia: the RBC's are abnormally large and lack normal 02 carrying ability

Mechanism of HCl Secretion

1) Active transport of Cl- from the cytoplasm of parietal cells into the canaliculi(lumen)
2) Na+ is actively transported from the lumen to the cytoplasm
3) K+ is passively transported into the lumen
4) H20 + C02 H2C03HC03- + H= ------ into the lumen
5) H+, K+ - ATPASE : K+ ---- Cytoplasm; H+ into canaliculi (lumen)
6) HCl is left in the lumen providing an extreme increase in concentration

Secretion of Pepsinogen
1) Peptic cells are stimulated by ACH
2) Pepsinogen + HCl ---- Pepsin = Active Enzyme

Pyloric Glands
-found in the pylorus &
antrum

A) Secrete large amounts of mucus
Thin mucus for lubrication/protection - slightly alkaline

B) Secrete Gastrin
Gastrin: Large polypeptide secreted by the "G-cells" of the small intestine
-secreted into the small intestine

-is then absorbed by the blood where it functions as a hormone to increase the secretion of HO by the oxyntic cells in the upper portion of the stomach

Controls gastric secretions:

1) Stimulates dorsal motor nuclei of the VAGI (In the brain stem)
2) Signal travels thru vagus nerve
3) Stimulates enteric/myenteric nervous plexus
4) Triggers release of NT's by gastric glands Gastrin releasing factor (peptide)

Stimulation of Acid Secretion
Stomach initiated signals

1) Long Vagovagal reflex: stimulus from the stomach mucosa transmitted all the way to the brain stem & back to the stomach via the vagus nerve

2) Short reflexes: originate locally and travel only through the local enteric nervous system

Review: Types of "Stimulus"
1) Touch/tactile (mechanoreceptor)
2) Distention
3) Irritation (mech. or chem.)
4) Chemical

Histamine's role in Gastric Secretions
-secreted by the parietal cell when stimulated by both gastric and ACH
-is a necessary CO-FACTOR for exciting significant acid secretion

Phases of gastric secretion (3)

1) Cephalic Phase - results from the sight, smell, thought or taste of food -stimulate the dorsal motor nuclei of the VAGI to the stomach -), increase in gastric secretion (20%)

2) Gastric Phase - stimulated by the presence of food in the stomach -> increase gastric secretions (70%)

3) Intestinal Phase - stimulated by the presence of food in the upper part of the small intestine - production of gastrin - increase gastric secretions

Pancreatic Secretion: (has 2 functions)

1) Endocrine (Ductless) secretions

a) Glucagon: secreted by the alpha cells of the Islets of Langerhans -cause liver to increase blood sugar levels

b) Insulin: secreted by the Beta cells of Islets of Langerhans -Decrease blood sugar levels

2) Exocrine secretions (via ducts)
-Pancreatic duct dumps its secretions into the duodenum

-secretions are regulated by: ACH, cholecystokinin, & secretin which are produced in the mucosal lining of the proximal small intestine

Pancreatic Exocrine Secretions: (cont)
-function to cause the release of digestive enzymes

Proteolytic Enzymes of the Pancreas

1) Trypsin - formed from the precursor trypsinogen
    1 ° function is the activation of the other enzymes:
    Chymotrypsin & Carboxypolypeptidase

2) Chymotrysin/Trypsin
    -function to break proteins into smaller peptides

3) Carboxypolypeptidase
    -splits proteins into individual amino acids by cleaving them off the ends of proteins

Trypsin Inhibitor Peptide: prevents the activation of trypsin and thus other pancreatic enzymes -protects the pancreas from being digested by the digestive enzymes

Enterokinase - enzyme that activates trypsinogen - trypsin
-is secreted by the intestinal mucosa when chyme comes in contact with the mucosa

Pancreatic Amylase: digests 70% of starches (CHO's) (the ptyalin in the saliva digest 30%)

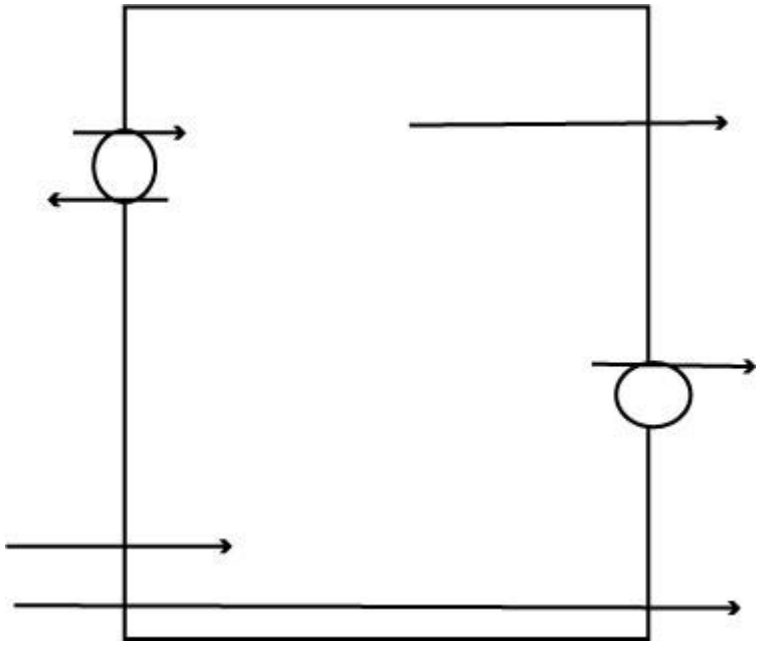
Pancreatic secretion of HC03- (Bicarb)
-pancreas secretes HC03- in the presence of secretin
-secretin: is produced by the "S-Cells" of the small intestine in response to acidic chyme

Mechanism of HC03- Secretion
1) C02 + H20 H2C03 - HC03- + H+

2) HC03- is transported into the lumen

3) H+ is exchanged for Na+ via H+ -Na+ ATPASE

4) Na+ + HC03- ---- NaHC03 = sodium bicarbonate which is alkaline in solution and reduces acidity



Cholecystokinin
-secreted by the I-Cells of the intestinal mucosa in the presence of proteases, peptones, and fatty acids

1 ° function:
Cause the gall bladder to constrict releasing bile into the small intestine

LIVER
The liver's function in digestion is secretion of bile salts

Functions of Bile:
1) Emulsification of fats (not soluble)
   Bile breaks fat globules into minute sized complexes
   Micelles + lipases (pancreas) -> further digestion of fats

2) Bile aids in the transport/absorption of fats (Fatty acids, monoglycerides, cholesterol & other lipids) Micelle: A complex of bile salts and lipids; they are H20 soluble and can be transported in the blood plasma

3) Bile is an important mechanism to the excretion of the breakdown products of Red Blood Cells:

RBC -> HGB --> Bilirubin

Fragile RBC in the spleen

free bilirubin in liver

conjugated bilirubin by intestinal bacteria

urobilinogen->in kidneys this is oxidized to form

Stercobilinogen Urobilinogen

converted to stercobilin in feces

<u>Composition of Bile</u>
-Bile salts, bilirubin, cholesterol, electrolytes, lecithin

<u>Storage and Concentration of Bile</u>
Gall Bladder: Bile is stored and concentrated here
-it is concentrated via active transport of Na+ & Cl- (out) which draws H20 with them
-Bile travels down the hepatic duct, up the cystic duct and into the gall bladder

<u>Release of Bile from the Gall Bladder</u>
Cholecystokinin - secreted into the blood by the "I-Cells" of the duodenum in response to fatty foods entering the duodenum

Cholecystokinin function: causes rhythmical contractions of the gall bladder (relax sphincter of Oddi) (also cause increase secretion of enzymes by the acinar cells of the pancreas)

Enterohepatic Circulation of Bile salts
-94% of the bile salts are reabsorbed by the small intestine; via diffusion; via active transport

Enterohepatic Circulation of Bile Salts

Small Intestine

Hepatic Portal Blood Vessels (Unoxygenated, nutrient rich blood)

Liver

Recirculated

Secretions of the Small Intestine

1) Brunner's Glands: secretes alkaline mucus in response to:
    a) Acidic chyme in small intestine
    b) Secretin ("S-Cells")
    c) Any chemical or tactile stimulus (irritants)
    d) Vagal stimulation

*SNS inhibits Brunner's glands

2) Crypts of Lieberkuhn -Line the entire surface of the small intestine -composed of 2 cell types
    a) Goblet cells: secrete mucus
    b) Enterocytes: secrete H20 & Electrolytes (Cl-, HC03)

Secretions of the Large Intestine
Crypts of Lieberkuhn -secrete mucus of alkaline ph (HC03-) which neutralizes the acids produced by digestion/bacteria

REPRODUCTIVE PHYSIOLOGY

Male Reproduction

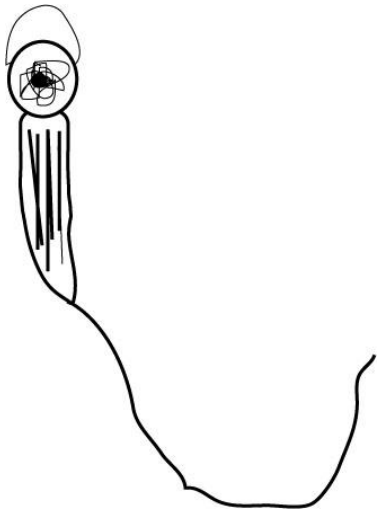
Spermatogenesis
The production and maturation of sperm
Occurs in the seminiferous tubules

Spermatozoa = mature sperm

Sertoli cells = (aka: sustentacular cells) cells that surround the spermatids, providing nutrients that support their development.

Acrosome: thick "cap" surrounding the head; composed of enzymes

1) Hyaluronidase - breaks down hyaluronic acid
2) Proteolytic enzymes dissolves cells surrounding egg



Head: contains nuclear material
Midpiece: houses mitochondria which produce Energy for motility

Axoneme: 11 Microtubules Structure 9:2 similar to cilia

Hormonal Factors that Stimulate Spermatogenesis

1) Testosterone
    -secreted by the interstitial cells of Leydig in the testis
    -essential for growth and division of spermatogonia
    -gives rise to
        a) Dihydrotestosterone
        b) Androstenedione - (precursor to testosterone)

*DHEA = Dihydroepiandrosterone - produced in the adrenal cortex, but is 2 steps removed from testosterone

2) Luteinizing Hormone (LH)
    -secreted by the Anterior Pituitary Gland
    -stimulates the Leydig cells to secrete testosterone

3) Follicle Stimulating hormone (FSH)
    -secreted by the Anterior Pituitary Gland
    -stimulates the Sertoli cells to support spermatogenesis

4) Estrogen
    -secreted by sertoli cells

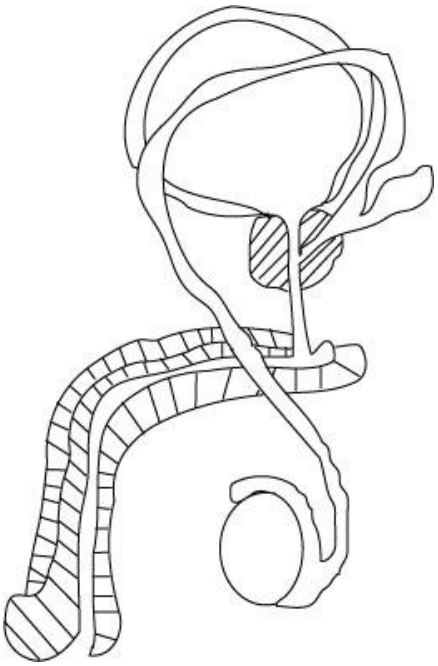
5) Growth Hormone (GH)
    -secreted by Ant. Pit.
    -promotes cell division
    -controls metabolic activity of testes

Maturation of Sperm
Epididymus - tubule 6 meters long; sperm are matured and stored here; sperm develop motility here

Storage of Sperm
Vas Deferens - 8" to 1 ft. tubule from epididymus to post. aspect of prostate
  -transport/storage of sperm to posterior prostate
  -is a muscular tube that contracts during orgasm
  -"dumps" sperm into post. prostate

Function of the Seminal Vesicles
Lobular blind-end sac
Secretory vesicles that secrete a mucoid material which contains:

Fructose
Citric Acid
Fibrinogen
Prostaglandins: thin vaginal/cervical mucus to make it easier for sperm travel



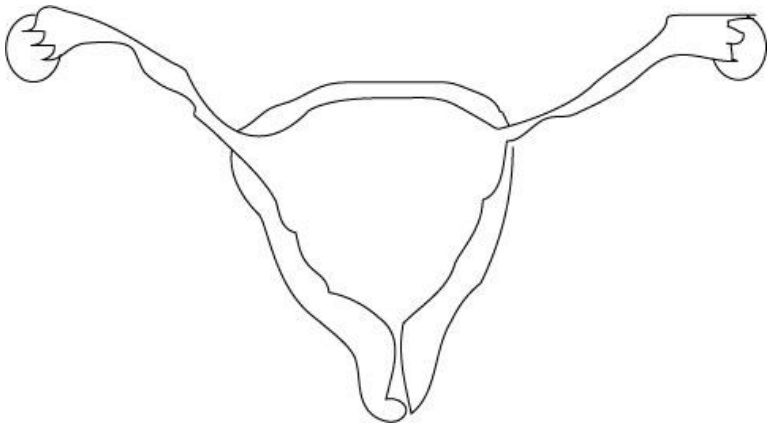
Functions of the Prostate Gland
-secretes a thin, milky, alkaline fluid -why alkaline?
Sperm requires a pH of 6.0 - 6.5 to be motile;
the vagina is acidic (pH 3.5 - 4.0)

Bulbourethal Glands (aka: Cowpers glands)
-located at the base of the penis
-pea sized
-produce a mucoid secretion during sexual arousal known as pre-ejaculate

Prostatic Urethra
portion of urethra traveling through the prostate;
- has pores thru which prostatic fluid is received

Profibrinolysin - "Clotting Factor" secreted by the prostate gland;
-function to hold sperm to the cervix for - 30 min, after which the anti-clotters begin dissolving
-Sperm can live in the female for 1 - 2 days
-There is a 4 day window during which impregnation can occur

Where does fertilization occur?
-In the lateral 1/3 of the fallopian tube



Fertilization --- implantation takes 7 days

HGH is detected - 14 days after fertilization

Capacitation of the Spermatozoa
-multiple changes which occur when the spermatozoa comes in contact with the fluids of the female genital tract enabling the sperm to perform "fertilizing duties"

1) Uterine & fallopian tube fluids Wash Away Inhibitory Factors
2) Excess cholesterol of the Acrosome is lost, weakening/softening the head of the sperm
3) The membrane of the sperm head becomes permeable to Ca++ which increases motility of sperm

Why does only one sperm enter the oocyte?

1) A few seconds to minutes after a sperm penetrates the zona pellucida, Ca++ ions diffuse through the oocyte membrane and cause cortical granules to be released which prevent binding of additional sperm and also cause bound sperm to fall off

2) After the sperm fuses with the oocyte membrane, the membrane depolarizes which prevents subsequent sperm penetration

The Male Sex Act
1) Erection of the Glans Penis

Stimulation -Parasympathetic impulses pass from the sacral portion of the spinal cord thru the pelvic nerves to the penis (Sacral Divisions S2, S3, S4)
-Parasympathetic fibers secrete Nitric Oxide which vasodilates arterioles

2) Lubrication
-PSNS stimulate urethal & bulbourethral glands to secrete mucus

3) Ejaculation -the reflex centers of the spinal cord begin to emit Sympathetic Impulses -L l & L2 levels pass through the genitals via hypogastric & pelvic nerves initiating constriction of the relevant glands and structures

4) Resolution - process 1 - 2 min. after ejaculation
-erection ceases
-decrease PSNS stimulation

Ejaculate: semen as it leaves the penis

Functions of Testosterone in Fetal Development

-the newly formed genital ridge secretes testosterone -testosterone secreted by the genital ridge/testes is responsible for the development of the penis & scrotum

Cryptorchidism - failure of one or both testis to descend from the abdomen into the scrotum; "hidden testicle" -Increased testosterone levels in infancy will cause it to descend; if it does not --> surgical intervention

Inguinal hernia

Effect of Testosterone on development of 1° & 2° Sex characteristics
-Testosterone causes enlargement of the penis, scrotum and testes by 8 fold at age 20

2° Sex Characteristics
1) Baldness = Increase testosterone ---- decrease head hair (genetic contrib. also)
2) Voice = Increased testosterone ---- lowered voice
3) Acne = Increased testosterone ---- increased thickness of skin
4) Increased Protein levels & protein deposition in tissue
5) Bone growth
6) Increase BMR
7) Body hair - pubis, umbilicus, face, chest

Control of Male Sex Hormones

Hypothalamus secretes: GnRH (gonadotropin - releasing hormone)

Stimulate Anterior Pituitary

(LH)Luteinizing Hormone Follicle-Stimulating Hormone (FSH)

Secretion of Testosterone Stimulate Spermatogenesis

Testosterone/LH Negative Feedback

Increased testosterone causes inhibition of Ant. Pit. to secrete LH

Inhibin - inhibits the secretion of FSH by the Ant. Pit.

Effect of hCG (human Chononic Gonadotropin) on Fetal Testes
-secreted by the placenta
-causes fetal testes to secrete testosterone
-promotes development of sexual organs

Female Physiology before Pregnancy; Female Hormones

Physiological Anatomy of the Female Sexual Organs
Organs: Ovaries, fallopian tubes, uterus & vagina

Development of Ova in the Ovaries
Oocyte: egg/ova; surrounded by Zona Pellucida & Corona Radiata

Primordial Follicle: the ovum surrounded by a single layer of granulosa cells

30th week of gestation = 6 million ova
Birth = 2 million ova
Puberty= 300,000 ---- 400,000 ova
13 - 46 years - 400 follicles will expel their ova

Female Hormone System

Hypothalamus

GnRH = Gonadotropic Releasing Hormone

Anterior Pituitary

FSH - Follicle Stim. Hormone LH - Luteinizing Hormone

ovaries

Ovaries secrete
1) Estrogen
2) Progesterone

Ovarian Cycle - 2 phases
-Averages 28 days in duration
-Begins on day 1 of menstruation
-Ovaries take turns releasing a single ovum per cycle

Menarche: the first menstrual cycle

-Prior to menarche the ganulosa cells that surround the oocyte produce:
Oocyte Maturation Inhibiting Factor which prevents eggs from maturing before the female is ready to handle a pregnancy; is closely linked to % body Fat

-The average age of menarche has decreased
current average age = 11 years old
= 12 -16 years

Why? Androgenic steroids in foods (dairy, meat)
Environmental influences = sex on TV
Sedentary lifestyle increase % body fat at earlier ages which may increase estrogen levels (estrogen is a cholesterol derivative)

"Follicular" phase of the Ovarian Cycle

1) FSH stimulates granulosa cells to produce Estrogen

2) Is'- 5th days in the cycle (during menstruation)
6 -12 follicles begin maturation out of which 1 follicle matures to a Graafian Follicle

3) Estrogen promotes the granulose cells of the follicle to form more FSH receptors

4) FSH and Estrogen combine to promote increased LH receptors on the granulosa cells

5) The follicular cells proliferate

6) Full maturation of 1 ° follicle, atresia of the rest

Ovulation
-2 days prior to ovulation, days 12 & 13 of the cycle, there is a spike in the levels of FSH & LH (particularly LH)

-Day 14, the follicle ruptures and releases the egg from the ovary
-All this time the endometrium is thickening

The "Luteal" Phase of Ovulation (aka. secretory phase)

-Luteinization of the Follicle
Follicle --> Corpus Luteum

-LH/FSH causes enlargement of the corpus luteum
-Corpus Luteum secretes progesterone (& some estrogen)
-If no fertilization/implantation occurs corpus luteum - corpus albicans
Progesterone & estrogen levels decrease (begin new cycle)

Functions of Progesterone

1) Increases the vascularity of endometrium
2) Increases the secretory functions of endometrium
-provides support for a baby by secreting glycogen, lipids, and proteins
3) Breasts: promotes development of the lobules & alveoli of the breast; swelling

Function of Estrogens
-cause puberty/sexual development

-Breasts:
1) Development of stromal tissue
2) Growth of extensive duct system
3) Deposition of Fat

-Skeleton
1) Causes rapid growth after puberty
2) Cause early uniting of the epiphyses with the shafts of the long bones, ceases growth (Women stop growing earlier than men)

-Fat deposition
1) Causes fat deposition in breasts, subcutaneous tissues, buttocks and thighs

Female Sexual Act

1) Stimulation is transmitted to the sacral segments of the cord through the pudendal nerve and sacral plexus Tactile stimulation of the clitoris, vulva and perineum

2) Erection/Lubrication -Parasympathetic signals release Nitric Oxide at the nerve endings which causes vasodilation of the arterioles and erection of the clitoris
-Parasympathetic signals stimulate Bartholins & Skene's Glands located medial to the labia minora to secrete mucus

-Increased blood flow to the vaginal wall allows components of the plasma to "sweat" into the vagina producing increased lubrication -The engorgement of the vagina also serves to increase stimulation

3) Orgasm
-perineal muscles contract rhythmically due to spinal cord reflexes (SNS)

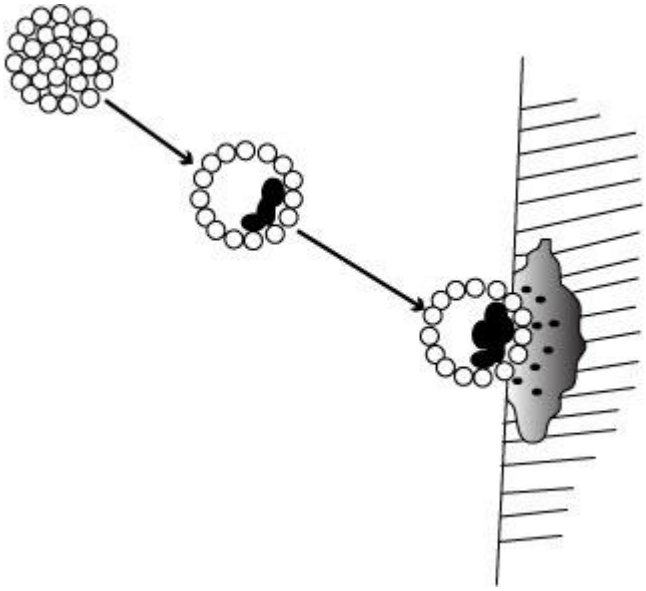
-dilation of the cervical canal for up to 30 minutes

Fertilization of the Ovum
-After ejaculation a few (thousand) of the'/z billion sperm travel through the uterus to the ampullae in the ovarian ends of the fallopian tubes -Fertilization occurs in the lateral 1/3 of the fallopian tube -Implantation occurs 7 days after fertilization

Ovulation 14 days
Fertilization = 2 - 3 days later

Development of Zygote

1) Morula- solid mass of cells (Day 1, 2 &3)
-inner cell mass becomes the embryo



2) Blastocyst
-inner cell mass becomes the
-outer cell mass becomes the extra embryonic membranes

1)Chorion - involved in producing the placenta

2)Amnion - inner sac, produces amniotic fluid

3) Syncytial Trophoblast
-secretes proteolytic enzymes which degrade the endometrium, so the egg "burrows" in

4) Division & Growth
-Trophoblast cells produce HCG Pregnancy tests - test for HCG which can be detected at 2 weeks after fertilization
-Initial nutrition for the embryo is provided by the trophoblastic cells

Corpus Luteum
-produces progesterone which is critical to maintaining the pregnancy for the embryonic stage (1St trimester)

-For 2"d & 3rd trimester HCG levels are high enough to maintain the pregnancy
'The end of the lst trimester is critical for miscarriage due corpus luteum shutting down

3 - 9 months / 12 - 40 weeks = Fetus (vs. embryo)

Hormonal Factors in Pregnancy
-Placenta forms large amounts of HCG, Estrogens, Progesterone & Human Chorionic Somatomammotropin

Function of Human Chorionic Gonadotropin (HCG)
-functions to prevent the involution of the corpus luteum at the end of the sexual cycle; causes the corpus luteum to secrete more hormones needed to maintain the pregnancy
-After the 12th week the placenta will take over these secretory functions

Functions of Estrogen in Pregnancy
1) Enlargement of the mother's uterus
2) Enlargement of the breasts and growth of the breast ductal structure
3) Enlargement of the external genitalia

Functions/Effects of Progesterone in Pregnancy
1) Develops decidual cells in the endometrium - nutrition of embryo
2) Decrease contractility of the uterus
3) Contributes to the development of conception and implantation
(Nutrition for morula/blastocyst; affects cell division)
4)Works with estrogen to prepare breasts

Human Chorionic Somatomammotropin
-secreted by the placenta at 5t week of pregnancy -aids in preparing the breasts for lactation -has some growth hormone properties -causes decrease in insulin sensitivity in the mother --- decrease glucose utilization in the mother so as to provide more nutrients for the fetus

Relaxin
-secreted by the corpus luteum and placenta -causes relaxation of the ligaments of the symphysis pubis
-softens the cervix

Weight gain in the pregnant woman
-Average weight gain is 24 lbs

-71bs = Fetus
-4 lbs = Amniotic Fluid, placenta & fetal membranes
-2 lbs = Uterus
-21bs = Breasts
-6 lbs = Extra fluid in the blood/extracellular fluid
-3 lbs = Fat stored

Preeclampsia (Toxemia of Pregnancy)
Autoimmune Reaction

-salt & H20 retention by the kidneys
-weight gain
-edema
-arterial spasm: brain, kidneys, liver
-increased art. Pressure

Caused by thickened glomerular tufts that contain a protein deposit in the basement membrane

Eclampsia - extreme condition of preeclampsia
-extreme vascular spasm through the body
-seizures, coma
TX: C-section, VD's

Parturition - Birth
-Increase estrogen to progesterone ratio increase uterine contractility -Oxytocin
- causes uterine contraction secrete by neurohypophysis (Post. Pit.)

Stages
1St Stage: The period of progressive cervical dilation lasting until the opening is as large as the head of the fetus (1 Ocm)

2°d Stage: Movement of the fetus' head rapidly into the birth canal ---- Birth

3rd Stage: Separation and delivery of the placenta

Lactation
Estrogen: growth of the ductal system

Progesterone: development of lobule - alveolar system

Prolactin: initiation of lactation
Milk formation: GH, Cortisol, parathyroid hormone and insulin are needed to provide A.A.'s, F.A.'s, glucose and calcium for the milk

Let-Down Reflex - milk must be ejected from the alveoli into the ductal system
-caused by oxytocin release which stimulates contraction of the outer walls of alveoli
-triggered by
1) sucking
2) handling a baby
3) crying of a baby

Fetal Physiology

Onset of Breathing after birth
-is initiated by sudden exposure to the exterior world (like getting a cold shower)
-slightly asphyxiated state triggers the respiratory centers

Fetal Circulation - Flow of oxygenated blood

Placenta

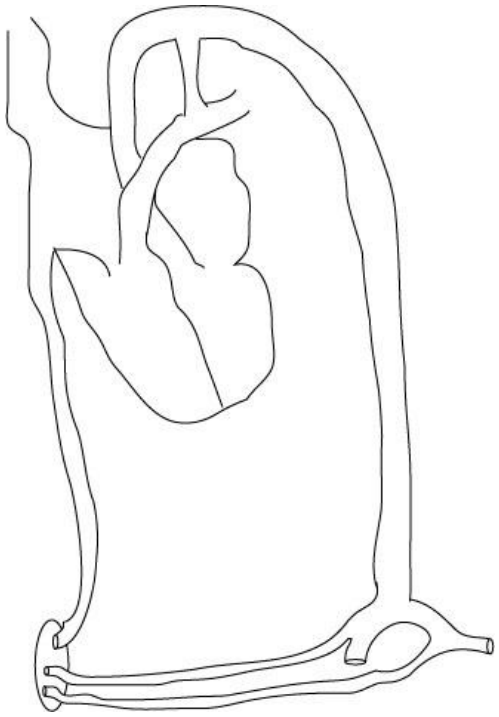
Umbilical Vein

Portal Vein - blood is mixed

Ductus Venosus - bypasses liver

Hepatic Vein

Inferior Vena Cava



Right Heart

1)Foramen ovale
2)Ductus arteriosis

Left Heart

Lungs

Ductus Arteriosis Body Tissues

Aorta

Umbilical arteries

Umbilical cord

Placenta

Circulatory Adjustments at Birth

systemic vascular resistance doubles pulmonary vascular

resistance Decreases 5 -fold

Closure of the Foramen Ovale
-attempted backflow from left atrium to right causes the valve (a flap on left side) to close over the opening

Closure of the Ductus Arteriosus

-functional closure: the muscle wall of the ductus arteriosus constricts -1 - 8 days
-anatomical occlusion by growth of fibrous tissue 1- 4 months

Closure of the Ductus Venosus

-Muscles contract to close vessel 1 - 3 hrs after birth