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Preface

These three volumes of Lecture Notes represent a yearlong effort on the part of the Kaplan Medical faculty to update our curriculum to reflect the most-likely-to-be-tested material on the current USMLE Step 1 exam. Please note that these are Lecture Notes, not review books! The Notes were designed to be accompanied by faculty lectures—live, on video, or on the web. Reading these Notes without accessing the accompanying lectures is not an effective way to review for the USMLE.

To maximize the effectiveness of these Notes, annotate them as you listen to lectures. To facilitate this process, we've created wide, blank margins. While these margins are occasionally punctuated by faculty high-yield "margin notes," they are, for the most part, left blank for your notations. Use them!!

Many students find that previewing the Notes prior to the lecture is a very effective way to prepare for class. This allows you to anticipate the areas where you'll need to pay particular attention. It also affords you the opportunity to map out how the information is going to be presented and what sort of study aids (charts, diagrams, etc.) you might want to add. This strategy works regardless of whether you're attending a live lecture or watching one on video or the web.

Finally, we want to hear what you think. What do you like about the notes? What do you think could be improved? Please share your feedback by E-mailing us at medfeedback@kaplan. com.

Thank you for joining Kaplan Medical, and best of luck on your Step 1 exam!

Kaplan Medical

USMLE Step 1 Anatomy

(Histology, Embryology, Gross Anatomy, and Neuroscience)

KAPLAN medical

SECTION I

Histology and Cytology

1 Cell Components

NUCLEUS

The nucleus (Fig 1-1-1) is the site of deoxyribonucleic acid (DNA) replication and transcription of DNA into p reairsQrjdbonucleic acid (RNA}jnqlecules. It contains all of the enzymes required for replication and repair of newly synthesized DNA, as well as for transcription and processing of precursor RNA molecules. It is enclosed by the nuclear envelope and contains the nuclear lamina, nucleolus, and chromatin.

Nuclear Envelope

The nuclear envelope is a double membrane containing pores that are approximately 90 nm in diameter. The outer nuclear membrane is continuous with the endoplasmic **rptirnlnryi**.

Nuclear Lamina

The nuclear lamina is a latticelike network of proteins that include lamins. Lamins attach chromatin to the inner membrane of the nuclear envelope and participate in the breakdown and reformation of the nuclear envelope during the cell cycle. Phosphorylationof th[g1aT]a f[h]y lamin kinase) during prophase of mitosis initiates nuclear disassembly into small vesicles.

Nucleolus

The nucleolus is responsible for ribosomal RNA (rRNA) synthesis and ribosome assembly. It contains three morphologically distinct zones:

- **Granular zone**—found at the periphery; contains ribosomal precursor particles in various stages of assembly.
- **Fibrillar zone**—centrally located; contains ribonuclear protein fibrils.
- **Fibrillar center**—contains DNA that is not being transcribed.

Chromatin

Chromatin is a complex of DNA, histone proteins, and nonhistone proteins.

- **DNA**—a double-stranded helical molecule that carries the genetic information of the cell. It exists in three conformations: B DNA, Z DNA, and A DNA.
- **Histone proteins**—positively charged proteins enriched with lysine and arginine residues. They are important in forming two types of structures in chromatin: nucleosomes and solenoid fibers. **The nucleosomes are the basic repeating units of the chromatin fiber, having a** diameter **of approximately 10** nm.
- **Nonhistone proteins**—include enzymes involved in nuclear functions such as replication, transcription, DNA repair, and regulation of chromatin function. They are acidic or neutral proteins.

Forms of Chromatin (Fig 1-1-1)

- **Heterochromatin**—highly condensed (30-nm solenoid fibers or higher states of condensation) and **transcriptionally inactive.** In a typical eukaryotic cell, approximately 10% of the chromatin is heterochromatin. Almost the entire inactive X chromosome (Barr body) in each somatic cell in a woman is condensed into heterochromatin.
- Euchromatin—a more extended form of DNA, which is potentially **transcriptionallyactive.** In a typical cell, euchromatin accounts for approximately 90% of the total chromatin, although only about 10% is being actively transcribed in the 10-nm fiber of nucleosomes.

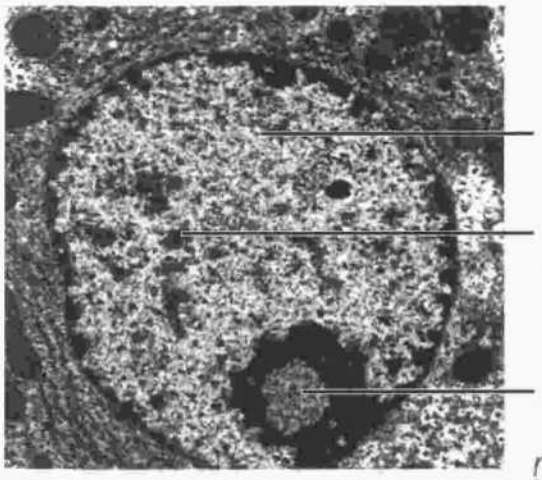


Figure 1-1-1. Nucleus

CYTOPLASM

Ribosomes

Ribosomes are composed of rRNA and protein. They consist of large (60S) and small (40S) subunits. Ribosomes are assembled in the nucleus and transported to the cytoplasm through the nuclear pores. The large ribosomal subunits are synthesized in the nucleolus, whereas the small subunits are synthesized in the nucleus.

- **Polysomes**—Ribosomes often form polysomes, which consist of a single messenger RNA (mRNA) that is being translated by several ribosomes at the same time. **The ribosomes move on the mRNA from the 5' end toward the 3' end. The two ribosomal subunits associate on themRNA, with the small** subunit **binding first.**

Forms of Ribosomes

Ribosomes exist in two forms:

- **Free polysomes** are the site of synthesis for proteins destined for the nucleus, peroxisomes, or mitochondria.
- **Membrane-associated polysomes** are the site of synthesis of secretory proteins, membrane proteins, and lysosomal enzymes.

Endoplasmic Reticulum

The endoplasmic reticulum exists in two forms, **rough_endoplasmic reticulum** (RER) and **smooth endoplasmic reticulum** (SER).

Rough Endoplasmic Reticulum f

RER is a single, lipid bilayer continuous with the outer nuclear membrane. It is organized into stacks of large flattened sacs called cisternae that are studied with ribosomes on the cytoplasmic side (Fig 1-1-2).

RER synthesizes proteins that are destined for theGolgi apparatus, secretion, the plasma membrane, an3 lysosomes. RER is very prominent in cells that are specialized in the synthesis of proteins destined for secretionje.g., pancreatic acinar cells).

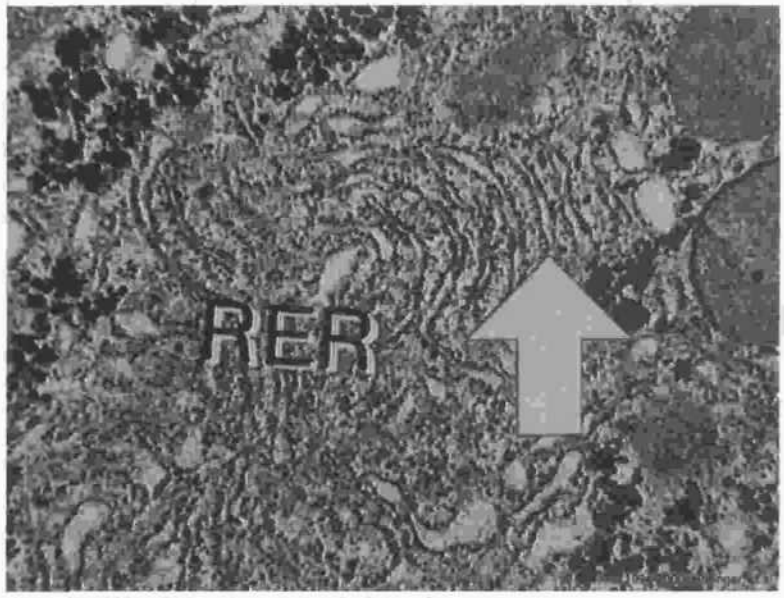


Figure 1-1-2. Rough Endoplasmic Reticulumi

Smooth Endoplasmic Reticulum ^ej-mcL <Xun±hj;.4^o

SER is a network of membranous sacs, vesicles, and tubules continuous with the RER, but lacking ribosomes (Fig 1-1-3).

SER contains £D2¥mes involved in jJi£j)iosynthesis of phospholipids, triglycerides, and sterols.

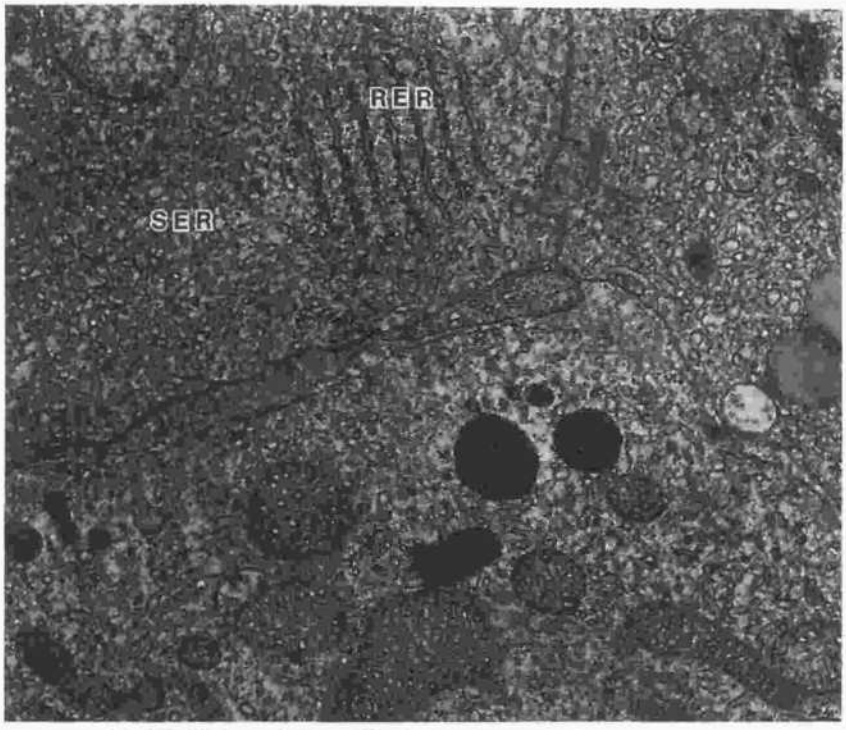


Figure 1-1-3. Human Corpus Luteum of Pregnancy

Functions of SER

Detoxification Reactions

These are reactions that make compounds water soluble so that they can be excreted. Two types of reactions that increase solubility are:

- **Hydroxylation** reactions—by way of hydroxylase complexes containing cytochrome P450 a flavoprotein, and a nonheme iron protein
- **Conjugation** reactions—the transfer of polar groups (i.e., glucuronic acid) from the active carrier UDPglucuronic acid to the toxic water-insoluble molecule

Glycogen Degradation and Gluconeogenesis

Removal of the phosphate group from glucose-6-phosphate by the enzyme glucose-6 phosphatase, an integral membrane protein of the SER. This controls the formation of free glucose from glycogen and via gluconeogenesis.

Reactions in Lipid Metabolism

Lipolysis begins in the SER with the release of a fatty acid from triglyceride. The SER also the site where lipoprotein particles are assembled.

Sequestration and Release of Calcium Ions

In striated muscle the SER is known as the **sarcoplasmic reticulum** (SR). The sequestration and release of calcium ions takes place in the SR.

Golgi

Do not confuse the Golgi apparatus with the Golgi tendon organs of the cell or any other factor bearing his name. Dr. Camillo Golgi was a prolific Italian histologist. Other structures or processes bearing his name include Golgi's silver stain for nerve cells, the cycle of Golgi for the development of the malaria parasite, the inhibitory Golgi cells of the cerebellum, and the acroblast, a part of the Golgi material of the spermatid known as the Golgi remnant.

Golgi Apparatus

The Golgi apparatus consists of disc-shaped smooth cisternae that are assembled in stacks (dictyosomes), having a diameter of approximately 1 p,m and associated with numerous small membrane-bound vesicles (Fig 1-1-4).

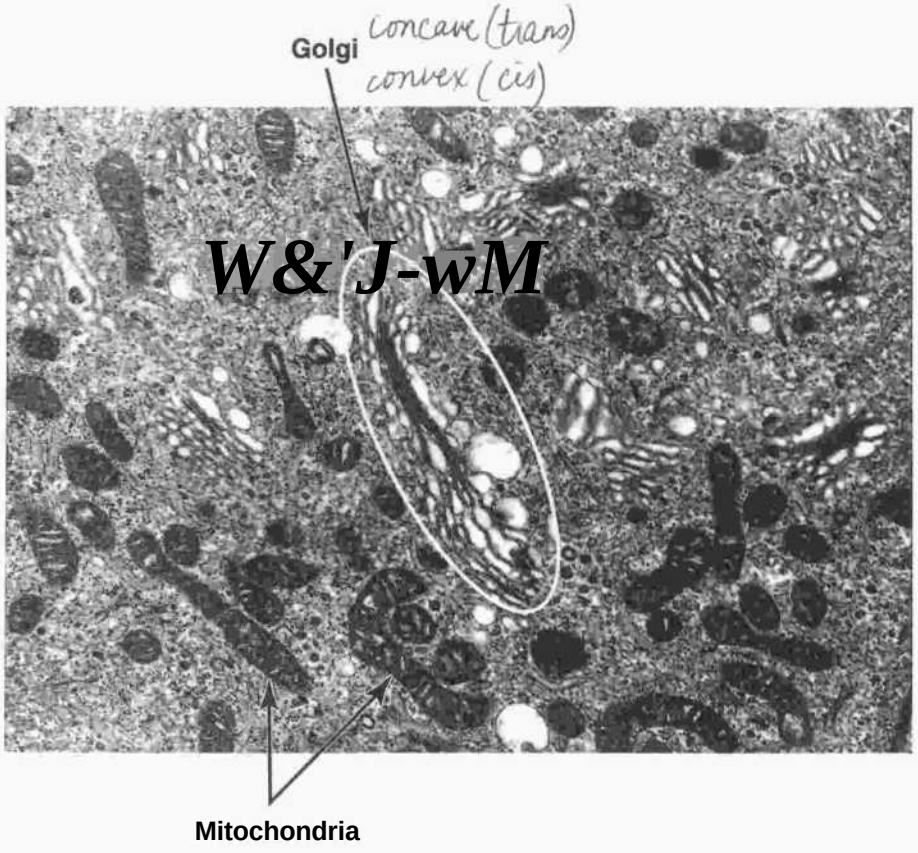


Figure 1-1-4. Cytoplasm

The Golgi apparatus has two distinct faces:

- **The cis (forming) face** is associated with the RER.
- **The trans (maturing) face** is often oriented toward the plasma membrane. The trans-most region is a network of tubular structures known as the trans-Golgi network (TGN) (Fig 1-1-5).

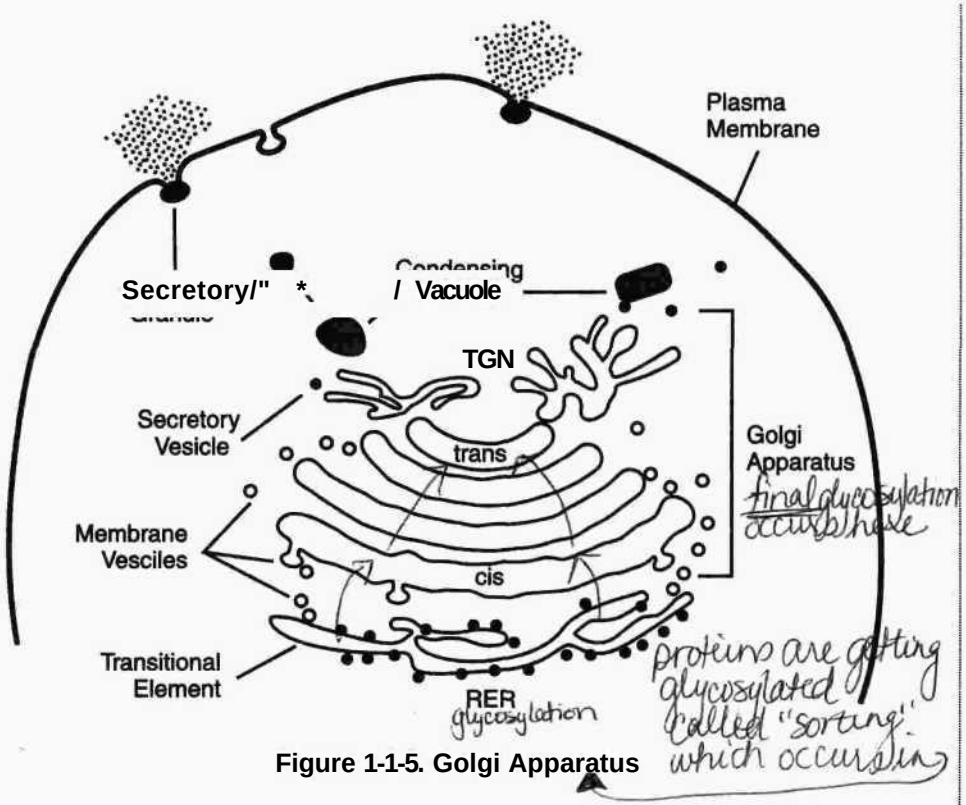


Figure 1-1-5. Golgi Apparatus

Functions of the Golgi Apparatus

Proteins and Lipids

The Golgi apparatus is the site of posttransiatinnal modification and sorting of newly synthesized proteins and lipids.

Glycoproteins

Further modification of the carbohydrate moiety of glycoproteins produces complex and hybrid oligosaccharide chains. This determines which proteins remain in the Golgi apparatus or leave the Golgi apparatus to become secretory proteins, lysosomal proteins, or part of the plasma membrane. Two diseases are caused by a breakdown in this process, I-cell disease and hyperproihsulinemia (see related box and margin note).

Clinical Correlate

HyperproInsullnemla

Hyperproinsulinemia is characterized by elevated levels of prginsulin in the serum resulting from the failyre of a peptidase to cleave proinsulin to insulin and C-peptide in the golgi apparatus. The clinical manifestations are similar to those seen in patients with noninsulin-dependent diabetes.

Clinical Correlate

I-Cell Disease

Phosphorylatlon of mannose in glycoproteins targets proteins to lysosomes. Phosphate is added in a two-step sequence of reactions that are catalyzed by /V-acetylglucosamine-phosphotransferase and /V-acetylglucosaminidases.

A deficiency in /V-acetylglucosamine-phosphotransferase results In I-cell disease (mucojjpidosis II), in which a whole family of enzymes is sent to the wrong destination. It is characterized by huge inclusion bodies in cells caused by the accumulation of undegraded glycoconjugates in lysosomes missing the hydrolases that normally degrade these macromolecules. The missing enzymes are found in the plasma and other body fluids, where they have normal levels of activity. **The absence of the mannose-gjihgsphate orrthe hydrolases results In their secretion rather than their Incorporation Into lysosomes.**

The disease results in skeletal abnormalities, coarse features, restricted joint movements, and psychomotofTetardation. Symptoms are generally noted at birth, and the life span is less than 10 years.

A somewhat less severe form of the disease with a later onset and potential survival into adulthood is called pseudo-Hurler polydystrophy.

There is no treatment for either disease, but prenatal diagnosis is available.

Lysosomes

Lysosomes are spherical membrane-enclosed organelles that are approximately 0.5 (xm in diameter and contain enzymes required for intracellular digestion (Fig 1-1-6).

Lysosomes consist of two forms:

- **Primary lysosomes** have not yet acquired the materials to be digested. They are formed by budding from the trans side of the Golgi apparatus.
- Secondary lysosomes are formed by the fusion of the primary lysosome with the substrate to be degraded and have contents that are in various stages of degradation.

Lysosomes contain approximately 60 hydrolytic enzymes. These include nucjg; ases for degrading DNA and RNA, Upases for degrading Upids, glycgsidases jbr degrading glycoconjugates (glvcoprofeins, proteoglycans$_T$-and.glycoUpids), gro_-teases and peptidases for degrading proteins, and a varietyjotphosp^atases.

- All lysosomal enzymes are acid hydrolases, with optimal activity at a pH of approximately *5l).*
- The synthesis of the lyso§omd4iydrQlasesoccurs in the RER; the hydrolases aretransferrejQajhg_Golgi apparatusTwHeTTthey are modified and packaged into lysosomes.

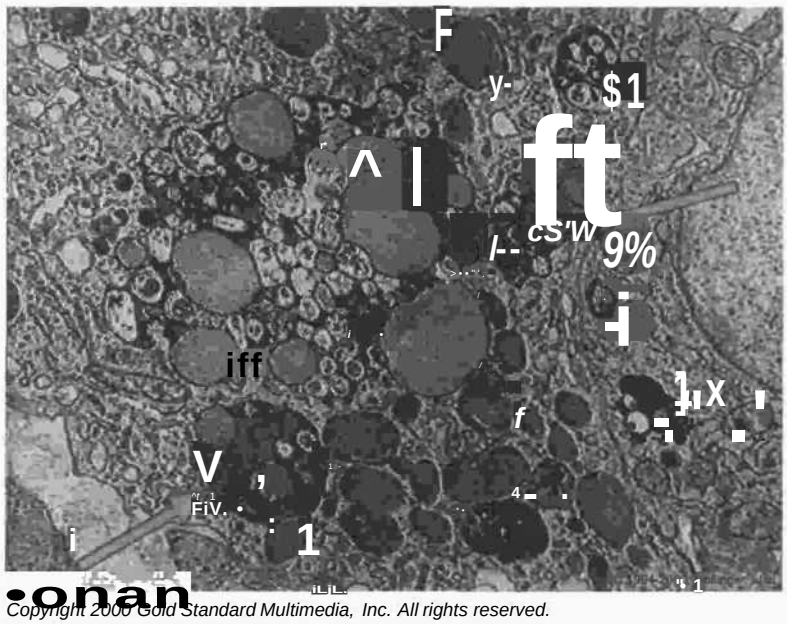


Figure 1-1-6. Lysosomes

Peroxisomes

Peroxisomes are a heterogeneous group of small, spherical organelles with a single membrane and a diameter that ranges from approximately 0.15 to 0.5 |xm (Fig 1-1-7).

Peroxisomes contain a number of enzymes that transfer hydrogen atoms from organic substrates (urate, D-amino acids, and very long chain fatty acids) to molgcular_oxygen_vvith the formation of hydrogen peroxide. Catalase, the major peroxisomal protein, degrades the hydrogen peroxide to water and oxygen.

Peroxisomal enzymes are synthesized on free polysomes. After translation, the enzymes are incorporated directly into peroxisomes.

Peroxisomes have several functions:

- Synthesis and degradation of hydrogen peroxide
- ^Oxidation_of_xeryilpng chain fatty acids (> C24) starts in the peroxisome and proceeds until the carbon chain has been reduced to a length of approximately 10 carbons. Oxidation of the residual 10 carbons is completed in the mitochondria.
- Phospholipid exchange—peroxisomes contain enzymes that convert phosphatidylserine and phosphatidylethanoiarnine.
- Bile acid synthesis

Clinical Correlate

Peroxisome Deficiency

Several genetic diseases are associated with the impairment or absence of peroxisomes. These patients fail to oxidize very long chain fatty acids and accumulate bile acid precursors. The four most common disorders are:

- Zellweger (cerebrohepatorenal) syndrome
- Neonatal adrenoleukodystrophy
- Infantile Refsum disease
- Hyperpipecolatemia

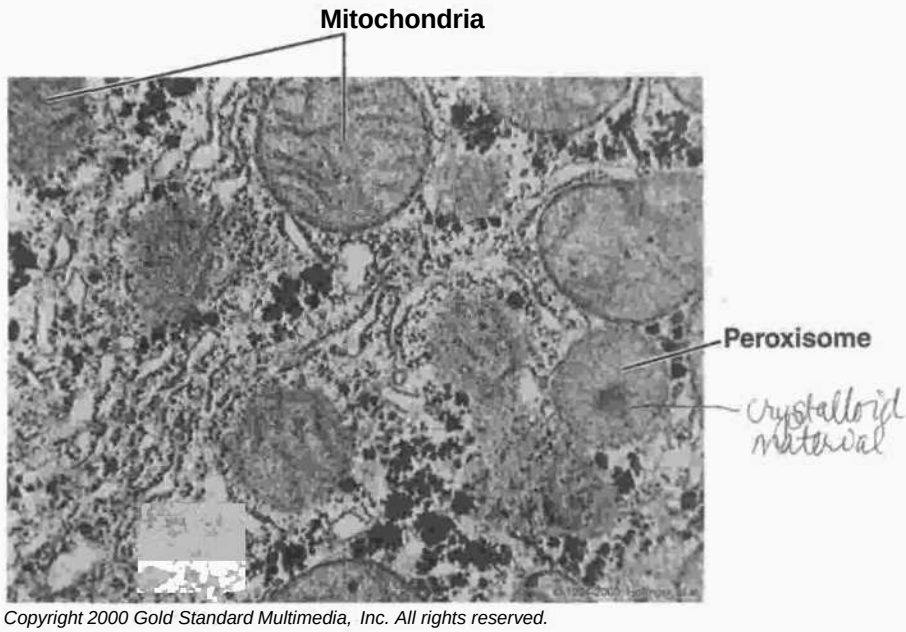


Figure 1-1-7. The Peroxisome

Mitochondria

Mitochondria have two membranes with a width of about 0.5 urn, and a length that can vary from 1 to 10 u.m (Fig 1-1-8). They synthesizejidenosine triphosphate (ATP), contain their own double-stranded circular DNA, and make some of their own proteins. Mitochondria have several compartments.

Outer Membrane

The outer membrane is smooth, continuous, and highly permeable. It contains an abundance of porin, an integral membrane protein that forms channels in the outer membrane through which molecules of less than 10 kD can pass.

Inner Membrane

The inner membrane is inagejgjgafcile to most small ions (Na^+, K^+, H^+) and small molecules (ATP, adenosine diphosphate, pyruvate). The impermeability is likely related to the high content of the lipid cardiolipin.

- The inner membrane has numerous infoldings, called **cristae.** The cristae greatly increase the total surface area. They **contamthe engyjnes for electron transport and oxidative phosphorylation.** *•fftrtypff&ALO*
- The number of mitochondria and the number of cristae per mitochondrion are proportional to the metabolic activity of the cells in which they reside.

Intermembrane Compartment

The intermembrane compartment is the space between the inner and outer

membranes. It contains enzymes that use ATP to phosphorylate other nucleotides (creatine phosphokinase and adenylate kinase).

Matrix

The matrix is enclosed by the inner membrane and contains:

* Dehydrogenases—oxidize many of the substrates in the cell (pyruvate, amino acids, fatty acids), generating reduced nicotinamide adenine dinucleotide (NADH) and reduced flavin adenine dinucleotide ($FADH_9$) for use by the electron transport chain and energy generation.
- A double-stranded circular DNA genome—encodes a few of the mitochondria! proteins. Mitochondrial DNA is always inherited from the mother, resulting in thp rnatprnaLtrgnsmission or disease¥of energy metabolism.
- RNA, proteins, and rjhnspTnps—although there is some protein synthesis, most mitochondrial proteins are synthesized in the cytoplasm and are transferred into the mitochondria.
- Intramitochondrial granules—contain calcium and magnesium. Their function is not known, but it is believed that they may represent a storage site for calcium.

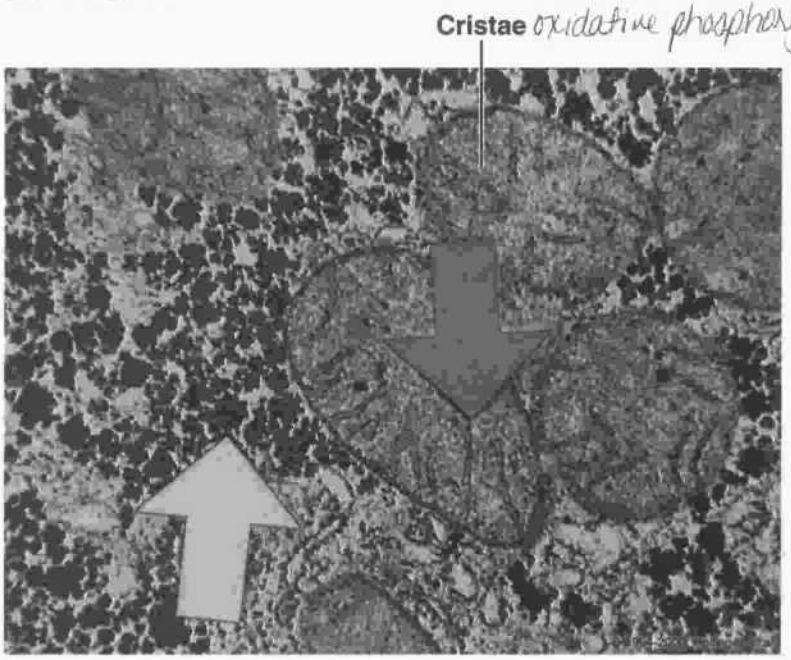


Figure 1-1-8. Mitochondriaip

Cytoskeleton

The cytoskeleton provides a supportive network of tubules and filaments in the cytoplasm of eukaryotic cells. It is composed of microtubules, intermediate filaments, and microfilaments.

Clinical Correlate

Chédiak-Higashi syndrome

Jghediakjjigashi-sypdipme is characterized by a defect in minrntiihnlfi-pnjyjnfiri7gtipn. This leads to defects in cytoplasmic granules including:

- Delayed fusion of phagosomes with lysosomes in leukocytes, thus preyeotiog-pbagocyjosis of bacteria.
- Increased fusion of melanosomes in melanocytes, leading to albinism.
- Granujajixleiects4aiiatural killer cells and platelets.

Clinical Correlate

Actin-Binding **Drugs**

Actin-binding drugs (e.g., cytochalasin B) can interfere with the polymerization-depolymerization cycle of microfilaments. Processes such as endocytosis, phagocytosis, cytokinesis, and cytoplasmic and amoeboid movements are all inhibited by cytochalasin B.

Microtubules

Microtubules are polymers of tubulin that undergo rapid assembly and disassembly. They are found in the cytoplasmic matrix of all eukaryotic cells.

Tubulin

The major component of microtubules is tubulin, a protein dimer composed of two different polypeptides, a-tubulin and fj-tubulin.

Polymerization of tubulin to form microtubules is accomplished by microtubule organizing centers and two types of accessory proteins, tau proteins and microtubule-associated proteins. Microtubules grow from the organizing centers. Calcium ions can block or reverse polymerization.

Microtubules play a role in:

- Chromosomal movement during meiosis and mitosis. **Microtubule assembly is an important eventinspindle formationr~**
- Intracellular vesicle and organelle transport. Two specific microtubule-dependent ATPases, **kinesin and dynein,** are involved in generating the force that drives-teanspQrt, with the microtubular structure playing a more passive role in intracellular transport.
- Ciliary and flagellarmoyement.

IntermediateFilaments

Intermediate filaments are intermediate in thickness (10-nm diameter) between microtubules and microfilaments. They function primarily in structural roles and contain several types of tissue-specific proteins:

- **Cytokeratins**—found in epithelial tissue
- **Desmin**—found in smooth muscle; Z disks of skeletal and cardiac muscle
- **Vimentin**—found in cells of mesenchymal origin (endothelial cells, fibroblasts, chondroblasts, vascular smooth muscle)
- Neurofilaments—found in neurons
- dial **fibrillary acidic protein** (GFA)—found in astrocytes

Microfilaments

Microfilaments have a diameter of 6 nm and are composed of **actin.** Each actin filament (F-actin) consists of two strands of actin twisted into a helical pattern with 13.5 molecules of globular actin (G-actin) per turn of the helix.

Two types of movement are associated with microfilaments:

- Local movement takes advantage of the polymerization and depolymerization properties of microfilaments.
- Sliding filament movement is generated by the interaction of actin filaments with myosin filaments.

CELL SURFACE

Basement Membrane

The basement membrane is a sheetlike structure that underlies virtually all epithelia. It consists of the following:

- **Basal** lamina—composed of type IV collagen, glycoproteins (e.g., laminin), and proteoglycans (e.g., heparan sulfate) (Fig 1-1-9).
- **Reticular lamina**—composed of delicate reticular fibers.

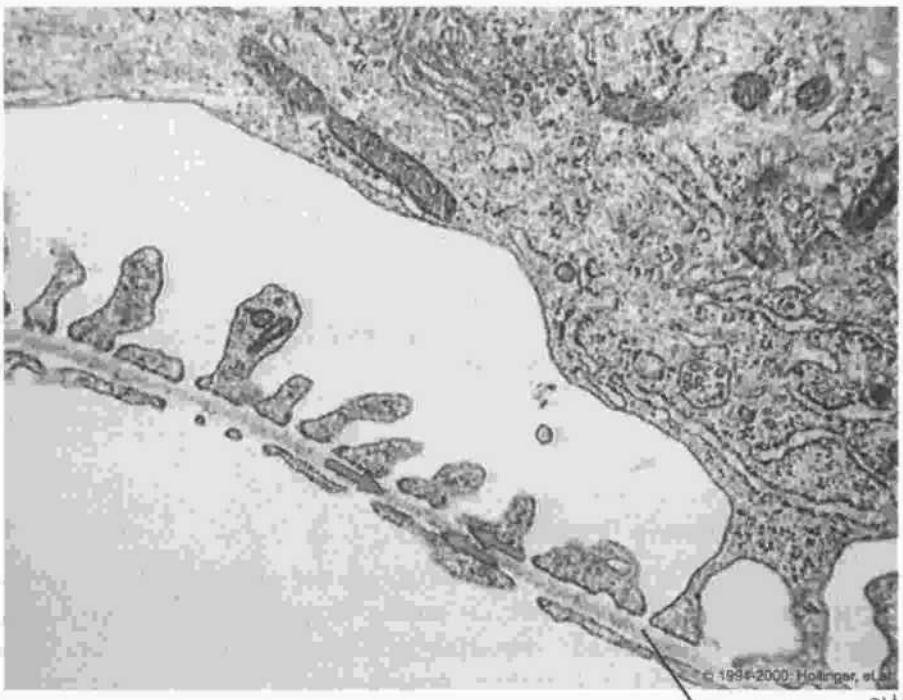


Figure 1-1-9. Basal Lamina

Lateral Surface Specializations

The lateral surface specializations are illustrated in Figure 1-1-10.

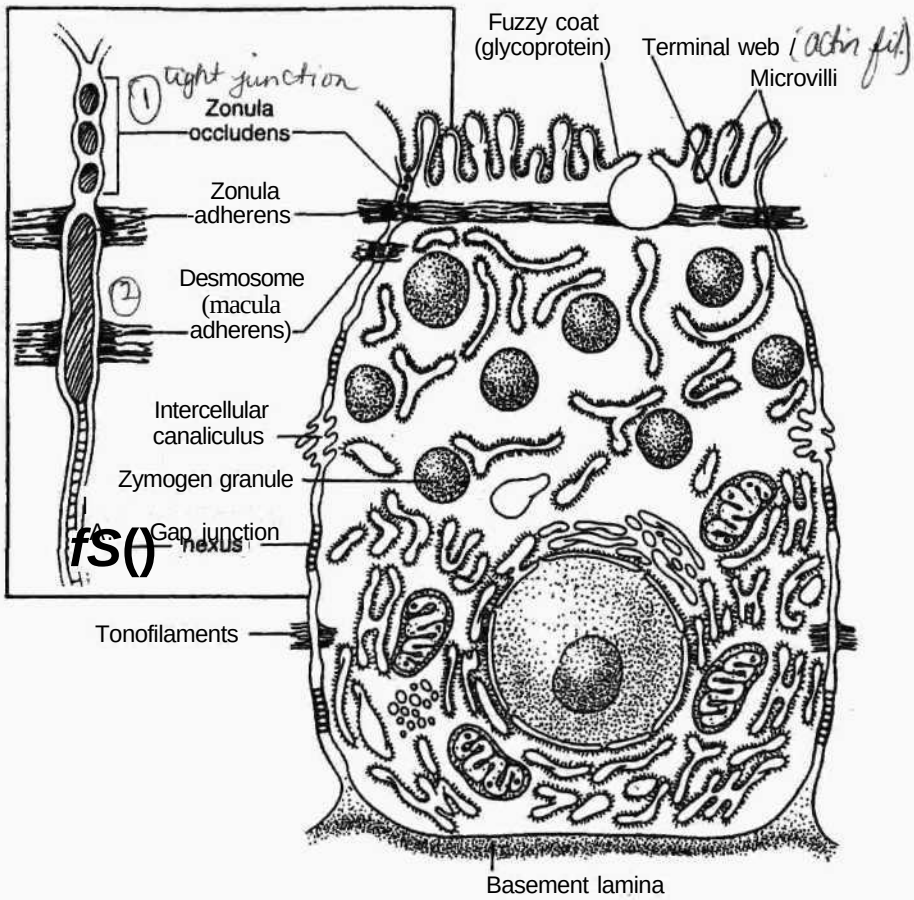


Figure 1-1-10. Surface Specializations Found on Simple Columnar Epithelial Cells

Tight Junction (Zonula Occludens)

The tight junction is formed by the fusion of opposed cell membranes (Figs 1-1-10). These ridges of fusion present as "sealing strands" seen in freeze-fracture replicas (Fig 1-1-11). It extends completely around the apical cell borders to seal the underlying intercellular clefts from contact with the outside environment. It constitutes the anatomic component of many barriers in the body.

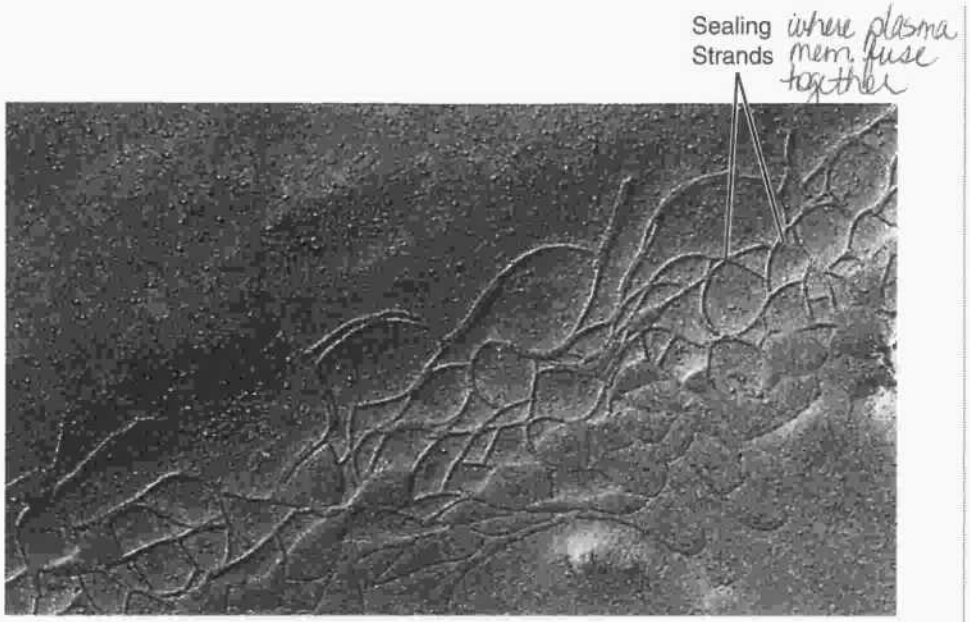


Figure 1-1-11. Freeze-Fracture Replica of a Tight Junction

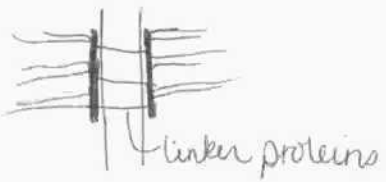
Zonula Adherens

A zonula adherens (adherent junction) often lies basal to the zonula occludens (Fig 1-1-10). It is a bandlike junction that serves in the attachment of adjacent epithelial cells.

Desmosome *odAn^urn/*[1] (^ ^p^w^muj rMMxeU* qf, <l,

The desmosome (macula adherens) is formed by the juxtaposition of two disk-shaped plaques contained within the cytoplasm of each adjacent cell (Fig 1-1-12).

- **Intermediate filaments** (tonofilaments) radiate away from the plaques (not seen in Fig I-1-11). These intermediate filaments are anchored by desmoplakins (plaques) that also bind to transmembrane linker proteins, linking adjacent cells.
- **Desmosomes** are most common in lining membranes, are subject to wear and tear, and are considered spot welds that hold cells together.



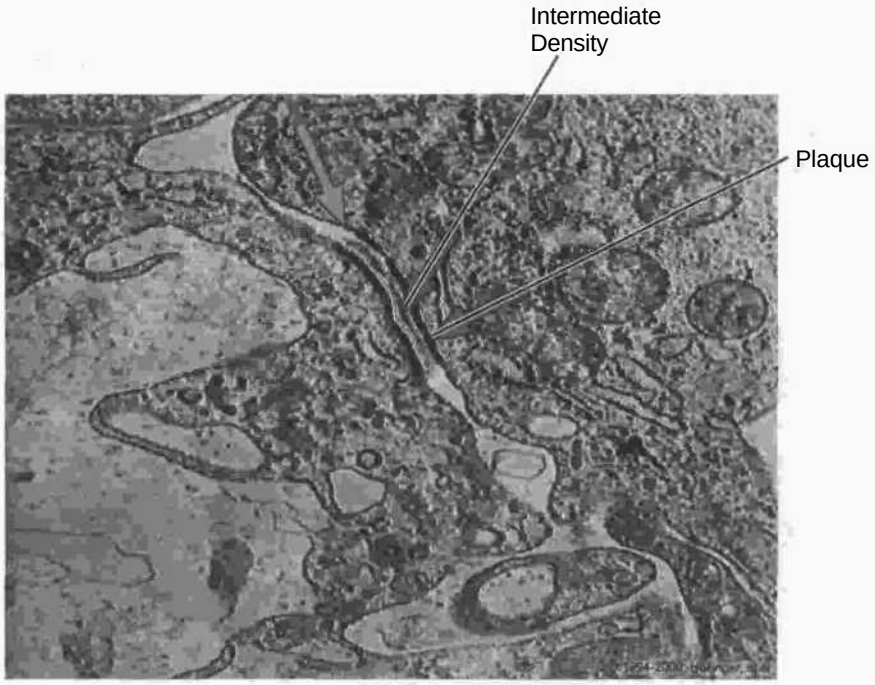


Figure 1-1-12. Desmosome

GapJunctionCMnvyuuu^,^^ f ^ ^ c a ^ % L ^)

The gap junction is an area of gommupjcation between adjacent cells that allows the passage of very small particles ancTlons across a small intercellular gap within the junction (Fig 1-1-13).

The gap junction consists of a hexagonal lattice of tubular protein subunits called **connexons,** which form hydrophilic^hannels connecting the cytoplasm of adjacenT ceDs (Fig 1-1-14). **This permits the direct passage of ions and small molecules between cells to conduct electrical impulses.**

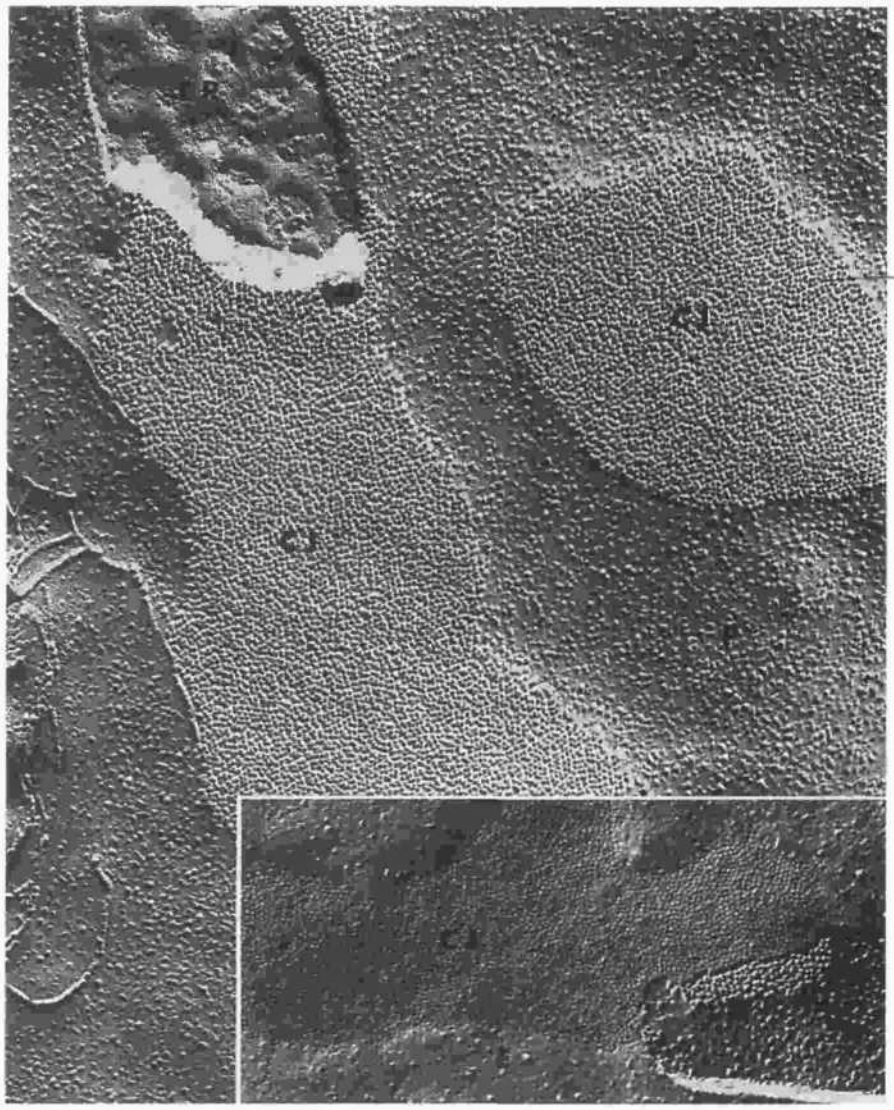
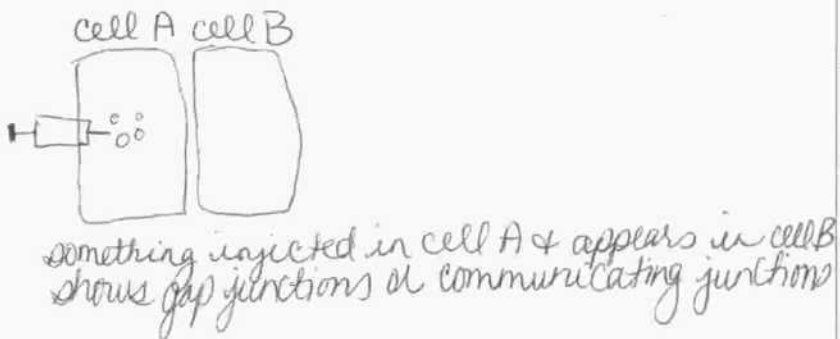


Figure 1-1-13. Freeze-Fracture Replica of a Gap (Communicating) Junction (CJ)



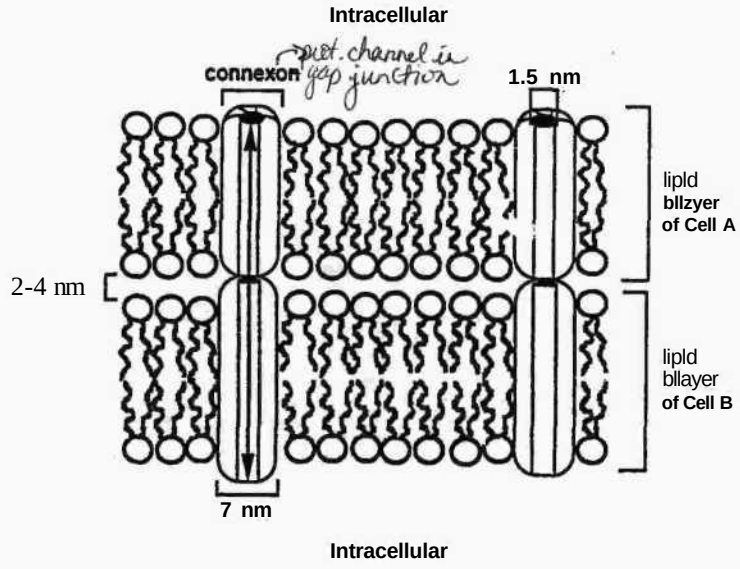


Figure 1-1-14. Gap Junctions

Apical (Free) Surface Specializations

Microvilli *jforrifo %Ao&Aj&h'o7^*

Microvilli are apical cell surface evaginations of cell membranes that function to increase the cell surface area available for absorption (Fig 1-1-15). A thick glycocalyx coat covers them. The core of each microvillus contains actin microfilaments. It is anchored in the apical cell cytoplasm to the terminal web, which itself is anchored to the zonula adherens of the cell membrane.

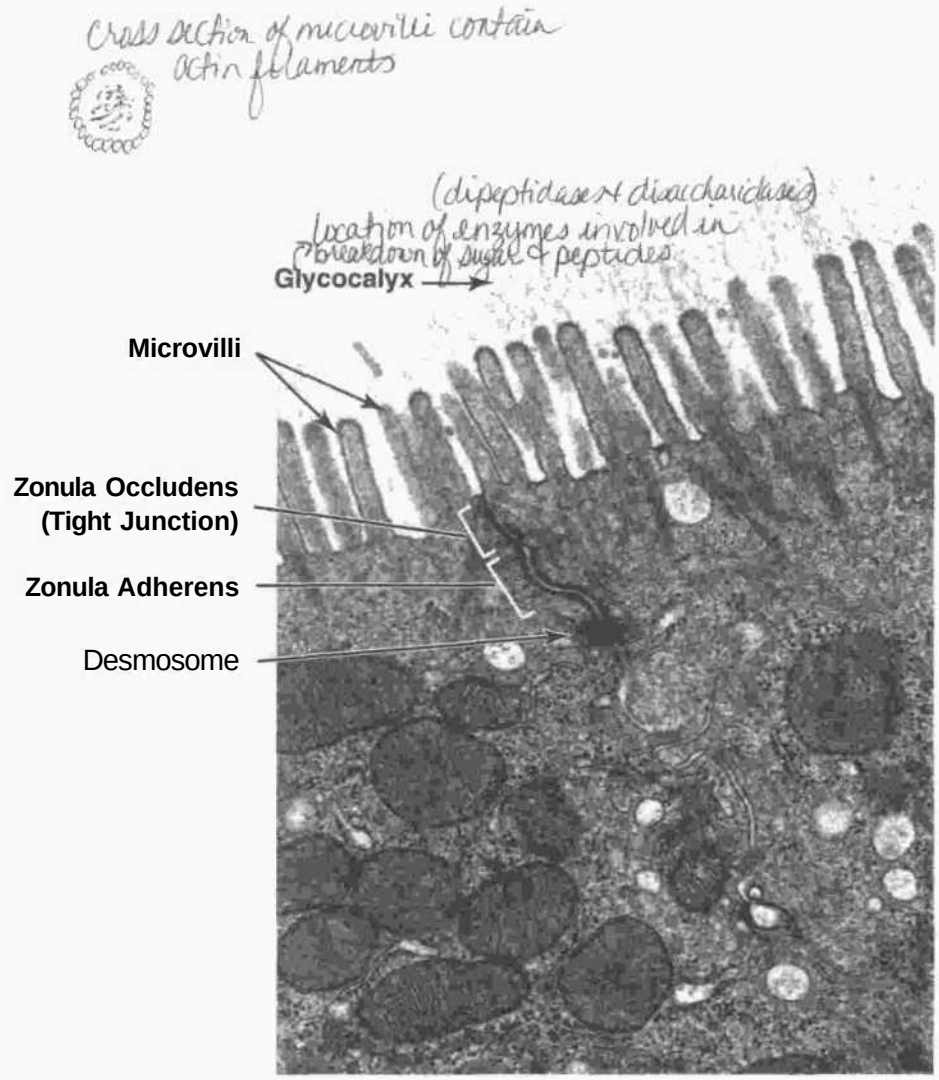


Figure 1-1-15. Apical Cell Surface/Cell Junctions

Note

Stereocilia are elongated microvilli found at the apices of cells lining the epididymis, ductus deferens, and hair cells of the inner ear, where they play a role in auditory sensation.

Note

Flagella are longer than cilia but have the same microstructure; a prominent example is in the sperm, where the single flagellum provides motility.

Clinical Correlate

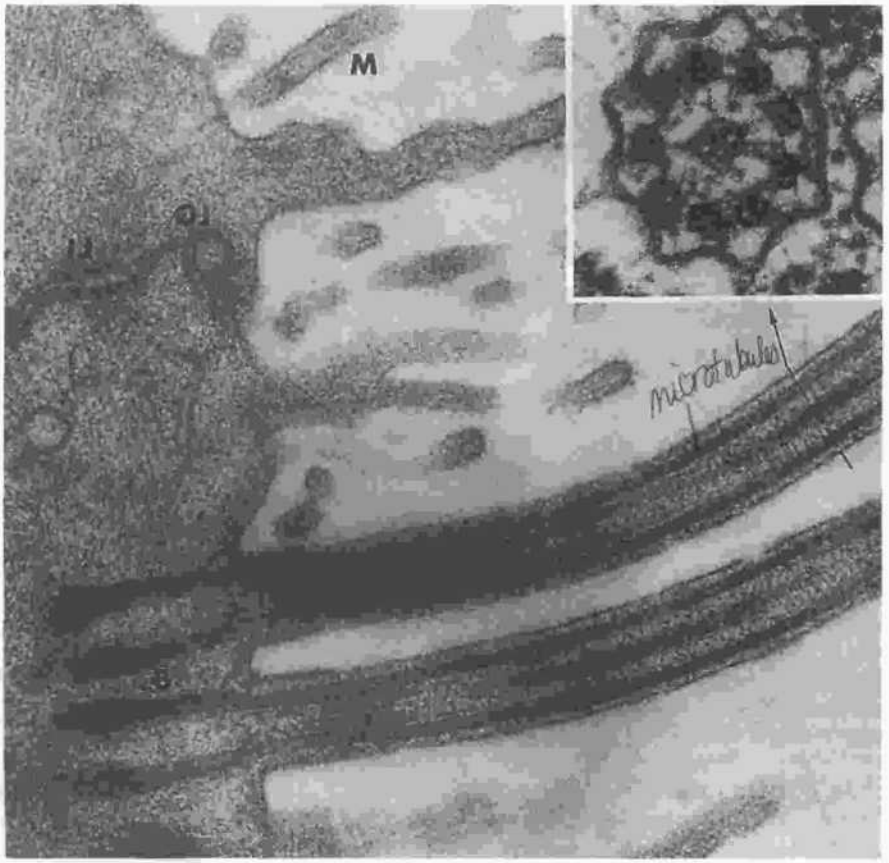
Kartagener's Syndrome

Absent or aberrant dynein arms are found in the cilia and flagella of individuals suffering from Kartagener's syndrome (a subset of immotile cilia syndrome). Such individuals often have chronic sinusitis and bronchiectasis as well as infertility and, in some cases, situs inversus.

Cilia

Cilia are apical cell surface projections of cell membrane that contain microtubules (Figs 1-1-16 and 1-1-17). They are inserted on centriole-like basal bodies present below the membrane surface at the apical pole.

Cilia contain two central microtubules surrounded by a circle of nine peripheral microtubule doublets. The peripheral doublets are fused so that they share a common tubule wall and form two subtubules, A and B. Adjacent doublets are connected to one another by **nexin** links (Fig 1-1-17).



B = Basal Body
IJ = Intermediate Junction
M = Microvillus
OJ = Occluding Junction

Figure 1-1-16. Cilia

9 in periphery
2 in center

if defective cilia will not move

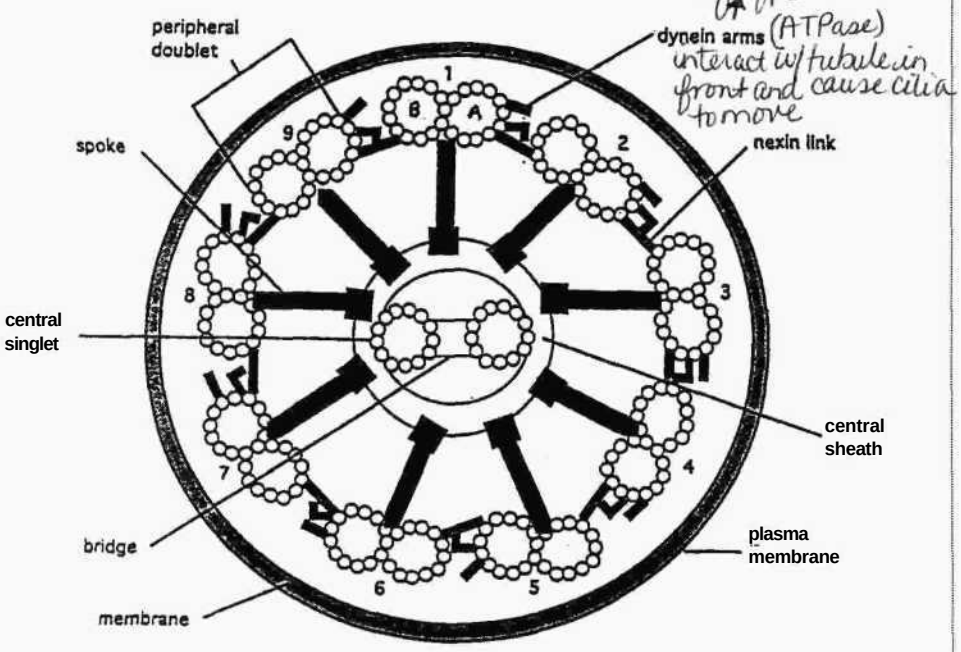


Figure 1-1-17. Structure of the Axoneme of a Cilium

Movement of Cilia

A pair of dynein arms is attached to each A subtubule. The arms bind to ATP and rearrange themselves so that a binding site for the B subtubule in the tip of the arm is exposed. The B tubule interacts with the binding site, causing the arm to snap back and movement to occur. Each cycle of a single dynein arm slides adjacent doublets 10 nm past each other.

plia move back and forth to propel fluid and particles in one direction. They are imporlajitin_filearing jnucus from the respiratory tract.

Nervous Tissue

2

NEURONS

Neurons are composed of three basic parts: the cell body (soma or perikaryon); the dendrites, which receive information from other neurons; and a single axon, which conducts electrical impulses away from the cell body (Fig 1-2-1).

Cell Body

The cell body contains a large vesicular nucleus with a single prominent nucleolus, mitochondria, and other organelles. It has abundant RER, reflecting high rates of protein synthesis. At the light microscopic level, the RER stains intensely with basic dyes and is referred to as Nissl substance.

Microtubules and neurofilaments contribute to the neuronal cytoskeleton and play important roles in axonal transport. Pigment granules such as lipofuscin ("wear and tear" pigment) and melanin (found in some catecholamine-containing neurons) may be seen in the cytoplasm.

Dendrites

Dendrites are neuronal processes that receive information and transmit it to the cell body. Extensive dendritic branching serves to increase the receptive area of the neuron.

Axons

Axons are thin, cylindrical processes typically arising from the perikaryon (or from a proximal dendrite) through a short pyramidal-shaped region called the axon hillock. The cell membrane of the axon is called the axolemma, and the cytoplasm of the axon is called the axoplasm.

Axonal Transport

Axons contain abundant microtubules and neurofilaments. Axon fast transport uses microtubules. It proceeds in both anterograde and retrograde directions. Anterograde transport is powered by kinesins, whereas retrograde transport is powered by **dynein.**

Synaptic Boutons

Axons terminate in specialized endings known as synaptic boutons, which contain synaptic vesicles full of neurotransmitter.

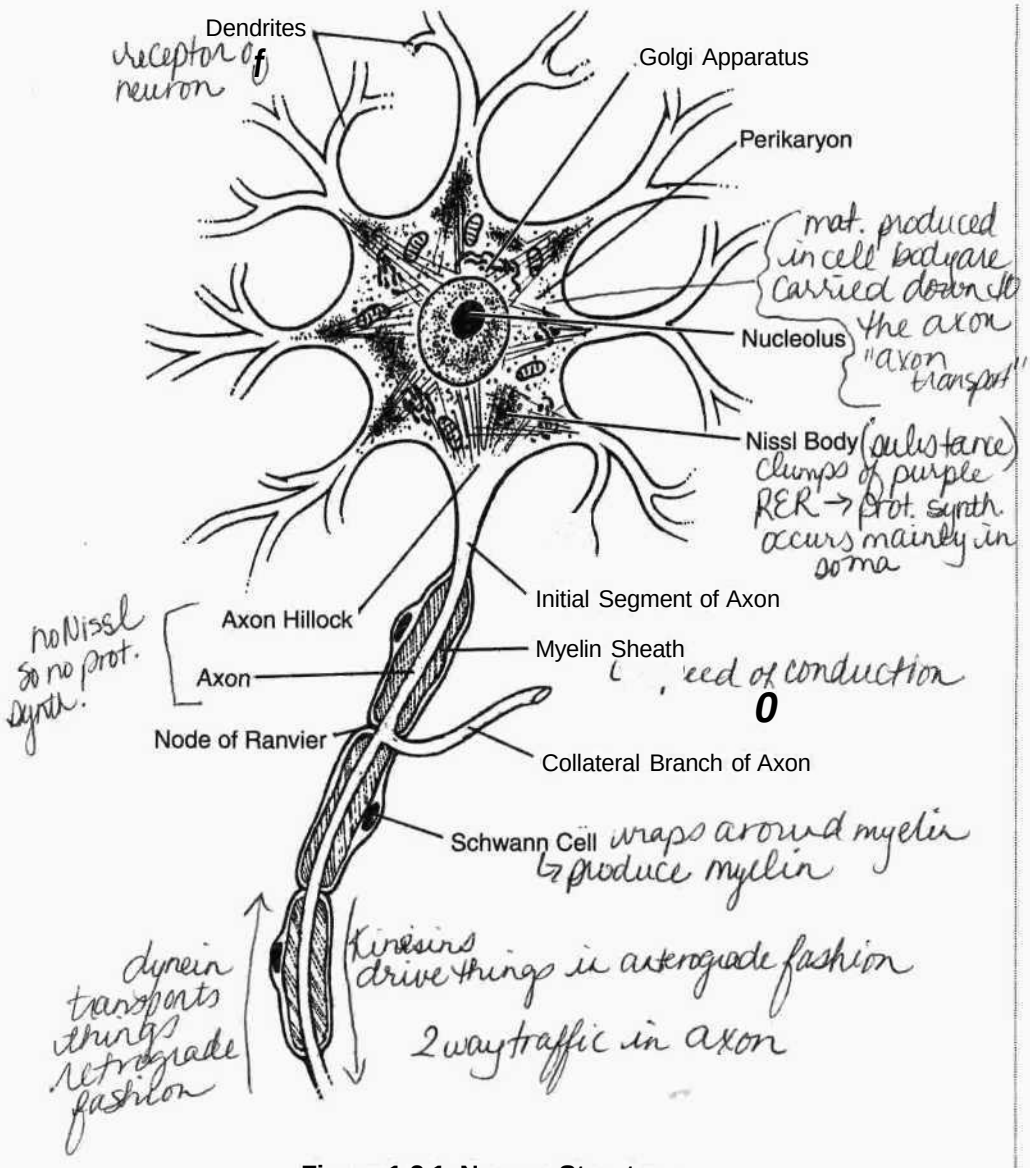


Figure 1-2-1. Neuron Structure

Myelin M

Axons may be unmyelinated or myelinated, depending on the type of covering provided by their supporting cells.

Unmyelinated Axons

Unmyelinated axons in peripheral nerves are surrounded by the cytoplasm of Schwann cells.

- These axons have a small diameter and a relatively slow conduction velocity.
- A single Schwann cell may ensheath several axons.

Clinical Correlate

The degeneration of oligodendrocytes results in many of the so-called demyelinating disorders, such as multiple sclerosis.

Myelinated Axons

Myelinated axons are larger in diameter and are ensheathed in myelin (Fig 1-2-2).

Schwann cells are the myelin-forming cells of the peripheral nervous system (PNS). Myelination in the PNS begins during the fourth month of development. One Schwann cell will myelinate only one axan in peripheral nerves.

Oligodendrocytes are the myelin-forming cells of the central nervous system (CNS). In the CNS, myelination begins during the fourth month of development and continues into the second decade of life. **An individual oligodendrocyte is able to myelinate many axons.**

Node of Ranvier

At the junction between two myelin-producing cells, there is a discontinuity in the myelin. This creates a "collar" of naked axon, called a node of Ranvier, which is exposed to the extracellular space (Fig 1-2-1). **The action potential slaps from node to node in a process called saltatory conduction.** Myelinated axons conduct action potentials rapidly.

Composition

Because myeh'n is of membrane origin, it is rich in phospholipids and cholesterol.

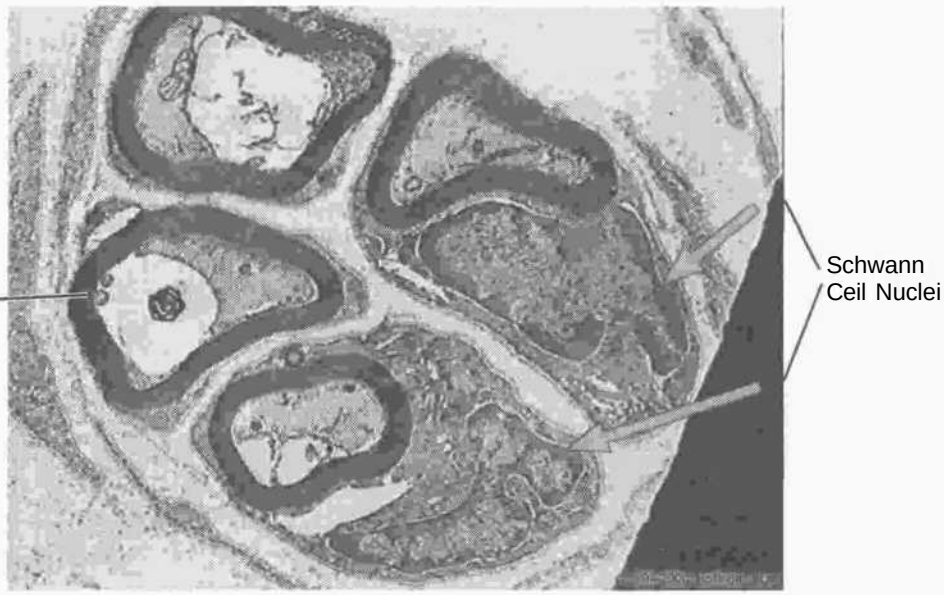


Figure 1-2-2. Axons Cut in Cross Section

Classification of Neurons by Neuronal Processes

Unipolar Neurons

Unipolar neurons have one axon and no dendrites and probably occur only during development.

Pseudounipolar Neurons

Pseudounipolar neurons have a single process close to the perikaryon, which divides into two branches. One branch extends to a peripheral ending, and the other extends to the CNS. Pseudounipolar neurons are found in dorsal root ganglia and most cranial ganglia.

Bipolar Neurons

Bipolar neurons have one axon and one dendrite. Bipolar neurons are found in the cochlear and vestibular ganglia as well as in the retina and olfactory mucosa.

Multipolar Neurons

Multipolar neurons have one axon and multiple dendrites. Most neurons in the body are multipolar (e.g., ventral horn neurons in the spinal cord).

Classification of Neurons by Functional Role

Motor Neurons

Motor neurons control effector organs and muscle fibers.

Sensory Neurons

Sensory neurons receive sensory stimuli from the internal or external environment and relay them to the CNS.

Synapses

Synapses are specialized membrane junctions designed for the unidirectional communication between neurons or between neurons and effector cells (Fig 1-2-3). The pre- and postsynaptic membranes are separated by only 20 nm; this space is called the synaptic cleft.

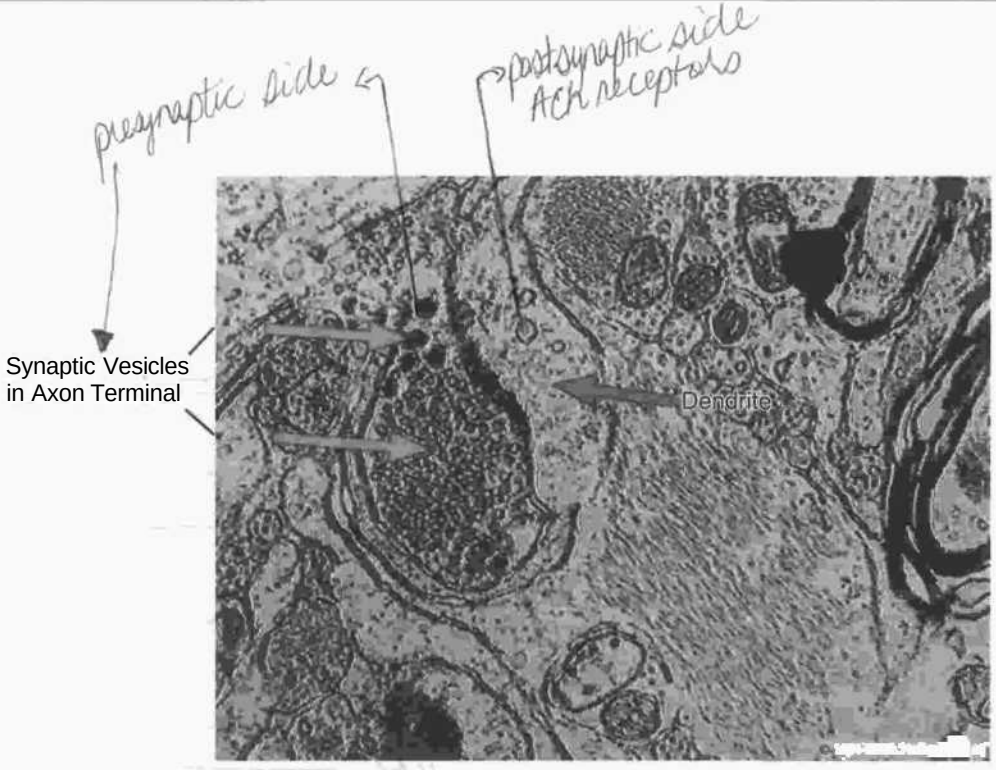


Figure 1-2-3. Axodendritic Synapse

Location

Synapses are either between an axon and a dendrite (axodendritic) or between an axon and a cell body (axosomatic). Synapses between dendrites (dendrodendritic) and between axons (axoaxonic) also occur.

Synaptic Vesicles

Synapses contain synaptic vesicles. They consist of 30- to 50-|xm spherical or ovoid structures in the axoplasm that contain neurotransmitter (e.g., acetylcholine [ACh]). Neurotransmitter is released into the synaptic deft at the synapse when synaptic vesicles fuse with the presynaptic membrane.

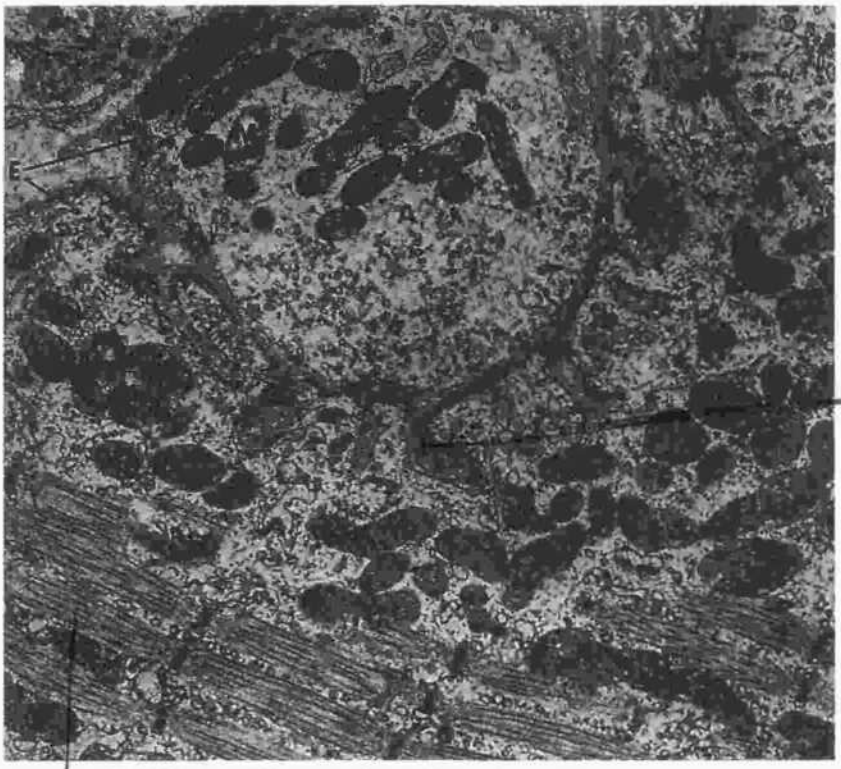
- Neurotransmitters may either excite (depolarize) or inhibit (hyperpolarize) the postsynaptic membrane, depending on the type of receptor to which it binds.
- Certain neurotransmitters are inactivated in the synaptic cleft by enzymatic degradation (e.g., ACh is broken down by acetylcholinesterase [AChE]), whereas others are taken up by the presynaptic cell (e.g., norepinephrine) in a process called reuptake.

Neuromuscular Junction

The neuromuscular junction occurs at the motor end plate. It is the synapse between neurons and muscle cells (Fig 1-2-4).

At the neuromuscular junction, the axon forms a number of small branches that fit into groves on the muscle where the postsynaptic membrane is convoluted into numerous folds, called the subneural clefts.

ACh released from the axon depolarizes the sarcolemma via the acetylcholine nicotinic receptors.



A = Axoral Terminal
M = Mitochondria
E = Basal Lamina

Figure **1-2-4. Portion of a Motor End Plate along a** Skeletal Muscle Fiber

Clinical Correlate

Myasthenia Gravis

Myasthenia gravis is a disease characterized by weakness and easy fatigue of muscles. It can be life threatening if swallowing and breathing is affected. It is caused by an autoimmune response to the ACh receptor. Normally, old receptors are constantly removed by endocytosis and transported to and degraded by the lysosomes. These are replaced by new receptors, which are manufactured by the Golgi apparatus and then inserted into the junctional folds. The normal half-life of a receptor is about 10 days. In myasthenia gravis, the half-life is reduced to about 2 days, resulting in a marked decrease in the number of available receptors.

Administration of AChE inhibitors has both diagnostic and therapeutic value. By slowing the rate of ACh degradation, they increase the binding time of ACh to the remaining receptors. The usual response is prompt improvement in muscle power. An original clinical diagnosis of myasthenia gravis becomes questionable should no improvement be observed.

NEUROGLIA

Neuroglia (nerve glue) serve as the connective tissue cells of the nervous system. Although they do not generate or transmit neural impulses, they play an important role in the normal functioning of the nervous system. They form the myelin sheaths of axons and provide metabolic support to neurons. Neuroglia of the CNS include microglia, astrocytes, oligodendrocytes, and ependymal cells. In the PNS, neuroglia cells consist of Schwann cells.

Astrocytes

Astrocytes are the largest of the neuroglial cells. They have centrally located nuclei and numerous long processes with expanded vascular end-feet, or pedicels, which attach to the walls of blood capillaries.

Astrocytes are important in controlling the microenvironment of nerve cells and participate in the maintenance of the blood-brain barrier.

Oligodendrocytes

Oligodendrocytes have small nuclei and contain abundant mitochondria, ribosomes, and microtubules.

Oligodendrocytes myelinate axons in the CNS.

Microglia

Microglia are small, deiree, elongated cells with elongated nuclei. They originate from the mesoderm, unlike other neuroglial cells, which originate from the neuroectodeim

Microglia are phagocytic and are part of the **mononudear phagocyte system.**

Ependymal Cells

Ependymal cells line the ventricular cavities of the brain and the central canal of the spinal cord. They are capable of mitosis and can develop long processes that deeply penetrate the neural tissue.

Cilia on the ependymal cells help move cerebrospinalfluidArough the ventricles.

Schwann Cells

Schwann cells contain elongated nuclei that lie parallel to the axons of peripheral neurons.

Schwann cells myelinate peripheral axons.

Muscle Tissue

3

GENERAL FEATURES

Muscle is classified as skeletal, cardiac, or smooth. Some general features of all three types of muscle are summarized in Table 1-3-1.

Table 1-3-1. General Cytologic Features of the Three Types of Muscle

Skeletal	Cardiac	Smooth
Striated, unbranched fibers	Striated, branched fibers	Nonstriated, fusiform fibers
Multinuclear	Single nucleus	Single nucleus
Strong, quick, discontinuous, voluntary contraction	Strong, quick, continuous, involuntary contraction	Weak, slow, involuntary contraction

SKELETAL MUSCLE

General Features

A gross view of skeletal muscle and the connective tissue (CT) investments are demonstrated in Figure 1-3-1. Note the three levels of connective tissue:

- **Endomysium**—CT that surrounds individual muscle fibers
- **Perimysium**—CT that surrounds groups (fascicles) of muscle fibers
- Epimysium—CT that surrounds the entire muscle

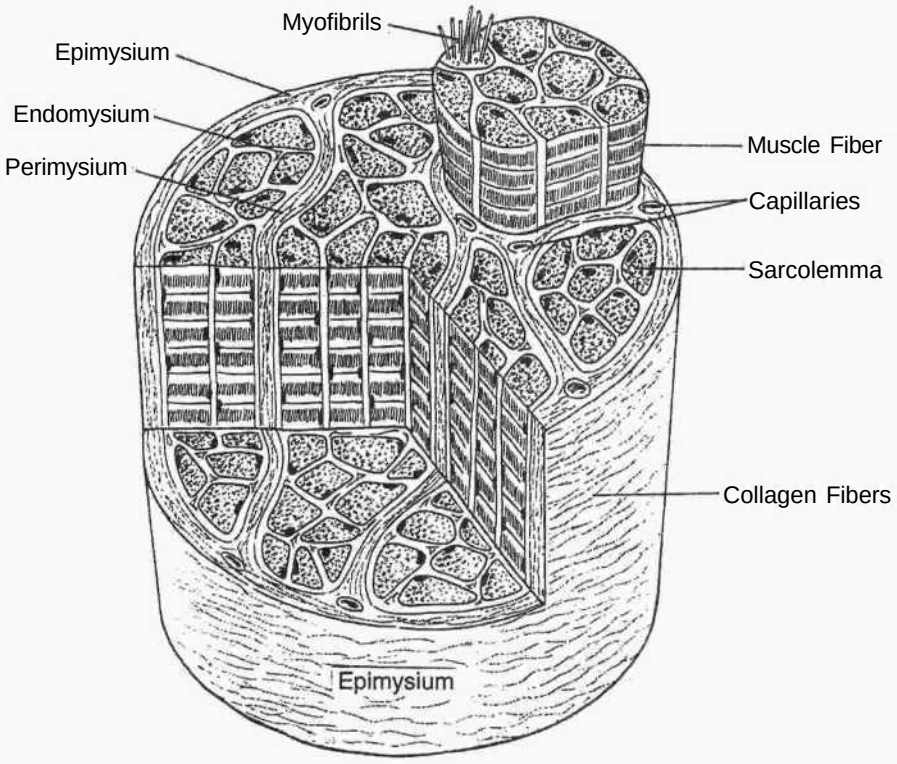


Figure 1-3-1. Connective Tissue Investments of a Striated Skeletal Muscle

Fibers

Skeletal muscle fibers consist of long cylindrical fibers with multiple ovoid nuclei located peripherally beneath the sarcolemma (plasma membrane) and with striations composed of alternating dark and light bands.

- The dark bands are called A bands because they are anisotropic (birefringent) in polarized light. In the center of the A band a paler region, the H band, is seen in relaxed muscle.
- The light bands are called I bands (isotropic), and a dark transverse line, the Z line, bisects each I band.

These bands and the Z lines are well demonstrated in electron micrographs of skeletal muscle (Fig 1-3-2).

Myofibrils

Skeletal muscle fibers contain 1- to 2-mm myofibrils that lie in the sarcoplasm (cytoplasm) parallel to the long axis of the muscle fiber (Fig 1-3-2). Myofibrils are composed of a series of sarcomeres that consist of interdigitating polarized thin filaments and bipolar thick filaments (Fig 1-3-3). The sarcomeres are the basic units of contraction of striated muscle.

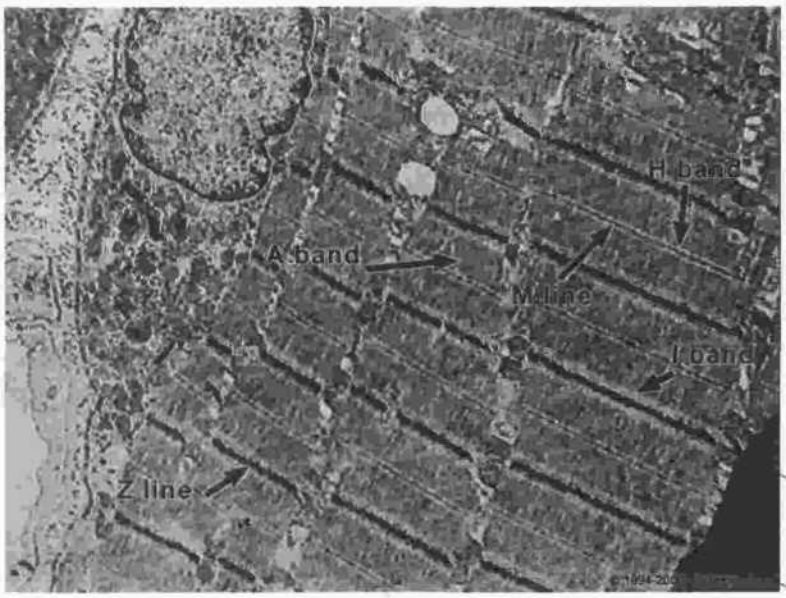


Figure 1-3-2. EM of Skeletal Muscle

Sarcomere Structure

The banding pattern seen in striated muscle is caused by the arrangement of thin and thick myofilaments (Fig 1-3-3).

- Thick filaments occupy the central portions of the sarcomere.
- Thin filaments attach at one end to the Z line and run parallel to, and between, the thick filaments.
- I bands are composed of thin filaments only.
- A bands are composed mostly of thick filaments and the thin filaments between them.
- H bands are composed of thick filaments only.

Thin Filaments

Thin filaments are composed of the proteins actin, tropomyosin, and troponin.

- Actin is a long fibrous structure (F-actin) composed of two strands of spherical or globular G-actin monomers twisted in a double helix. The filament is polar and contains myosin-binding sites on the G-actin monomers.
- Tropomyosin is a polar molecule containing two polypeptide chains in the form of an a-helix. The tropomyosin molecules lie head-to-tail to form filaments that lie in the grooves of the actin helix.

- **Troppnin** (Tn) is composed of three polypeptides: TnT binds to tropomyosin at intervals along the thin filament, TnC binds calcium ions, and Tnl inhibits actin-myosin interaction.

Thick Filaments

Thick filaments are composed of mypjin. Myosin is a molecule that contains a tail and two heads.

- The tail fiber is formed from portions of two heavy chains, which are wound in a coil.
- The heads are globular regions formed by the association of part of one heavy chain with two light chains. **Myosin heads function as active sites for ATPase activity and as actin-binding sites.**

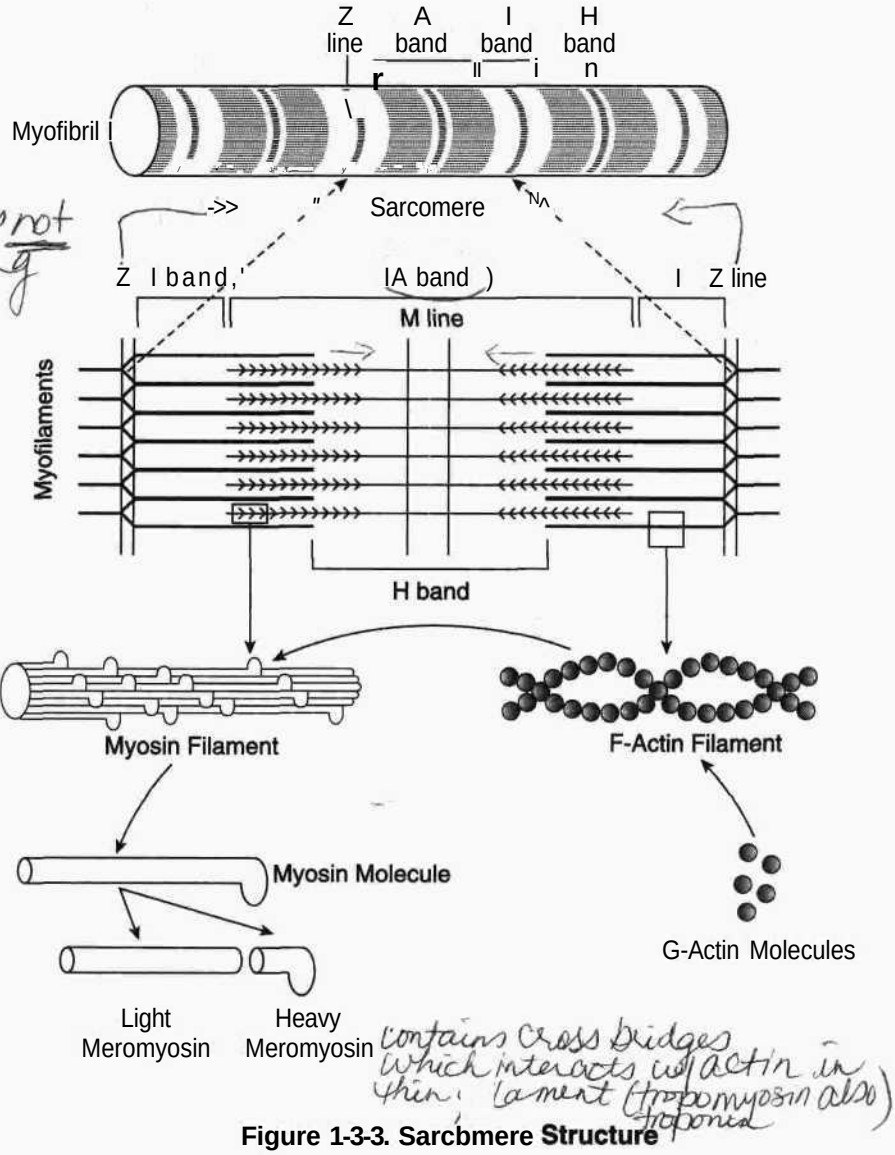


Figure 1-3-3. Sarcbmere Structure

Transverse Tubular System

Skeletal muscle fibers contain fingerlike invaginations of the sarcolemma that surround each myofibril. These invaginations constitute the transverse (T) tubule system (Fig 1-3-4). Note the following:

- Each T tubule lies between the two cisternae of the sarcoplasmic reticulum (SR) to form a triad.
- There are two triads in each sarcomere, which are present at the junction between the A and I bands.
- These units serve to couple excitation of muscle cells to their contraction (excitation-contraction coupling).

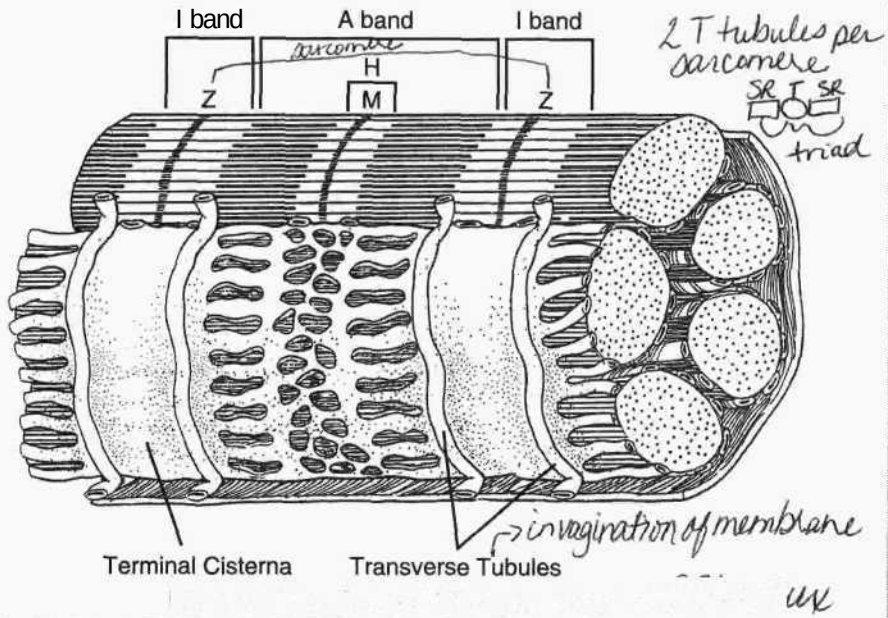


Figure 1-3-4. Striated Muscle Fiber Showing Sarcoplasmic Reticulum and T-tubule System

CARDIAC MUSCLE

Cardiac muscle has an arrangement of sarcomeres similar to that in skeletal muscle as well as a T tubule system associated with the SR (near the Z line). However, unlike skeletal muscle fibers, the fibers are electrically coupled through gap junctions.

- Cardiac muscle fibers are joined together by junctional complexes called intercalated discs. These and other differences are summarized in Table 1-3-2.

SMOOTH MUSCLE

Smooth muscle is found in the walls of blood vessels and hollow viscera. Bands of smooth muscle cells can be found in the erector pill muscles of the skin.

Gap Junctions

Gap junctions electrically couple smooth muscle cells.

Filaments

Smooth muscles contain actin and myosin filaments, but the filaments are not arranged in orderly arrays as in skeletal muscle.

- Bundles of myofilaments course obliquely in the cell, forming a lattice-like arrangement.
- A sliding filament mechanism of contraction is thought to occur.
- Thin filaments insert into dense bodies located within smooth muscle cytoplasm and attached to their membranes.

Contraction

Smooth muscle contraction may be triggered by various stimuli such as autonomic nerves or hormones. Depolarization of the cell membrane results in an influx of Ca^{2+} from outside the cell. Ca^{2+} is sequestered in eitherthe cell membrane or in the sparse SR.

SUMMARY

Some of the principal ultrastructural features of the three types of muscle are summarized in Table 1-3-2.

Table 1-3-2. Ultrastructure Comparison of the Three Types of Muscle

Skeletal	Cardiac	Smooth
Overlapping actin and myosin filaments, forming a characteristic banding pattern	Overlapping actin and myosin filaments, forming a characteristic banding pattern	Actin and myosin do not form a banding pattern
T tubules form triadic contacts with SR at A-I junction	T tubules form dyadic contacts with SR near Z line	Lack T tubules; have limited SR
Sarcolemma lacks junctional complexes between fibers	Junctional complexes between fibers (intercalated discs), including gap junctions	Gap junctions
Troponin	Troponin	i^CalmodulinJ)
Z disks—intermediate filament protein is desmin	Z disks—intermediate filament protein is desmin	Dense bodies in intermediate filament protein is desmin; or vimentin in vascular smooth muscle

4 Lymphoid Organs

young person - sup. mediastinum
comes MiTnv pharyngeal pouch III

THYMUS

The thymus is encapsulated and contains trabeculae. It has cortical and medullary regions (Fig 1-4-1). The thymus contains epithelial reticular cells and Hassall's corpuscles in the medulla and lack^gernunal_cgnters. The thymus protects developing T cells by the blood-thymus barrier that consists of:

- A capillary wall, connective tissue, a basement lamina of epithelial reticular cells, and cytoplasm of epithelial reticular cells.

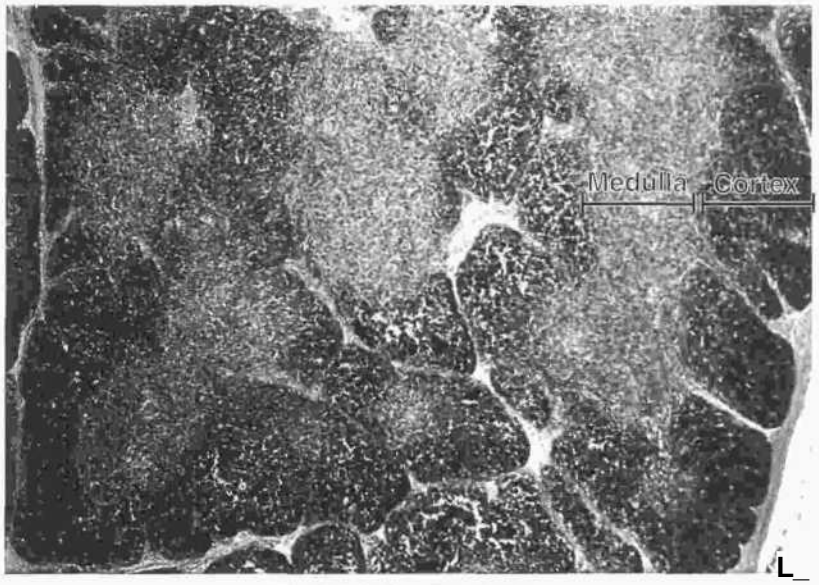


Figure 1-4-1. Thymus

LYMPH NODE

The lymph node is associated with afferent and efferent lymphatic vessels. It is surrounded by a capsule, has trabeculae, and can be divided into outer cortical, inner cortical (paracortical), and medullary regions (Fig 1-4-2):

- The outer cortex contains most of the nodules and germinal centers. **It is populated by mqstofthej? lymphocytes.**
- **The inner cortex is populated by T lymphocytes.**

Dendritic Cells

The lymph node contains dendritic cells, which are antigen-presenting cells.

High Endothelial Venules

High endothelial venules form the site of repopulation of lymph nodes and are found in the paracortical zone.

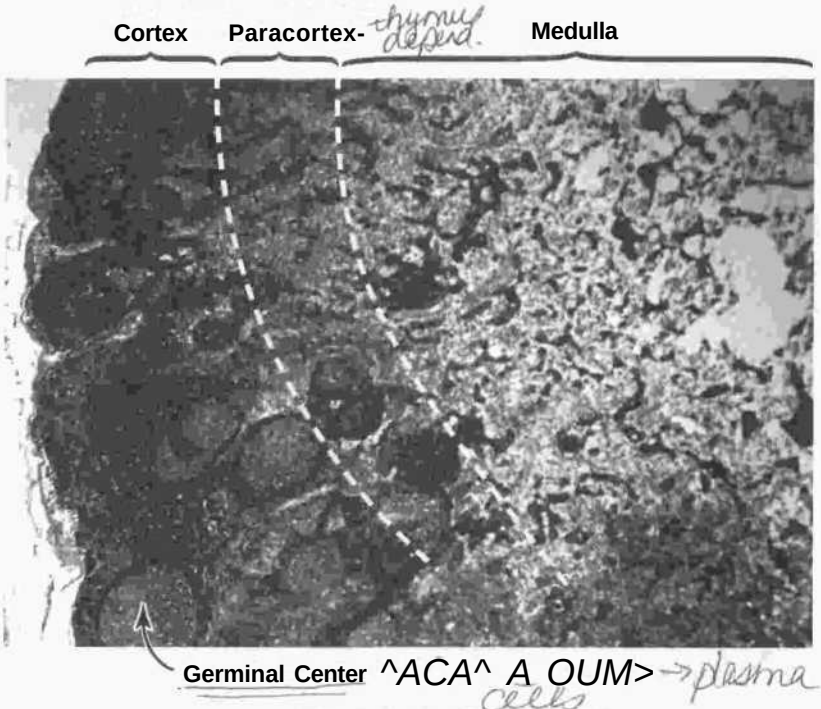


Figure 1-4-2. Lymph Node

SPLEEN

The spleen has an extensive blood supply consisting of trabecular arteries, central arteries, penicillar arteries, sinusoids, red pulp veins, and trabecular veins. It **is** surrounded by a capsule, has trabeculae, and is divided into red and white pulp (Fig 1-4-3).

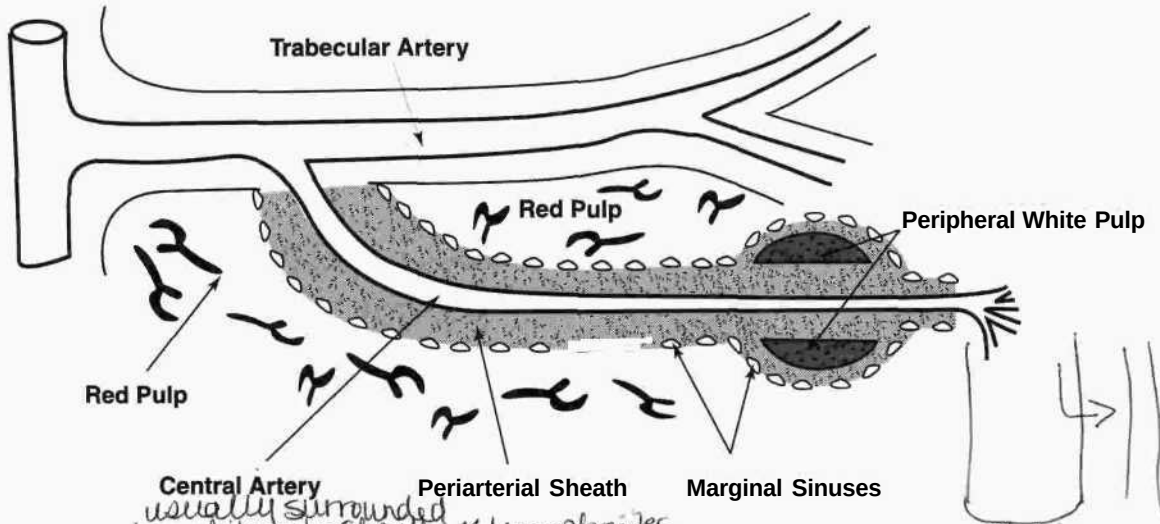
White Pulp

White pulp consists of lymphoid tissue that ensheaths the central arteries (periarterial sheath) along with the associated nodules and germinal centers. The periarterial sheath is populated mainly by T lymphocytes. The peripheral white pulp and germinal centers are populated mainly by B lymphocytes.

Red Pulp

Red pulp **consists of splenic cords (of Billroth) and venous sinusoids.** Defective red blood cells resulting from aging or disease (as in sickle cell anemia, hereditary spherocytosis, or thalassemia syndromes) are delayed in their passage from Billroth's cords into the venous sinusoids and phagocytosed by macrophages lining the cords.

White Pulp - Lymphoid Tissue (Periarterial Sheath + Peripheral White Pulp)



FiguTe I-4-3t8pleenSch«matic

mm)
(Mil laries

usually surrounded by white pulp sheath of lymphocytes

splenic cord

B cells found in periphery of white pulp
T cells - found in center of white pulp

healthy RBC's have no problem doing this, but sick RBC's get stuck in splenic cord, so if diseased RBC the splenic cord function is to destroy "filter"

Integument 5

GENERAL FEATURES

The integument consists of the skin (epidermis and dermis) and associated appendages (sweat glands, sebaceous glands, hairs, and nails). It is considered to be the largest organ in the body. The integument constitutes approximately 16% of total body weight. The integument functions to protect the body from injury, desiccation, and infection. It also participates in sensory reception, excretion, thermoregulation, and maintenance of water balance.

EPIDERMIS

Ectoderm

The epidermis is the outermost layer of the integument (Fig 1-5-1). It is a stratified squamous epithelial layer of ectodgrmj] nrigin. It is devoid of blood vessels and consists of four or five layers from deep to superficial.

Layers

The layers of the epidermis are: *-fjii*

of these layers make keratin

Ectoderm

- **Stratum basale** (stratum germinativum) is a proliferative basaVlayer of columnar-like cells that contain the fibrous protein keratin.
- **Stratum spinosum** is a multilaminar layer of cuboidal-like cells that are bound together by means of numeroujLile^mnsoiiiaLjunctions.

keratinocytes held together by desmosomes

Clinical Correlate

Pemphigus

Pemphigus is an autoimmune blistering disorder caused by disruption of desmosomes linking keratinocytgs.

Psoriasis

Psoriasis results from an increase in the number of proliferating cells in stratum basale plus stratum spinosum. In addition, there is an increase in the rate of cell turnover. This results in greater epidermal thickness and continuous turnover of the epidermis.

Clinical Correlate

Albinism

Albinism occurs when melanocytes are unable to synthesize melanin (either by absence of tyrosinase activity or inability of cells to take up tyrosine).

Vitiligo

Vitiligo is a disorder in which melanocytes are destroyed. It is thought to occur secondary to autoimmune dysfunction, leading to depigmentation.

Clinical Correlate

Bullous Pemphigoid

Bullous pemphigoid is an autoimmune blistering disorder of the dermjs--epidermis junction. Immunofluorescence studies demonstrate the presence of lgGJhatjs_ directed against an antigen in the lamina lucida.

Stratum granulosum consists of flat polygonal cells filled with basophilic keratohyalin granules. Viewed at the electron microscopic level, these cells also contain numerous membrane-coating granules.

- **Stratum lucidum** is the transitional zone of flat eosinophilic or pale-staining anucleated cells only found in regions with a thick stratum corneum.

Stratum corneum is the superficial stratum consisting of several layers of flat, anucleated, and cornified (keratinized) cells.

Cell Types

The epidermis contains several cell types:

Keratinocytes arethe most numerous and are responsible for the production of the family of keratin proteins that provide the barrier function of

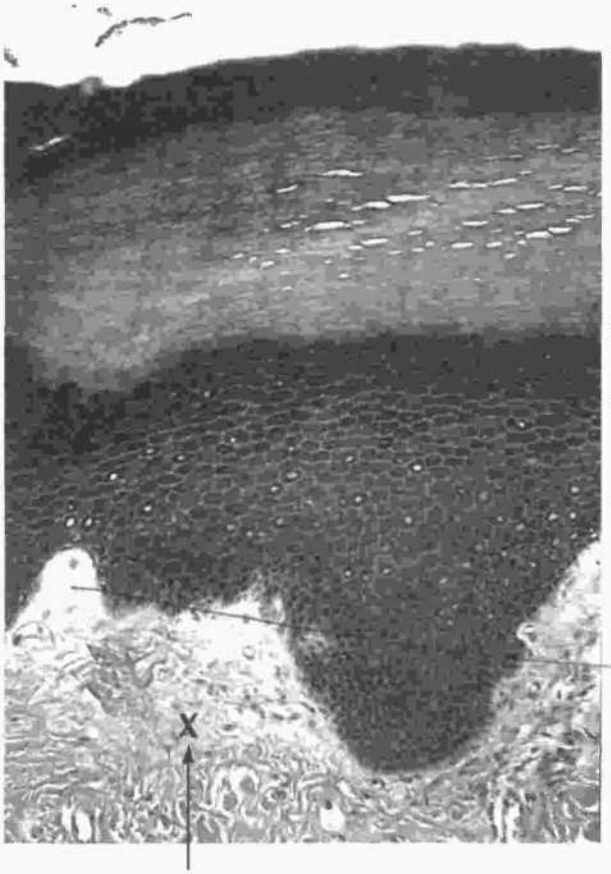
- Melanocytes are derivaaves of neuraLcKst ectoderm. They are found in the dermis and are also scattered among the keratinocytes in the basal layers of the epidermis. These cells produce the pigmentjnelanin in the form of melanosomes that are transferred to keratinocyjes.
- **Langerhans cells** are members of the immune system and function as antigen-presenting cells.
- **Merkel cells** are found in the bajsal epidermis and appear to function in concert with the nerve fibers that are closely associated with them. At the electron microscopic level, their cytoplasm contains numerous membrane-bound granules that resemble those of catecholamine-producing cells.

DERMIS *mesoctiAsy^ (tKCJft*

The dermis is a connective tissue layer of mesodermal origin below the epidermis and its basement membrane.

Dermis-Epidermal Junction

The dermis-epidermal junction is characterized by numerous papillary interdigitations of the dermal connective tissue and epidermal epithelium, especially in thick skin. This increases the surface area of attachment and brings blood vessels in closer proximity to the epidermal cells.



BURNS
1° - minor damage to epid.
2° - major damage to epid. hair, outer root sheath survive, can repithelialize
3° - damage to epidermis & dermis

epidermis
no blood vessels

Meissner's corpuscles (touch)

Pachinian corpuscles (vibration)

Figure 1-5-1. Skin

HYPODERMIS

The hypodermis is a layer of loose vascular connective tissue infiltrated with adipocytes, and it corresponds to the superficial fascia of gross anatomy. The hypodermis fastens the skin to underlying muscles and other structures.

SWEAT GLANDS

Sweat glands are epidermal derivatives. Two types are compared in Table 1-5-1.

Table 1-5-1. Features of Eccrine and Apocrine Sweat Glands

	Eccrine	Apocrine
Size	0.4 mm diameter	3-5 mm diameter
Location	Essentially everywhere with some exceptions (e.g., glans penis)	Axillary, areolar, and anal region
Site of opening	Skin surface	Hair follicles
Discharge	Watery, little protein, mainly H_2O, NaCl, urea, NH_3, and uric acid	Viscous, odor producing
Innervation	Cholinergic	Adrenergic

SEBACEOUS GLANDS

Sebaceous glands are simple, branched holocrine acinar glands. They usually discharge their secretions onto the hair shaft within hair follicles. They are found in the dermis throughout the skin, except on the palms and soles. Sebaceous glands lubricate hairs and cornified layers of the skin to minimize desiccation.

HAIR

Hairs are long, filamentous projections consisting of keratinized epidermal cells. They develop from epidermal invaginations called hair follicles. Bundles of smooth muscle cells, called arrector pili muscles, are attached to the hair follicle at one end and to the papillary dermis at the other. Contraction of these muscles raises the hairs and dimples the epidermis ("goose flesh"). The follicles and associated sebaceous glands are known as pilosebaceous units.

NAILS

Nails, like hair, are a modified stratum corneum of the epidermis. They contain hard keratin that forms in a manner similar to the formation of hair. Cells continually proliferate and keratinize from the stratum basale of the nail matrix.

Respiratory System

6

GENERAL FEATURES

The respiratory system is divided into a condiicting^mction (nasal cavity, pharynx, larynx, trachea, bronchi, bronchioles), which carries the gases during inspiration and expiration, and a respiratory portion (alveoli), which provides for gas exchange between air and blood.

NASAL CAVITIES

The nasal cavities contain two major areas.

Respiratory Area

The respiratory area is lined by a psendastratified, ciliated, columnar epithelium. The epithelium contains gobletcells (respiratory epithelium) and a subjacent fibrous lamina propria with mixecTmucous and serous glands.

Mucus is carried toward the pharynx by ciliary motion. The lateral walls contain conchae, which increase the surface area and promote warming of the inspired air. This region is richly vascularized and innervated.

Olfactory Area

The olfactory area is located in the posterosuperior nasal cavity and is lined by a pseudostratified epithelium composed of bipolar neuronsjolfactory_cells), sup-

go up to cribiform plate to subarachnoid space

porting cells, brush cells, and basal cells.

The basal cells are stem cells that continuously turn over to replace the olfactory receptor cells. **This is the only example in the adult human where neurons are replaced.**

Under the epithelium, Bowman's glands produce serous fluid, which dissolves odorous substances.

PARANASAL SINUSES

Paranasal sinuses are cavities in the frontal, maxillary, ethmoid, and sphenoid bones that communicate with the nasal cavities. They contain a thin respiratory epithelium over a lamina propria containing numerous goblet cells, which produce mucus that drains into the nasal passages.

NASOPHARYNX

The nasopharynx is lined by a respiratory epithelium. The cilia beat toward the oropharynx, which is composed of a stratified, squamous, nonkeratinized epithelium.

Pharyngeal Tonsil

Located on the posterior wall of the nasopharynx, subjacent to the epithelium, is the pharyngeal tonsil, an aggregate of nodular and diffuse lymphatic tissue.

Clinical Correlate

Adenoldltls

Hypertrophy of the pharyngeal tonsil as a result of chronic inflammation results in a condition known as adenoiditis.

LARYNX

See Gross Anatomy section.

TRACHEA

The trachea leads to the terminal bronchioles. The major histologic changes occurring in the passage from the trachea to the bronchioles are summarized in Table 1-6-1.

Table 1-6-1. Histologic Features of Trachea, Bronchi, and Bronchioles

	Trachea	**Bronchi**	**Bronchioles**
Epithelia	Pseudostratified ciliated columnar (PCC) cells, goblet cells	PCC to simple columnar cells	Ciliated, some goblet cells, Clara cells in terminal bronchioles
Cartilage	16-20 C-shaped cartilaginous rings	Irregular plates	None
Glands	Seromucous glands	Fewer seromucous glands	None
Smooth muscle	Between open ends of C-shaped cartilage	Prominent	Highest proportion of smooth muscle in the bronchial tree
Elastic fibers	Present	Abundant	Abundant

RESPIRATORY BRONCHIOLES 5ftU ciliated

Respiratory bronchioles contain alveoli and branch to form two to three alveolar ducts, which are long sinuous tubes that often terminate in alveolar sacs. Alveolar sacs are spaces formed by two or more conjoined alveoli. They are lined by the simple squamous alveolar epithelium.

expiration - passive
lungs want to collapse b/c
elastic fibers

ALVEOLI

Alveoli are the terminal, thin-walled sacs of the respiratory tree that are responsible forjasexehange. There are approximately 300 million alveoli per lung, each one 200 to 300 mm in diameter (Fig 1-6-1). The alveolar epithelium contains two cell types.

Type I Cells 95% of surface

Type I cells cover almost all of the alveolar luminal surface and provide a thin surface for gas exchange. This simple squamous epithelium is sojhin (~25 nm) that its details are beyond the resolution of the light microscope.

Type **I cells constitute one component of the blood-air interface.**

- Oxygen in the alveoli is separated from the red blood cells of the alveolar capillaries by the type I cell.

- Its basal lamina is often conjoined with the basal lamina of the capillary and the capillary endothelial cell.
- The total thickness of all these layers can be less than 0.5 mm.

Type II Cells

Type II cells are cubpidal-like cells that sit on the basal lamina of the epithelium and contain membrane-bound granules of phospholipid and protein (lamellar bodies). The contents of these lamellar bodies are secreted onto the alveolar surface to provide a coating of sjufactant that reduces alveolar surface tension.

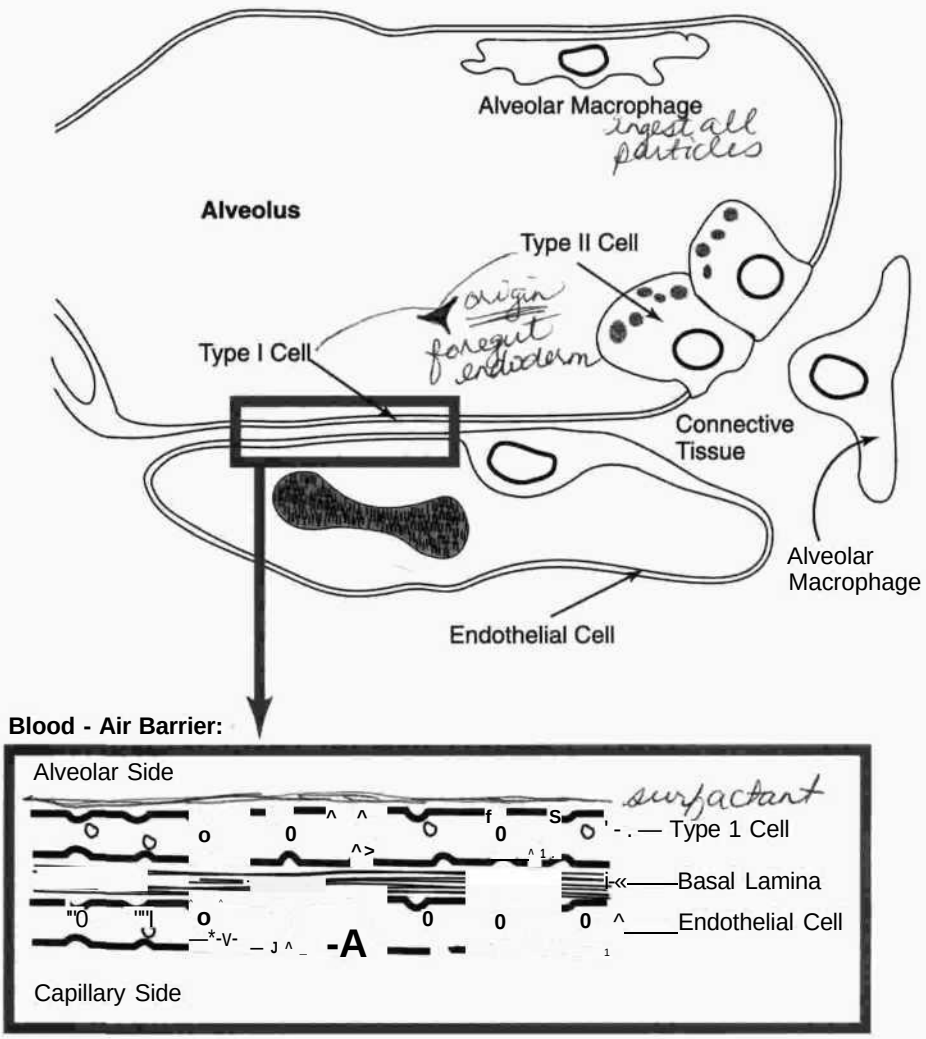


Figure 1-6-1. Alveolus and Blood-Air Barrier

ALVEOLAR MACROPHAGES

Alveolar macrophages (dust cells) are found on the surface of the alveoli. They are derived from monocytes that extravasate from alveolar capillaries; alveolar macrophages are part of the mononuclear phagocyte system.

Alveolar macrophages continuously remove particles and other irritants in the alveoli by phagocytosis. They derive from monocytes and form part of the mononuclear phagocyte system.

Gastrointestinal System

7

GENERAL FEATURES

The **gastrointestinal (GI) system** consists of the digestive tract and its associated glands.

DIGESTIVE TRACT

The major regional characteristics and cell types of the digestive tract are summarized in Table 1-7-1.

Table 1-7-1. Digestive Tract—Regional Comparisons

Region	Major Characteristics	Mucosal Cell Types at Surface	Function of Surface Mucosal Cells
Esophagus	Stratified squamous epithelium; nonkeratinized skeletal muscle in muscular is externa (upper 1/3): smooth muscle (lower 1/3)	-	
Stomach: body and fundus	Rugae: shallow pits; deep glands	Mucous cells	Secrete mucus. Form protective layer against acid. Tight junctions between these cells probably contributes to the acidjbarrier of the epithelium.

(continued)

basophilia - ant. of nu <JJU^ OCicLo (rnRKf), rf2bf\)

Table 1-7-1. Digestive Tract—Regional Comparisons (continued)

Region	Major Characteristics	Mucosal Cell Types at Surface	Function of Surface Mucosal Cells
		Chief, cells (pepsinogen, RER, basophilia) found in lards	Secrete pepsinogen and lipase precursor.
		Parietal cells (eosinophilic)	Secrete HC1 and intrinsic factor.
		Enteroendocrine (EE) cells	Secrete a variety of peptide hormones.
Stomach: pylorus	Deep pits; shallow branched glands	Mucous cells	Same as above.
		Parietal cells	Same as above.
		EE cells	High concentration of gastrin.
Small intestine:	Villi, plicae, and crypts (Fig 1-7-1)	Columnar absorptive cells	Contain numerous microvilli that greatly increase the luminal surface area, facilitating absorption.
Duodenum (Fig 1-7-2)	Brunner glands, which secrete an alkaline secretion	Goblet cells	Secrete acid glycoproteins that protect mucosal lining.
		Paneth cells	Contains granules that contain lysozyme. May play a role in regulating intestinal bacterial flora.
		EE cells	High concentration of cells that secrete cholecystokinin and secretin.
Jejunum	Villi, well-developed plica, crypts	Same cell types as found in the duodenal epithelium	Same as above.
Ileum (Fig 1-7-3)	Aggregations of lymph nodules called Peyer's patches	MMVOUS cells, found over lymphatic nodules and Peyer's patches	Endocytose and transport arisen from the lumen to lymphoid figlls.
Large intestine	Lacks villi, has crypts	Mainly mucus-secreting and absorptive cells	Transports Na^+ (actively) and water (passively) out of lumen.

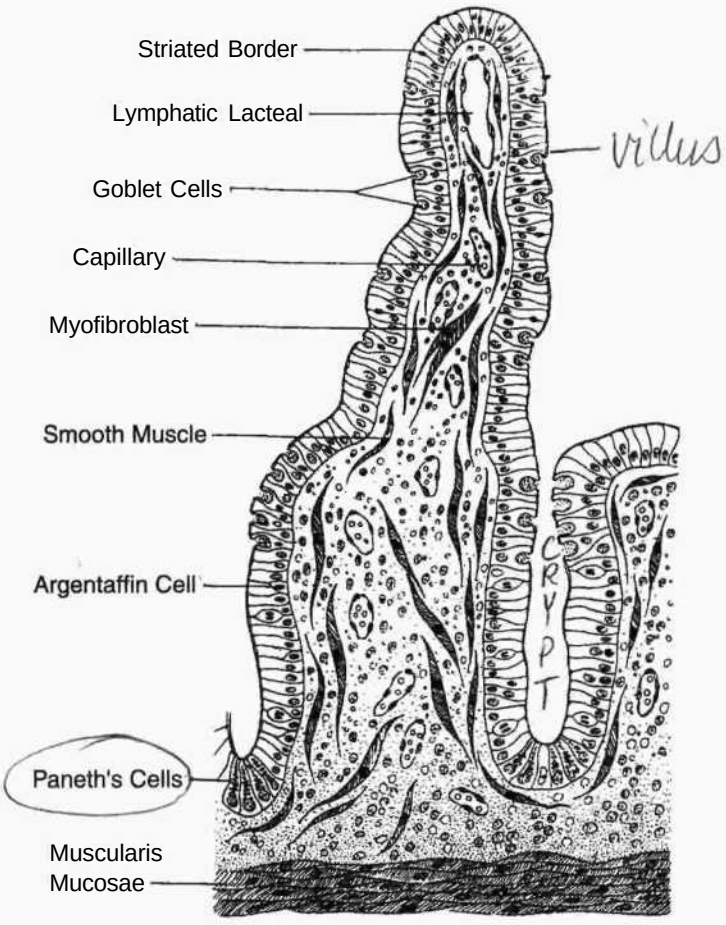


Figure 1-7-1. Structure of Small Intestine Villus and Crypts

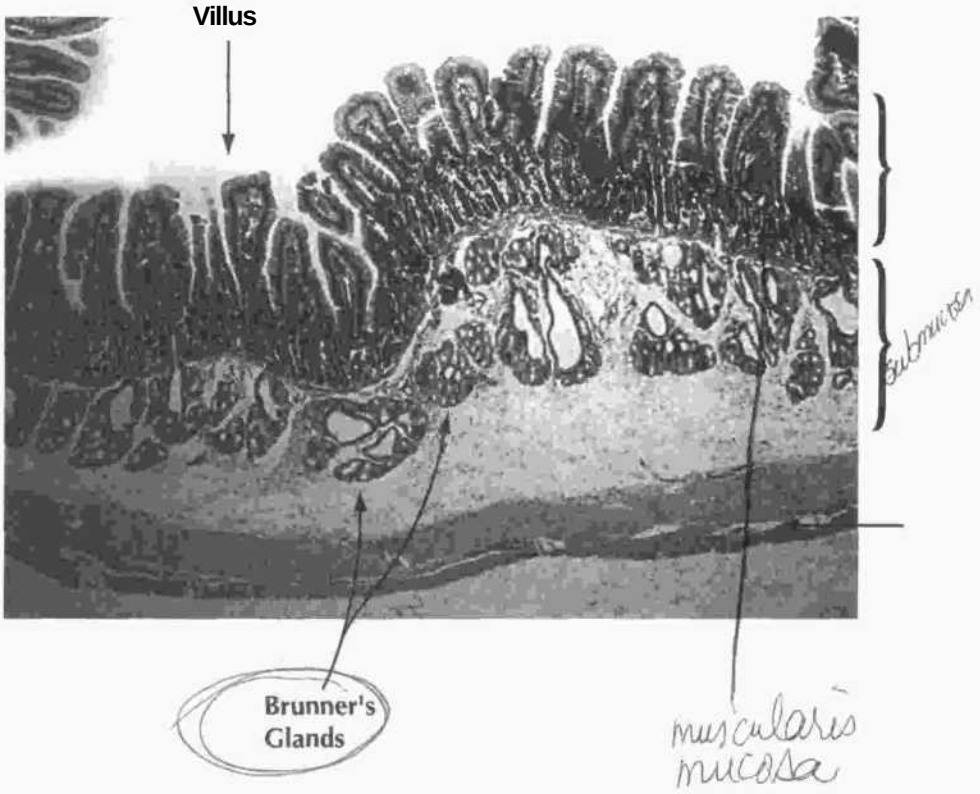


Figure I-7-2. Duodenum

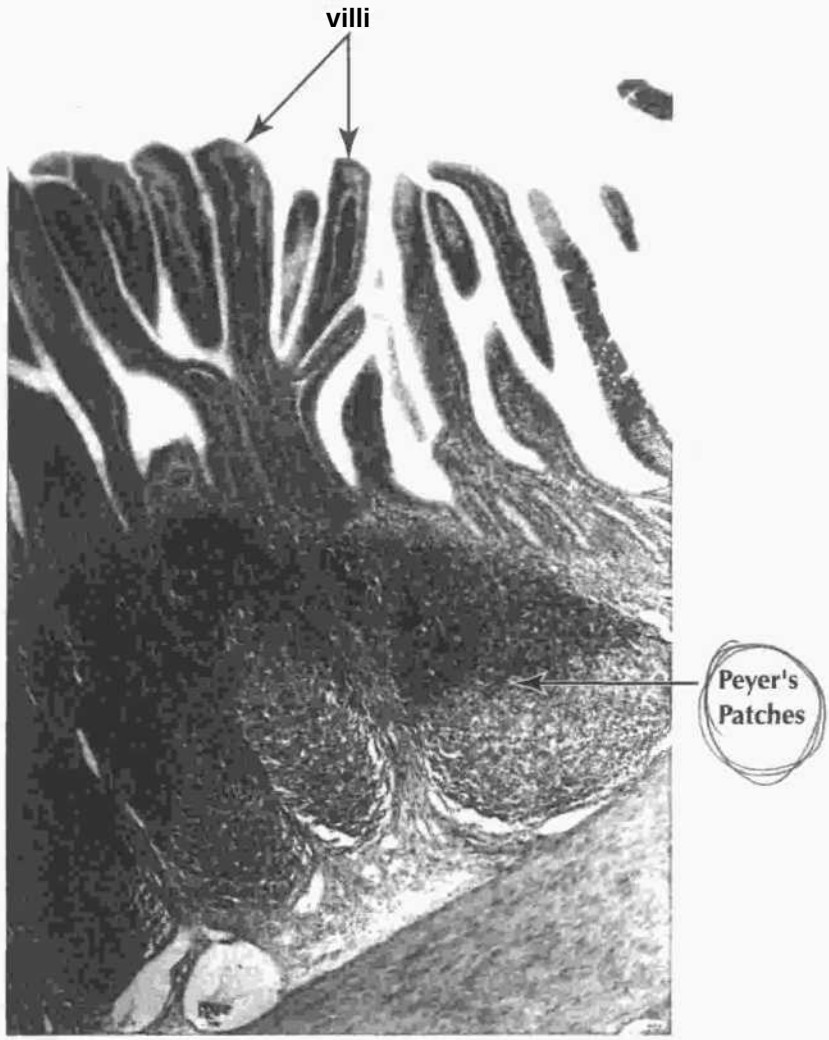


Figure 1-7-3. Ileum

ASSOCIATED GLANDS

Salivary Glands

Table 1-7-2. Comparison of the Major Salivary Glands

Gland	Acinar **Cell Type (histologic appearance)**	**Innervation**
Parotid	Serous (high amylase activity) "£&}f	Glossopharyngeal (IX)
Submandibular	Serous and mucous; mainly serous	Facial (VII)
Sublingual	Mucous and serous; mainly mucous	Facial (VII)

Pancreas a lot of RER

The exocrine portion of the pancreas consists of parenchymal cells arranged in the form of acini and a system of branching ducts that drain into the lumen of the small intestine.

Acini

Acini are composed of pyramidal serous-type cells, each of which produces membrane-bound granules of mixed enzymes for secretion. Pancreatic enzymes cleave proteins (e.g., trypsin, chymotrypsin, carboxypeptidase, elastase), carbohydrates (e.g., amylase), fats (e.g., lipase, lecithinase), and nucleic acids (e.g., ribonuclease, deoxyribonuclease).

Duct Cells

Duct cells secrete water, electrolytes, and bicarbonate (HCOJ), which dilute enzyme secretions and neutralize acidic chyme.

Liver fo ^ut erdederm der.

The liver is the largest gland of the body. It has multiple and complex functions, including exocrine secretion (via bile ducts into the duodenal lumen) and maintenance of optimal concentrations of various components of blood, which it receives via the portal vein from the digestive tract and spleen.

Liver Parenchyma

The liver parenchyma is divided into many small lobules shaped like polygonal cylinders (Fig 1-7-4).

- Each cylinder is composed of plates of cells arranged radially around a central vein. Between the plates are radial blood sinusoids.
- At the periphery of the lobules, branches of the portal vein, hepatic artery, bile ducts, and lymphatics course together.

Hepatocytes

Hepatocytes are 20- to 30-mm polyhedral cells (Fig 1-7-5). Liver regeneration can occur rapidly under some circumstances. As much as 90% can be replaced in about 2 weeks.

- Their six or more surfaces may either contact another cell to form gap junctions and bile canaliculi or form a free surface with microvilli exposed to the perisinusoidal space of Disse.
- Abundant glycogen in these cells takes the form of electron-dense granules that are clustered near the SER.
- There are several hundred mitochondria per liver cell.
- The hepatocyte produces proteins for export (e.g., albumin, prothrombin, fibrinogen), sgcjclesJbile, stores lipidsand carhohydrates, converts lipids and amino acids into glucose via the enzymatic process of gluconeogene-^sis, and detoxifies and inactivates drugs by oxidation, metfivTaTign, and con ugation.

Sinusoidsr H ^ W n(JJA.

The liver contains **sinusoids** (Figs 1-7-4,1-7-5, and 1-7-6) that are lined with fenestrated endothelial cells and scattered phagocytic Kupffer cells, which are part of tKelnononucIeaT phagocyte system.

- **Kupffer cells** phagocytize red blood cells and particles and contain cytoplasmic residual bodies of iron and pigments.
- Lipocytes also lie in the perisinusoidal space.

BiliarySystem

The liver contains a biliary system consisting of:

- **Bile canaliculi**—tubular spaces limited by the plasma membrane of several hepatocytes (Figs 1-7-4,1-7-5, and 1-7-6). These ducts empty into Hering's canals, which are small ducts composed of cuboidal cells.
- **Hepatic ducts**—receive Hering's canals and eventually form the right and left hepatic ducts, which join to form the common hepatic duct.
- **Common bile duct**—receives the common hepaticjmd cystic ducts.

Gallbladder

The **gallbladder** is lined by a surface epithelium composed of simple, tall, columnar cells. They bear irregular microvilli with a glycoprotein surface coat.

The gallbladder concentrates bile by active transport of Na^+, Cl^-, and water (especially of Na^+) from the cytoplasm to the intercellular space. From there, the water moves into blood vessels, and the bile is concentrated.

Contraction of the muscle layer **(muscularis externa)** of the gallbladder is induced by the hormone cholecystokinin, which is produced in the mucosa of the small intestine.

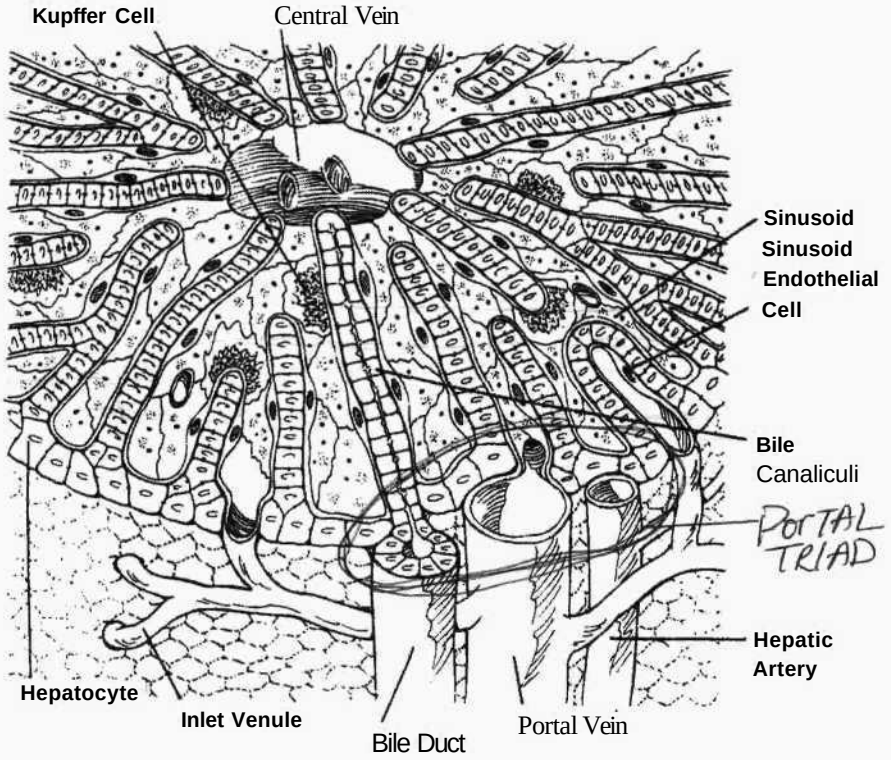
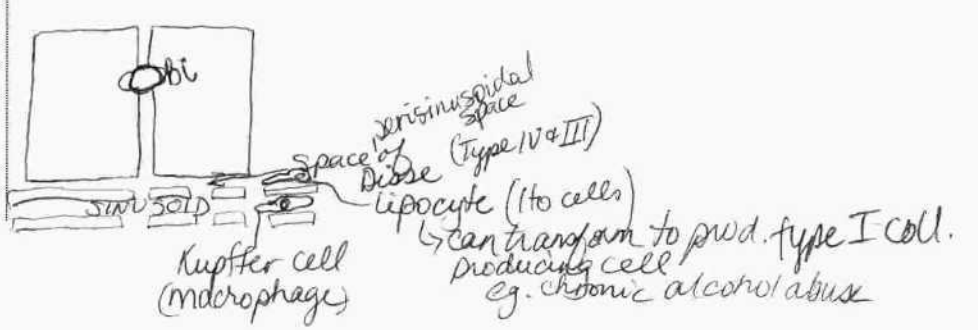


Figure 1-7-4. Organization of a Liver Lobule

Blood flow passes from periphery to central vein
Periphery grows first in dru- digestion
& 1° A- Cfcid rr the O_2 ... syskm



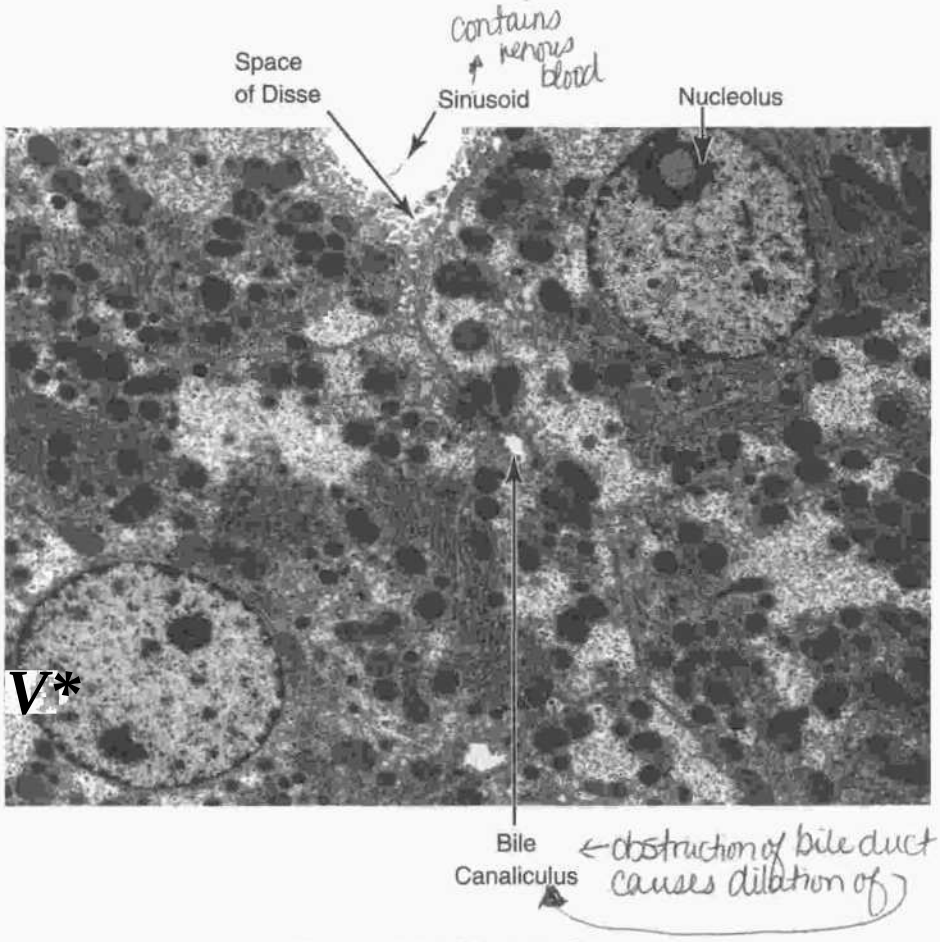
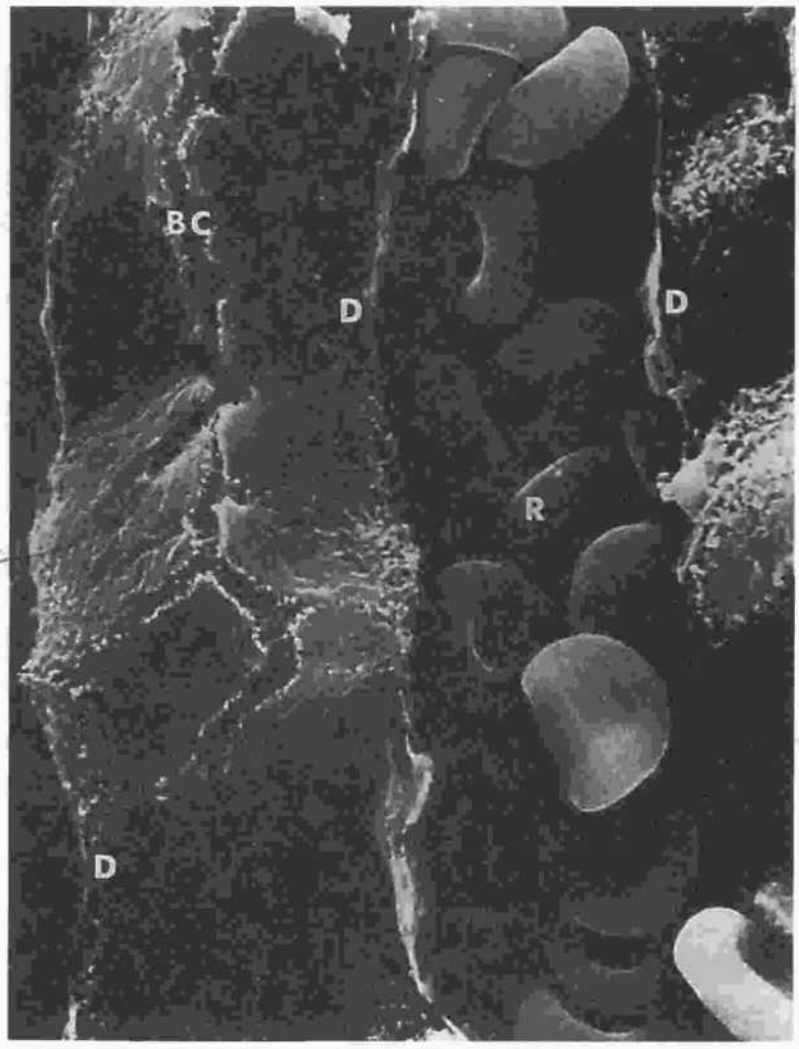


Figure 1-7-5. EM of the Liver



BC = Bile canaliculus
D = Perisinusoidal spaces of Disse
R = Red blood cells in a sinusoid

Figure I-7-6. Scanning Electron Micrograph of Hepatic Plates and Sinusoids in the Liver

Renal/Urinary System

8

KIDNEY

The kidney is divided into three major regions: the hilum, cortex, and medulla (Fig 1-8-1).

Hilum

The hilum is located medially and serves as the point of entrance and exit for the renal artery, renal vein, and ureter.

The renal pelvis, the expanded upper portion of the ureter, divides into two or three major calyces upon entrance into the kidney. These, in turn, divide into eight minor calyces.

Branches of the renal artery, vein, and nerve supply each part of the kidney.

Cortex

The cortex forms the outer zone of the kidney as well as several renal columns, which penetrate the entire depth of the kidney.

Medulla

The medulla appears as a series of medullary pyramids. The apex of each pyramid directs the urinary stream into a minor calyx.

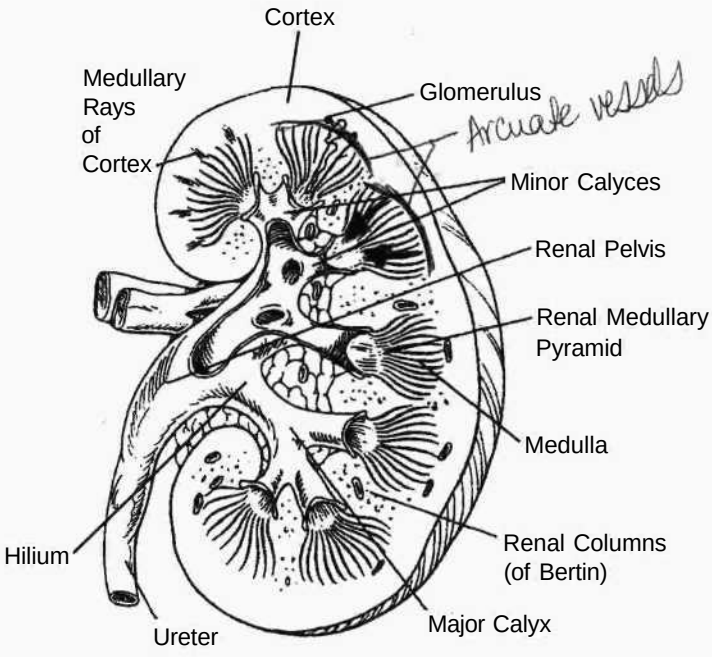


Figure 1-8-1. Organization of the Kidney

URINIFEROUS TUBULES

The uriniferous tubules consist of two functionally related portions called the nephron and the collecting tubule.

Nephron

The nephron consists of a renal corpuscle, proximal convoluted tubule, loop of Henle, and distal convoluted tubule (Fig 1-8-2).

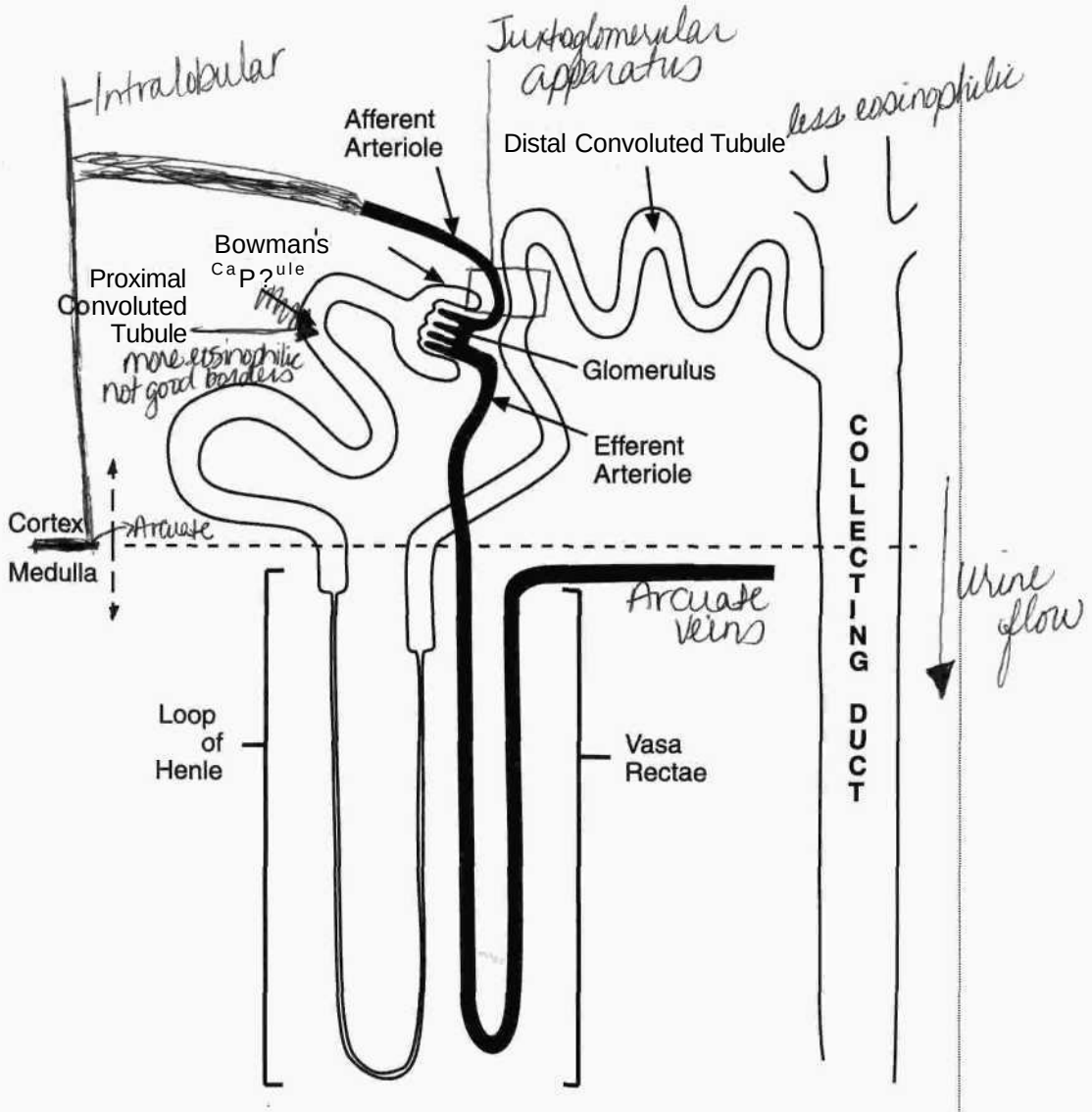


Figure 1-8-2. Nephron Diagram

Renal Corpuscle

The renal corpuscle consists of a tuft of capillaries, or glomerulus, surrounded by a double-walled epithelial capsule called Bowman's capsule (Fig 1-8-3).

Glomerulus

The glomerulus is composed of several anastomotic capillary loops interposed between an afferent and an efferent arteriole. The endothelium of the glomerulus is thin and fenestrated. Plasma filtration (ultrafiltration) occurs in the glomerulus.

Bowman's Capsule

Bowman's capsule consists of an inner visceral layer and an outer parietal layer (Fig 1-8-3). The space between these layers, the urinary space, is continuous with the proximal convoluted tubule epithelial lining.

- **The visceral layer** is composed of podocytes resting on a basal lamina, which is fused with the basal lamina of the capillary endothelium (Figs I-8-4,1-8-5, and 1-8-6).
- **The parietal layer** is composed of a simple squamous epithelium that is continuous with the proximal convoluted tubule epithelial lining.

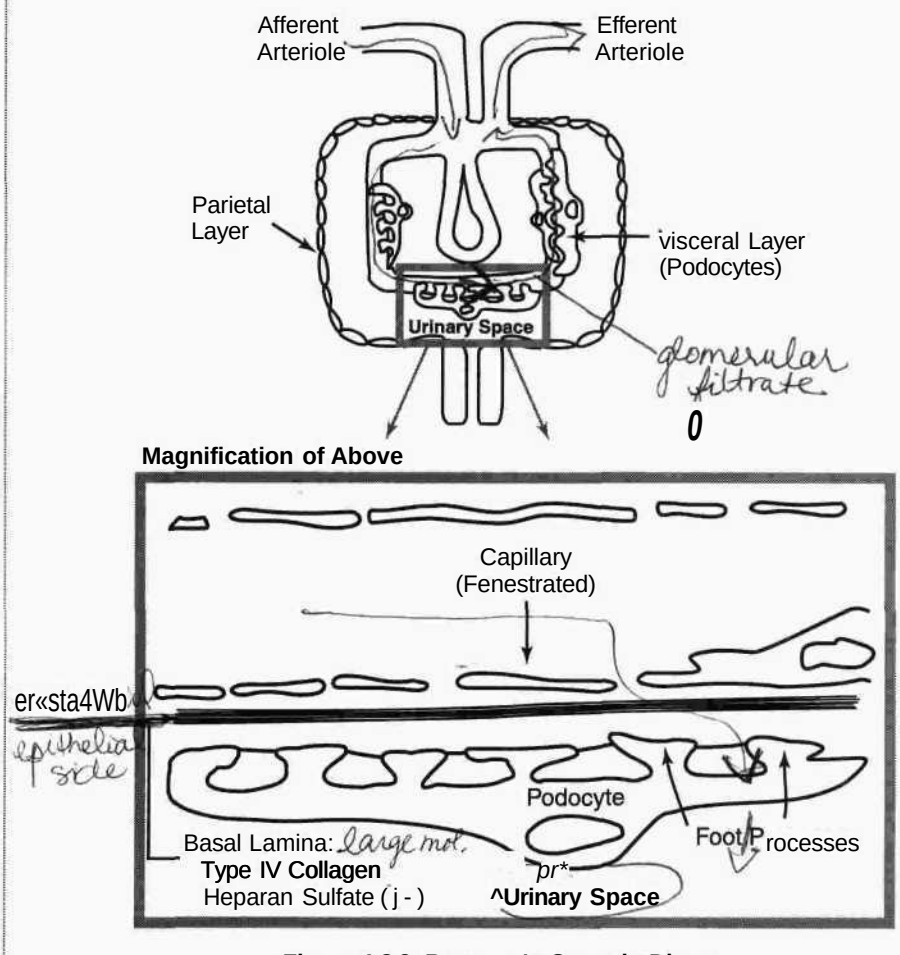


Figure 1-8-3. Bowman's Capsule Diagram

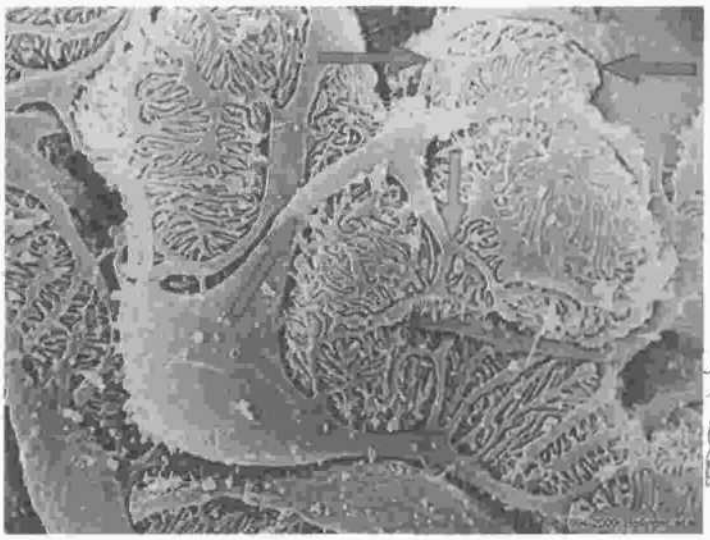


Figure 1-8-4. Scanning Electron Micrograph Demonstrating Podocytes With Their Processes (arrows)

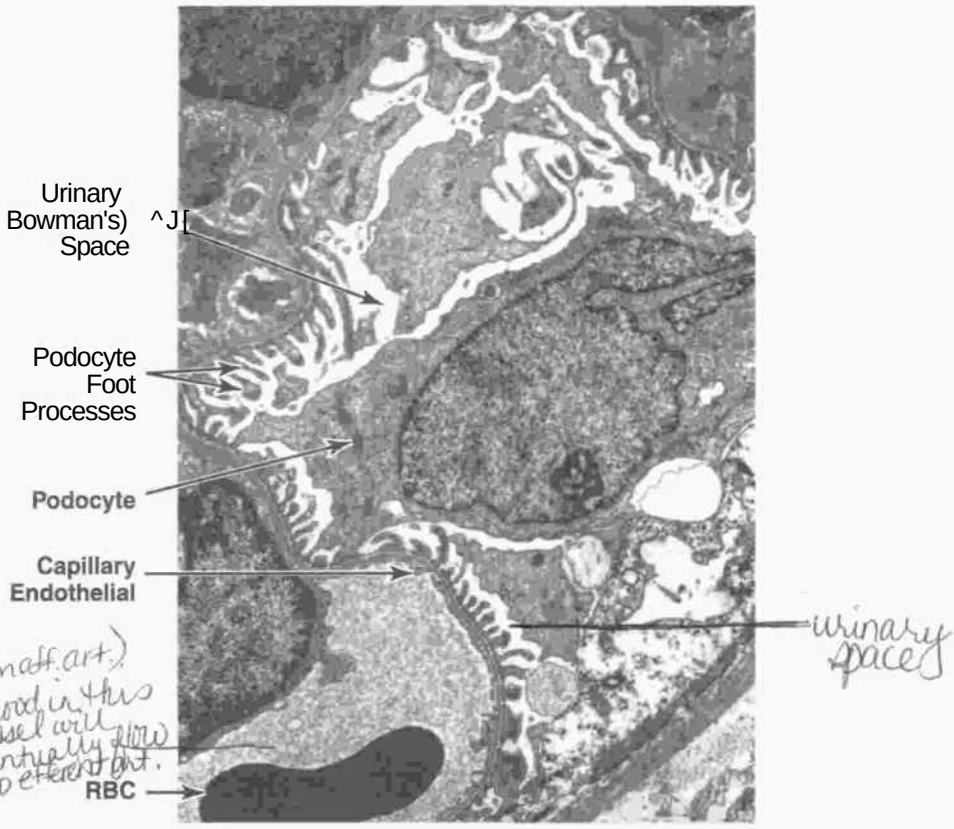


Figure 1-8-5. Transmission Electron Micrograph Demonstrating Podocytes

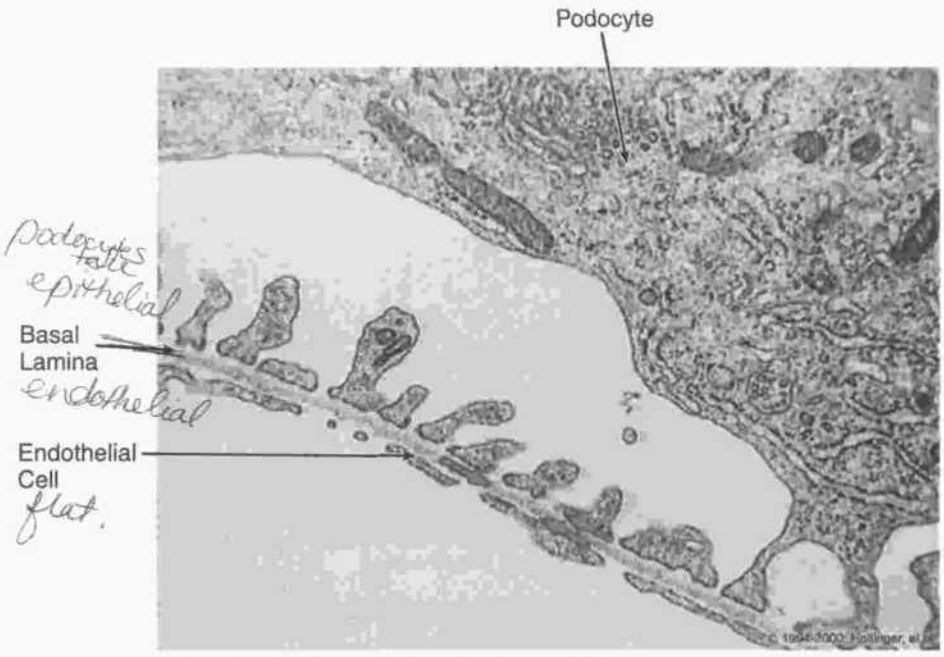


Figure I-8-6. Electron Micrograph Demonstrating Relationship Between Basal Lamina, Podocyte, and Endothelial Cell

Proximal Convoluted Tubule

The proximal convoluted tubule is the longest and most convoluted segment of the nephron. Its cells possess an apical brush border that provides a much greater surface area for reabsorption and secretion. Most of the components of the glomerular filtrate are reabsorbed in the proximal tubule.

LoopofHenle

The loop of Henle is a hairpin loop of the nephron that extends into the medulla and consists of thick and thin segments.

Distal Convoluted Tubule

The distal convoluted tubule is lined by cuboidal cells that reabsorb sodium and chloride from the tubular filtrate.

Collecting Tubules

Collecting tubules consist of arched and straight segments made up of cells that range from cuboidal to columnar. In response to vasopressin (also known as antidiuretic hormone, or ADH) secreted by the neurohypophysis, collecting tubules become permeable to water and, thus, are important in the kidney's role in water conservation and urine concentration.

VASCULAR SUPPLY

^Renal artery —• Interlobar arteries —• Arcuate arteries →
Interlobular arteries —^- Afferent arterioles —*- Glomeruli
—*- Efferent arterioles —»- Peritubular plexus
↘ Vasa recta

Vasa Recta

The **arteriolae rectae** and the corresponding **venae rectae** with their respective capillary networks comprise the **vasa recta,** which supplies the medulla.

The endothelium of the venae rectae is fenestrated and plays an important role in maintaining the **osmotic gradient** required for concentrating urine in the kidney fuBules.

JUXTAGLOMERULAR APPARATUS

The juxtaglomerular apparatus consists of juxtaglomerular cells, polkissen cells, and the macula densa (Fig 1-8-3).

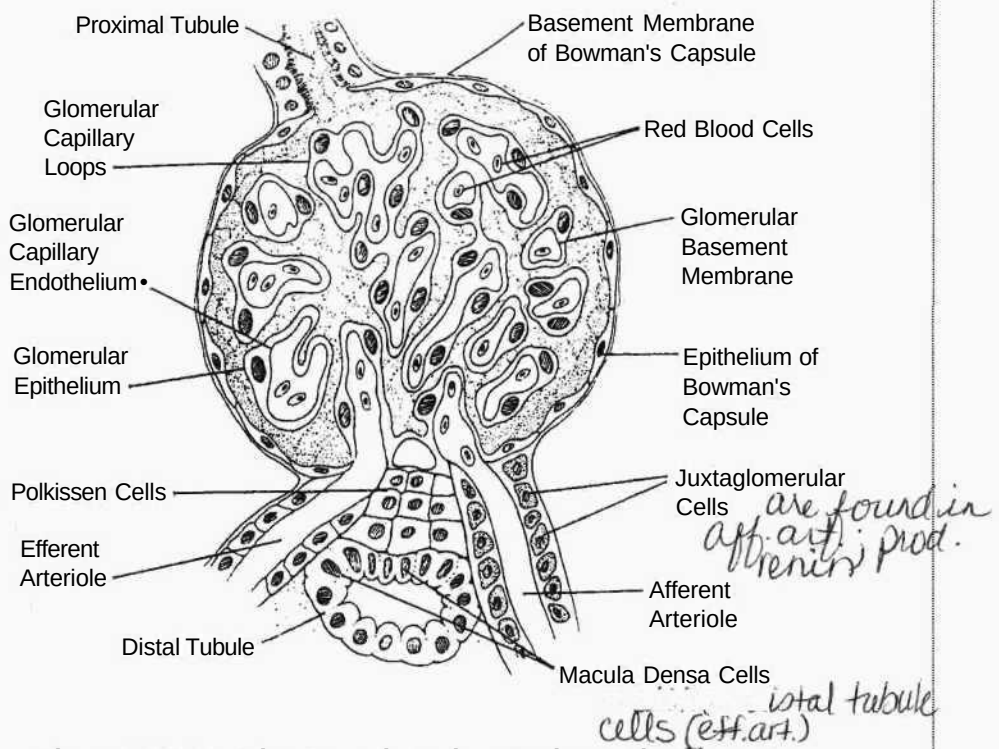


Figure 1-8-7. Renal Corpuscle and Juxtaglomerular Apparatus

Juxtaglomerular Cells

The juxtaglomerular cells are myoepithelial cells in the afferent arteriole. They secrete an enzyme called renin, which enters the bloodstream and converts the circulating polypeptide angiotensinogen into angiotensin **I.**

AngiotensinJ-is-eooygrted to **angiotensin II,** a potent vasoconstrictor that stimulates aldosterone secretion from the adrenal cortex. Aldosterone increases sodium and water reabsorption in the distal portion of the nephron.

Polkissen Cells

Polkissen cells are located between the afferent and efferent arterioles at the vascular pole of the glomerulus, adjacent to the macula densa. Their function is unknown.

Macula Densa

Cells of the distal tubule near the afferent arteriole are taller and more slender than elsewhere in the distal tubule. They constitute the macula densa. The macula densa is thought to sense sodium concentration in the tubular fluid.

Male Reproductive System

9

GENERAL FEATURES

The male reproductive system consists of the primary reproductive organs, the testes, and the secondary organs, including a complex series of genital ducts, the accessory glands, and the penis.

TESTES

The testes are composed of many seminiferous tubules and connective testicular stroma (Fig 1-9-1).

Seminiferous Tubules

The seminiferous tubules are the site of spermatogenesis. The epithelium is composed of supporting Sertoli cells and spermatogenic cells.

tavern UL&JU

SertoliCells

Sertoli cells are irregular columnar cells that extend from the basal lamina to the lumen and provide structural organization to the tubule.

- They synthesize testicular androgen-binding **protein,** which helps to maintain the high androgen levels within the seminiferous tubules. The androgen is necessary for spermatogenesis.
- They provide the **blood-testis barrier.** Tight junctions between adjacent Sertoli cells divide the seminiferous tubules into a basal compartment

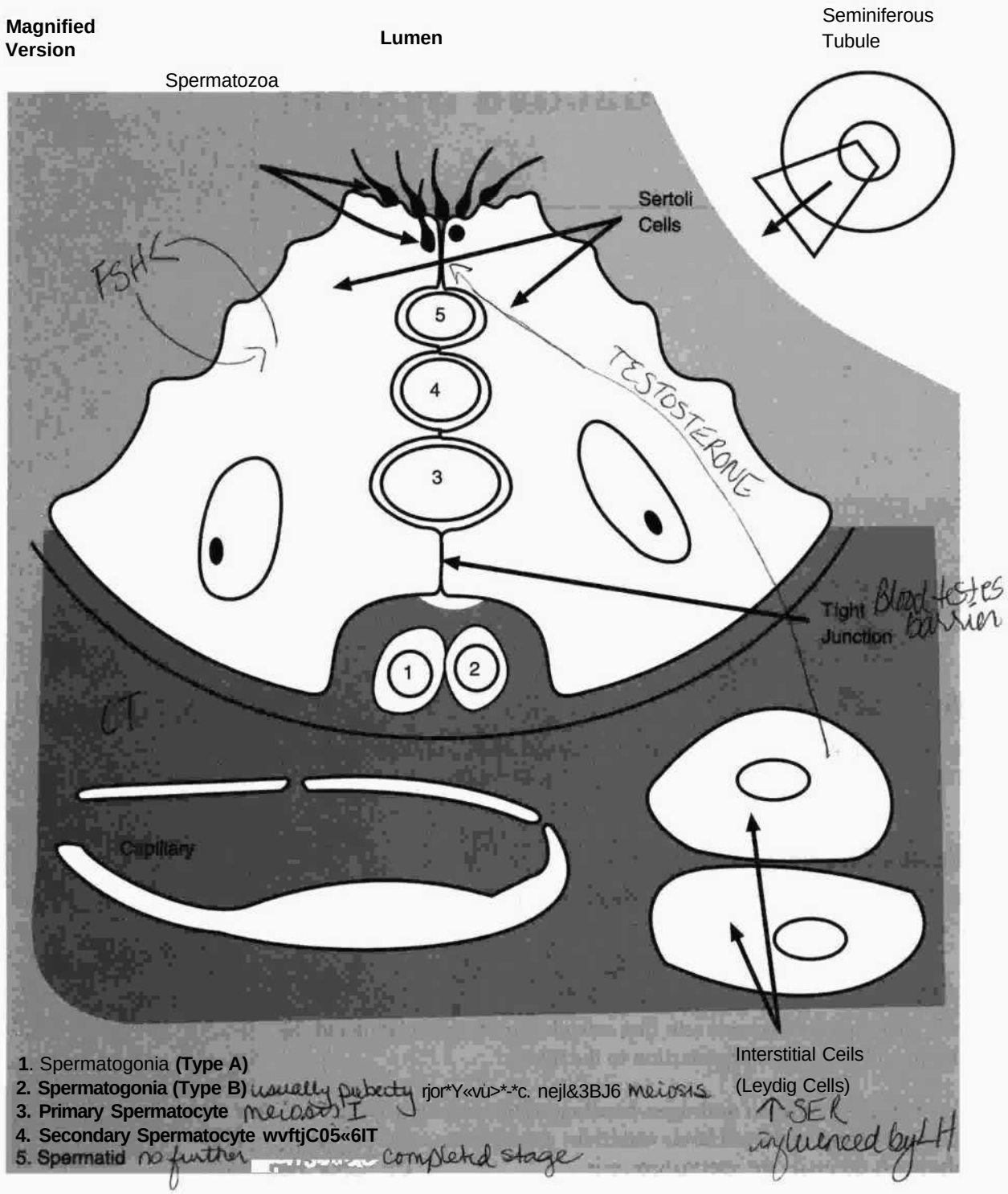


Figure 1-9-1. Seminiferous Tubule Diagram

(containing spermatogonia) and an adluminal compartment (containing spermatocytes and spermatids).

Spermatogenic Cells

Spermatogenic cells are the germ cells located between the Sertoli cells. They consist of spermatogonia, primary and secondary spermatocytes, spermatids, and spermatozoa (see Embryology section).

Spermatozoa

There are approximately 60,000 spermatozoa per cubic millimeter of seminal fluid, or 200 to 600 million in a single ejaculation (Figs 1-9-2 and 1-9-3).

The mature spermatozoa consist of a head and a tail.

- The head of the spermatozoon is pear-shaped, and chromatin is enclosed within the nuclear envelope. Covering the apex of the nucleus is the acrosome.
- The tail of the spermatozoon consists primarily of microtubules for the flagellum and mitochondria for energy.

1st stage: hyalinuronidase

2nd stage: acrosin. acrosomal rxn. is enzyme release to go through zona pellucida

3rd stage: fertilization
- complete meiosis in female of oocyte
- cortical rxn. prevents polyspermy

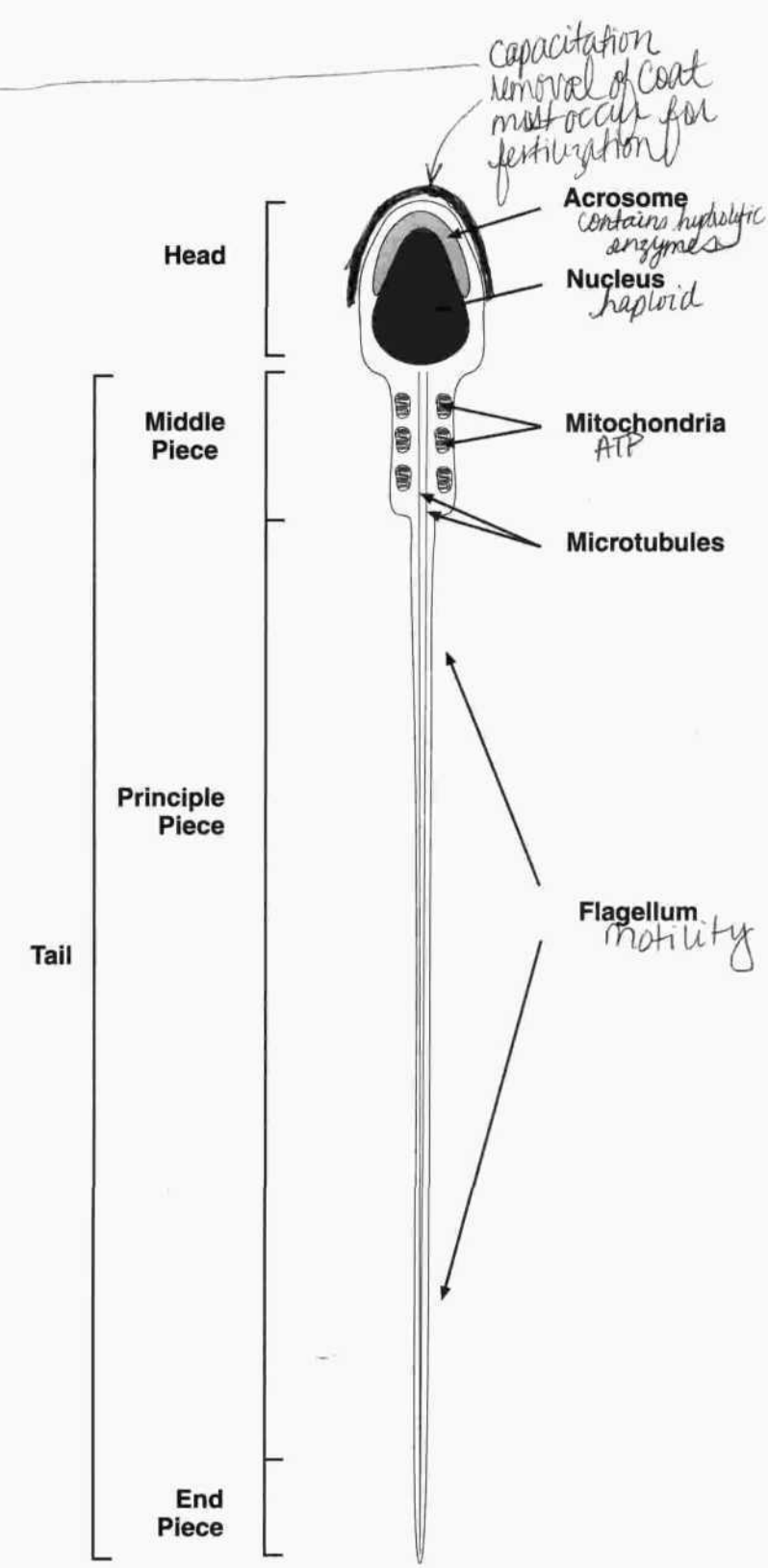


Figure 1-9-2. Spermatozoan

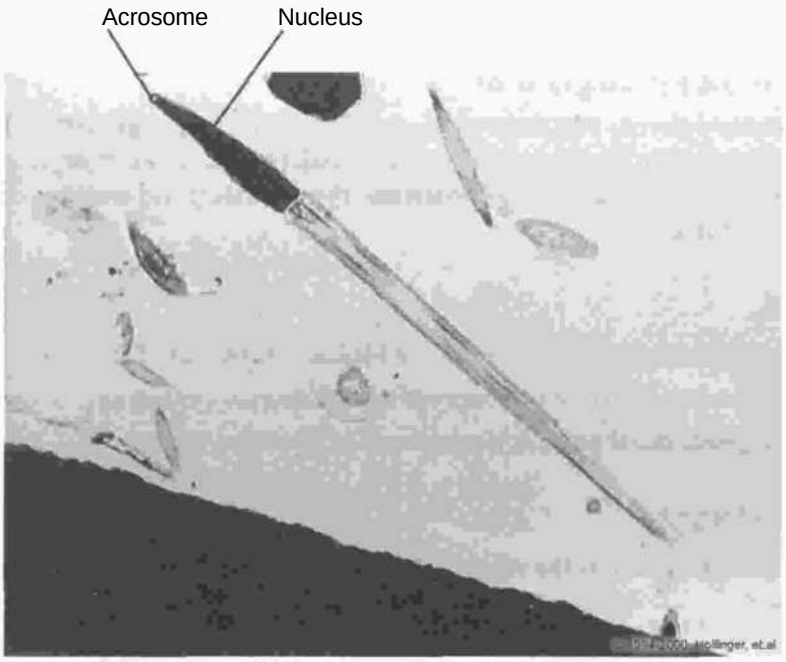


Figure 1-9-3. Electron Micrograph of a Spermatozoan

Interstitial Cells of Leydig

These are located between the seminiferous tubules in the interstitial connective tissue (Fig 1-9-1).

- They synthesize and secrete testosterone and 80% of the male estrogen.
- They have abundant SER, mitochondria with tubular cristae, and numerous lipid droplets containing cholesterol esters.
- They depend on the production of luteinizing hormone (LH) by the anterior pituitary gland for activity.

GENITAL DUCTS

- **Tubuli recti**—connect the seminiferous tubules with the rete testis. Continuous production of testicular fluid by Sertoli cells helps to move the gametes out of the seminiferous tubules.
- **Rete testis**—consists of an anastomosing labyrinth of channels within the mediastinum that converge toward the efferent ductules
- **Efferent** ductules—lined by a pseudostratified, ciliated epithelium
- **Ductus epididymis**—a single, elongated tortuous duct that may be 6 m or more in length *mlhJT) Jt^C&mz, tmn n^Ohib Cu4 (ft*

It is lined by a pseudostratified epithelium containing stereocilia.

It is here that sperm undergo maturation and develop increased motility and fertilizing capacity.

- **Ductus deferens (vas** deferens)—contains a thick muscular coat, which dilates distally into an ampulla. The ampulla gradually narrows to form the ejaculatory duct, which penetrates the prostate gland and empties into the urethra.

Urethra

- The male urethra extends from the bladder to the end of the penis.
- The prostatic portion is composed of transitional epithelium.
- The penile distal portion is composed of stratified epithelium.

Sperm Storage

Sperm storage occurs in the efferent ductules, epididymis, and proximal ductus deferens.

ACCESSORY GLANDS AND PENIS

Seminal Vesicles

The seminal vesicles secrete a slightly alkaline, viscous fluid into the semen that is rich injjuctose and serves as an energy source for the sperm.

They are not a storage organ for sperm.

Prostate Gland

The prostate gland produces a secretion rich in citric acid, lipids, zinc, and acid phosphatase activity.

It often contains concretions composed of protein and carbohydrate.

Bulbourethral (Cowper's) Gland

The bulbourethral gland secretes a viscous mucous fluid into the urethra for lubrication before ejaculation.

Penis

The penis is composed of three cylindrical bodies of erectile tissue:

- **Corpora cavernosa** contains irregular vascular channels, separated by trabeculae and surrounded by a fibrous capsule called the tunica albuginea.
- The inner surface of the tunica albuginea has a plexus of small veins that drain the cavernous spaces.
- **Corpus spongiosum** exhibits a similar arrangement of erectile tissue.
- **The trabeculae of erectile tissue** contain branches of the deep artery of the penis, which end in small arteries that open directly into the cavernous spaces.

Female Reproductive System

10

GENERAL FEATURES

The female reproductive system consists of the ovaries, fallopian tubes (oviducts, uterine tubes), uterus and cervix, vagina, external genitalia, and mammary glands.

OVARIES

The ovaries are divided into two regions:

- The **cortex**—contains ovarian follicles and cellular connective tissue
- The **medulla,** or **zona vasculosa**—the central deeper layer contains many large blood vessels and nerves.

Ovarian Follicles and Follicular Development

Follicles (Fig I-10-1) are located in the cortical stroma and are composed of oocytes surrounded by follicular (granulosa) cells.

- Approximately 400,000 follicles are present in the newborn ovaries. Only a small percentage of the oocytes (approximately 450) reach maturity in the **adult**
- The remaining follicles eventually degenerate through a process called atresia. Atresia may occur at any stage of follicular development.

Primordial Follicles

The primary oocyte surrounded by a single layer of flattened follicular cells.

Primary Follicles

The primary oocyte and one or more layers of cuboidal-like follicular cells.

Secondary Follicles

The follicular cavity (antrum), **cumulus** oophorus, and **corona radiata** develop CT surrounding the follicle. The CT develops into the theca interna and externa.

The **theca interna** produces androgens, which are converted into estradiol by granulosa cells.

The **zona** pellucida forms around the oocyte; it is rich in polysaccharides (periodic acid-Schiff [PAS]-positive).

Graafian Follicle

The graafian follicle is the mature follicle that extends through the entire cortex.

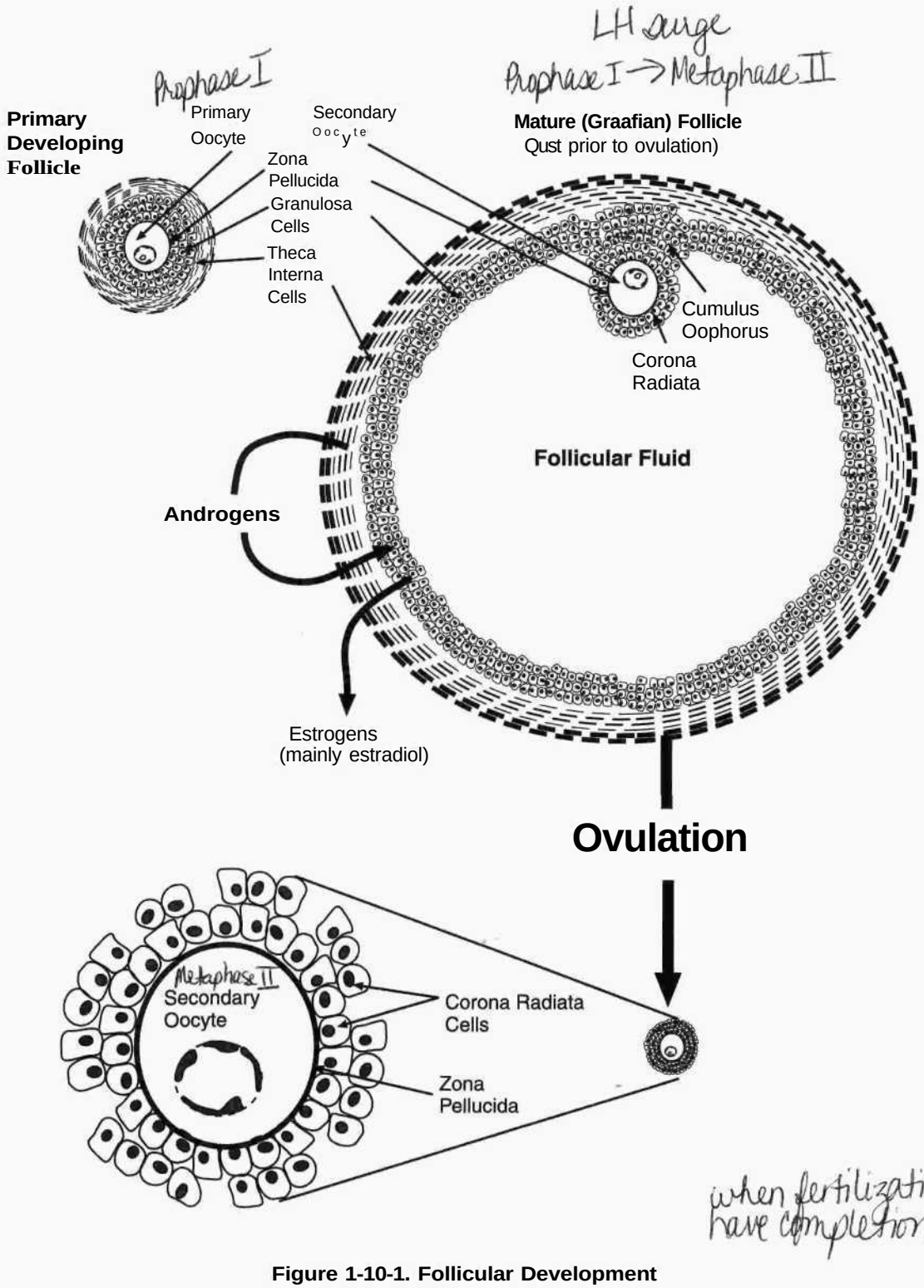


Figure 1-10-1. Follicular Development

Ovulation

An increase of **antral fluid** causes an increase in pressure on the wall of the follicle and on the thin layer of ovarian tissue at the surface of the ovary. The follicle eventually ruptures, and the ovum, along with its corona radiata, passes out of the ovary.

The ovum must be fertilized within 24 hours or it degenerates.

Corpus Luteum

Follicular changes after ovulation lead to the formation of **the corpus luteum.**

- Theca interna cells enlarge and become theca lutein cells—secrete estrogen.
- Follicular cells enlarge and become granulosa lutein cells—secrete progesterone.
- If the ovum is not fertilized, the corpus luteum reaches its maximal development approximately 7 days after ovulation and then begins to degenerate.
- If the **ovum is fertilized,** the corpus luteum increases in size for approximately 3 months. The corpus luteum persists until the 12th week before degenerating and is maintained by human chorionic gonadotropin (hCG) secreted by the developing embryo. After the 40th day of pregnancy, the placenta produces the progesterone necessary to maintain pregnancy.

FALLOPIAN TUBES

The Fallopian tubes are approximately 12 cm long, richly vascularized, and lined by a **ciliated mucosa** (cilia beat toward the uterus).

Regions of the Fallopian Tube

Infundibulum

The infundibulum is open to the peritoneal cavity with branched processes called fimbriae. It is covered with ciliated cells that beat toward the mouth of the tube.

Before ovulation, estrogens induce engorgement of blood vessels in the **fimbriae,** which expands the fallopian tube toward the surface of the ovary. Estrogens similarly induce growth and activity of the cilia as well as enhancement of the peristaltic contractions of the fallopian tube.

Ampulla

The ampulla is the thin-walled longest region of the oviduct.

(Fertilization) usually occurs in the ampulla.

- This is also the most frequent location of ectopic pregnancy.

Isthmus

The isthmus is a narrow, thick-walled segment nearest to the uterine wall.

Uterine(Interstitial)Segment

The uterine segment is the portion of the tube that traverses the uterine wall.

UTERUS

Uterine Wall

The uterine wall has three coats.

Endometrium

The endometrium is composed of simple columnar epithelium (ciliated and nonciliated cells), with two layers:

- The deeper **basal layer** is relatively thin and is not discharged during menstruation.
- The superficial **functional layer** alters during the menstrual cycle and is lost at menstruation.

Myometrium

The myometrium is composed of smooth muscle, connective tissue, and prominent blood vessels.

Perimetrium

The perimetrium consists of the peritoneal layer of the broad ligament.

Cyclic Endometrial Changes During the Menstrual Cycle

The average menstrual cycle lasts 28 days (Fig 1-10-2).

MenstrualStage

The first 3 to 5 days of the cycle are characterized by menstrual flow.

Proliferative(Estrogenic)Stage

- Begins during the later stages of menstrual flow and continues through the 13th or 14th day
- Is marked by regrowth of the endometrium, including epithelial cell pro-

liferation and growth of the spiral arteries

SecretoryPhase

- Continues the hypertrophy of the endometrium (no mitosis)
- There is increased vascularity and increased edema.

PremenstrualPhase

Consists mostly of changes in the spiral arteries that lead to the breakdown of the functional layer.

- Constriction of the spiral arteries leads to anoxia and ischemia.

Uterine Changes in Relation to the Ovary

Cyclic changes of the uterus are closely associated with cyclic changes of the ovary (Fig 1-10-2).

OnsetofMenstruation

The onset of menstruation corresponds to the involution of the corpus luteum.

ProliferativePhase

The proliferative phase is estrogen dependent. It corresponds to the preovulatory period of foUicular maturation. Ovulation normally occurs at the end of the proliferative phase, 14 days before menstruation begins—usually between the 10th and 14th day.

SecretoryPhase

The secretory phase is progesterone dependent and associated with the luteal phase of the ovary.

NoFertilization

- The corpus luteum degenerates 12 days after ovulation.
- A drop in progesterone and estrogen levels ensues.
- The functional layer degenerates and menstrual flow commences.

Fertilization

Uterine changes in relation to fertilization (see week 1 and 2 in embryology).

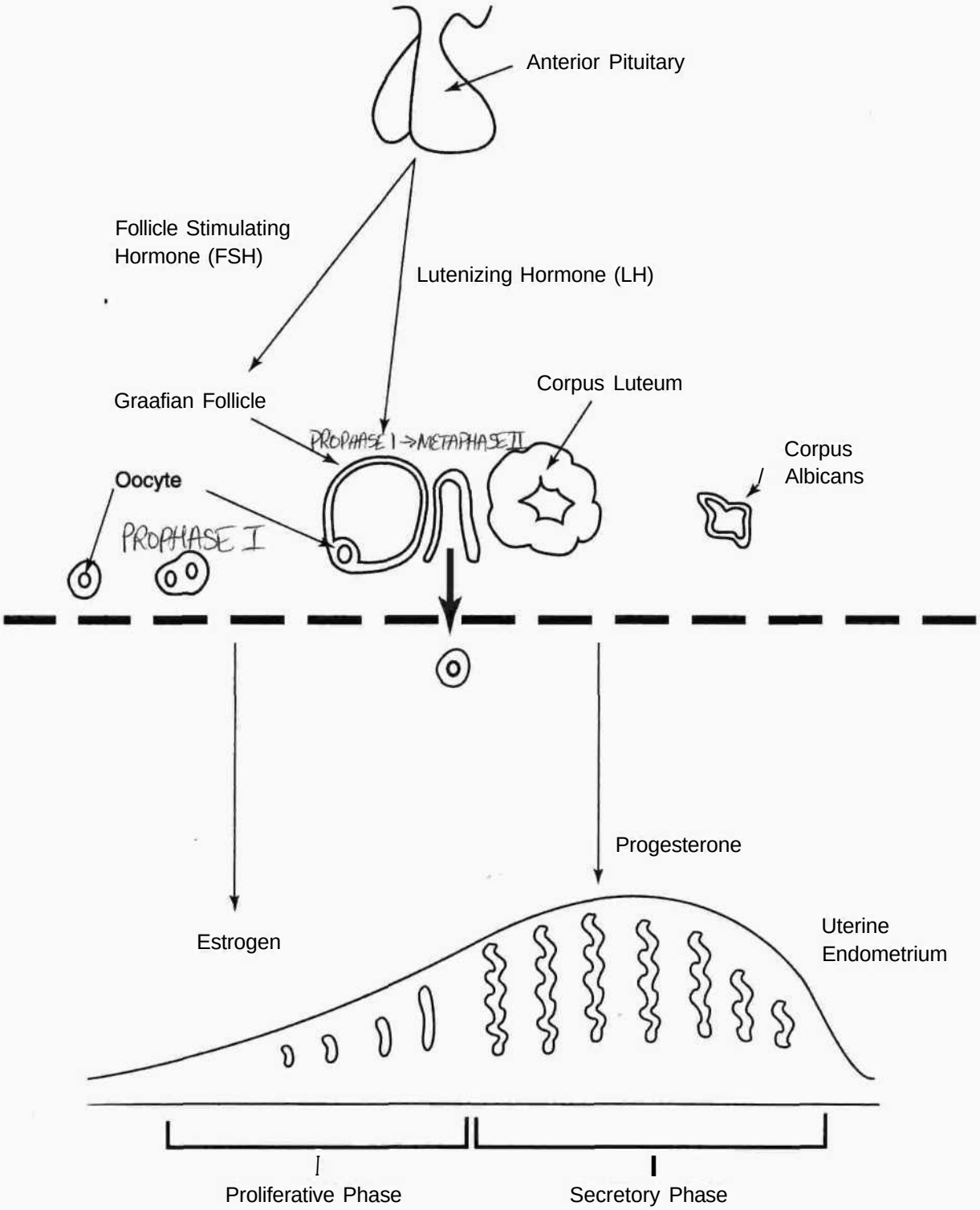


Figure 1-10-2. Menstrual Cycle

PLACENTA

The placenta permits exchange of nutrients and waste products between the maternal and fetal circulations (Fig 1-10-3).

Fetal Component

The fetal component consists of the chorionic plate and villi. It lies adjacent to the spaces near the endometrial decidua through which the maternal blood circulates.

The Maternal Component

The maternal component is composed of the **decidua** basalis.

Maternal blood vessels from the decidua conduct blood into the intervillous spaces of the placenta, where floating villi are present.

Placenta! ***Barrier***

Maternal blood is separated from fetal blood by cytotrophoblast, syncytiotrophoblast, a basement membrane, and fetal capillary endothelium.

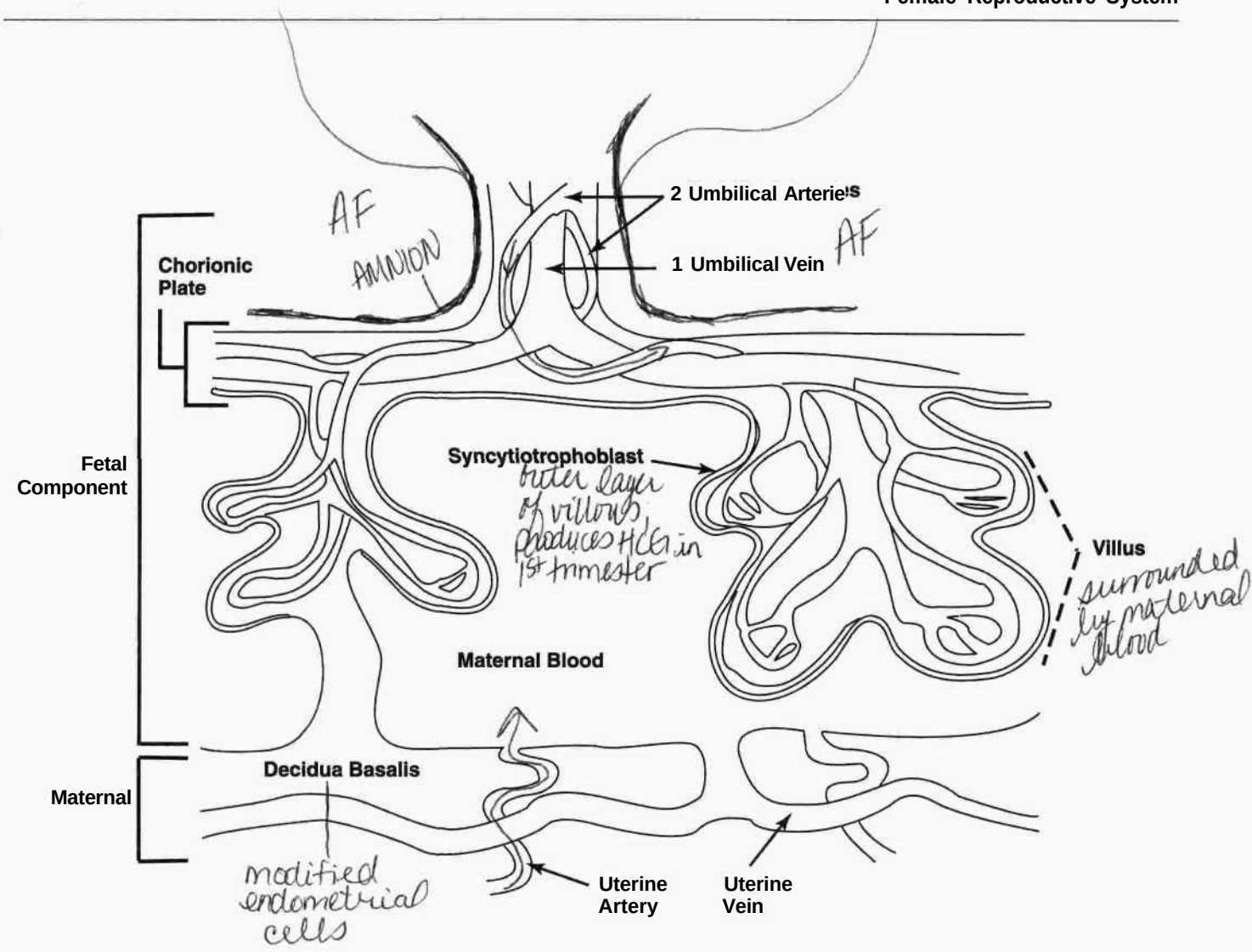


Figure 1-10-3. Placenta

VAGINA

- The vagina extends from the vestibule of the external genitalia to the cervix.
- It contains no glands. The mucus lubricating it originates from the glands of the cervix and the vestibular glands.
- It is lined by a stratified squamous epithelium that is rich in glycogen.

Vaginal Changes Caused by Changes in Estrogen Levels

Estrogenic Phase

During the estrogenic phase vaginal fluid has a lower pH than during the rest of the cycle, resulting from the formation of lactic acid by bacteria metabolizing glycogen.

Post-Estrogenie Phase

The drop in estrogen levels induces a decrease in glycogen levels, which in turn causes an increase in vaginal pH and, thus, an increase in the likelihood of infection.

MAMMARY GLANDS AND EXTERNAL GENITALIA

See Gross Anatomy and Embryology sections.

SECTION II

Early Embryology

Gonad Development

1

PRIMORDIAL GERM CELLS

Primordial germ cells arise in the wall of the yolk sac.

INDIFFERENT GONAD

At week 4, primordial germ cells migrate into the indifferent gonad, which forms in a longitudinal elevation of **intermediate mesoderm** called the **urogenital ridge.**

TESTES AND OVARY

The indifferent gonad will develop into either the testes or ovary.

Testes

Development of the testes is directed by:

The *Sry* **gene** on the short arm of the Y chromosome, which encodes for **testes-determining factor (TDF).**

Testosterone, which is secreted by the Leydig cells.

Müllerian-inhibiting factor (MIF), which is secreted by the Sertoli cells.

Ovary

No factors are involved.

Meiosis

Meiosis occurs within the testes and ovary. This is a specialized process of cell division that produces the male gamete **(spermatogenesis)** and female gamete **(oogenesis).** There are notable differences between spermatogenesis and oogenesis, discussed below.

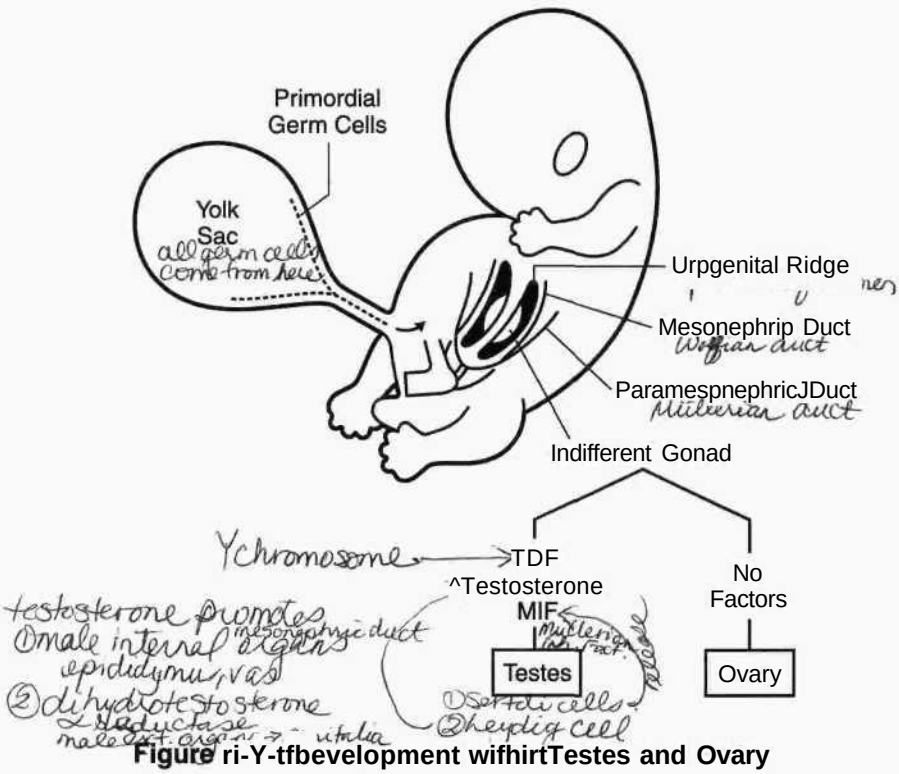


Figure ri-Y-tfbevelopment wifhirtTestes and Ovary

Meiosis consists of two cell divisions, meiosis I and meiosis II.

Meiosis I

In meiosis I, the following events occur:

Synapsis—the pairing of 46 homologous chromosomes

Crossing over— the exchange of segments of DNA

Disjunction—the separation of 46 homologous chromosomes **without** centromere splitting

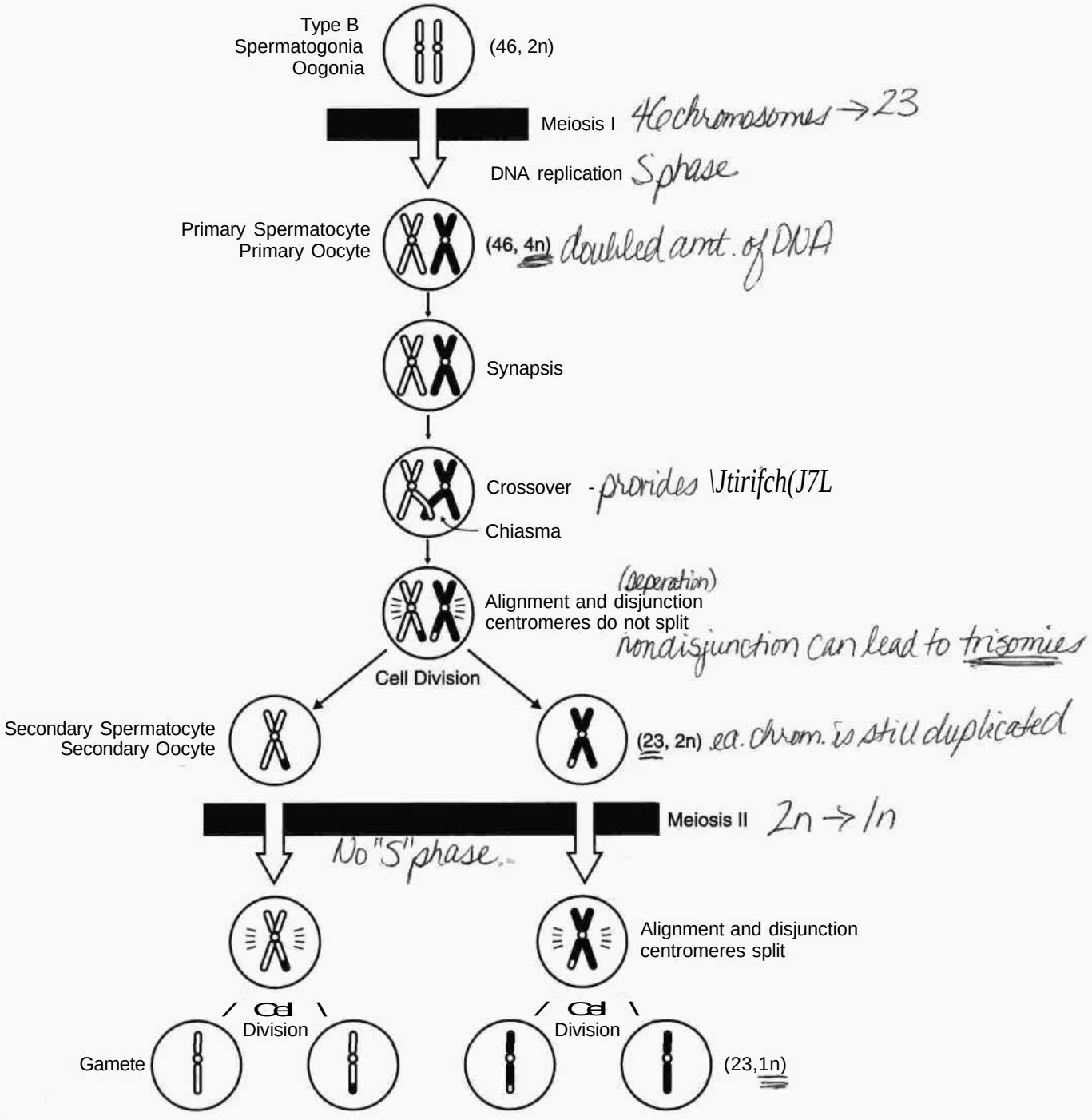


Figure 11-1-2. Meiosis

Meiosis II

In meiosis II:

- Synapsis does not occur.
- Crossing over does not occur.
- Disjunction occurs **with** centromere splitting.

Spermatogenesis

Primordial germ cells arrive in the indifferent gonad at week 4 and remain **dormant untiTpubcrty.**

When a boy reaches puberty, primordial germ cells differentiate into **type A spermatogonia**, which serve as stem cells throughout adult life.

Some type A spermatogonia differentiate into **type B spermatogonia.**

Type Bjpgrrnatogpnia enter meiosis I to form **primary spermatocytes.**

Primary spermatocytes form two **secondary spermatocytes.**

Secondary spermatocytes form two **spermatids.**

Spermatids undergo **spermiogenesjs,** which is a series of morphological changes resulting in the mature **sjerm**.

Oogenesis

Primordial germ cells arrive in the indifferent gonad at week 4 and differentiate into oogonia.

Oogonia enter meiosis I to form **primary oocytes.** All primary oocytes are formed by **month 5 of fetal life** and remain **arrested** in **propjiasje (diplotene) of meiosis I** until puberty.

No oogonia are present at birth.

When a girl reaches puberty, a primary oocyte completes meiosis I to form a secondary oocyte and polar body.

The secondary oocyte becomes **arrested in metaphase of meiosis II** and is ovulated.

At fertilization within the uterine tube, the secondary oocyte completes meiosis II to form a **mature oocyte** and **polar body.**

Weeki: Beginning of Development

2

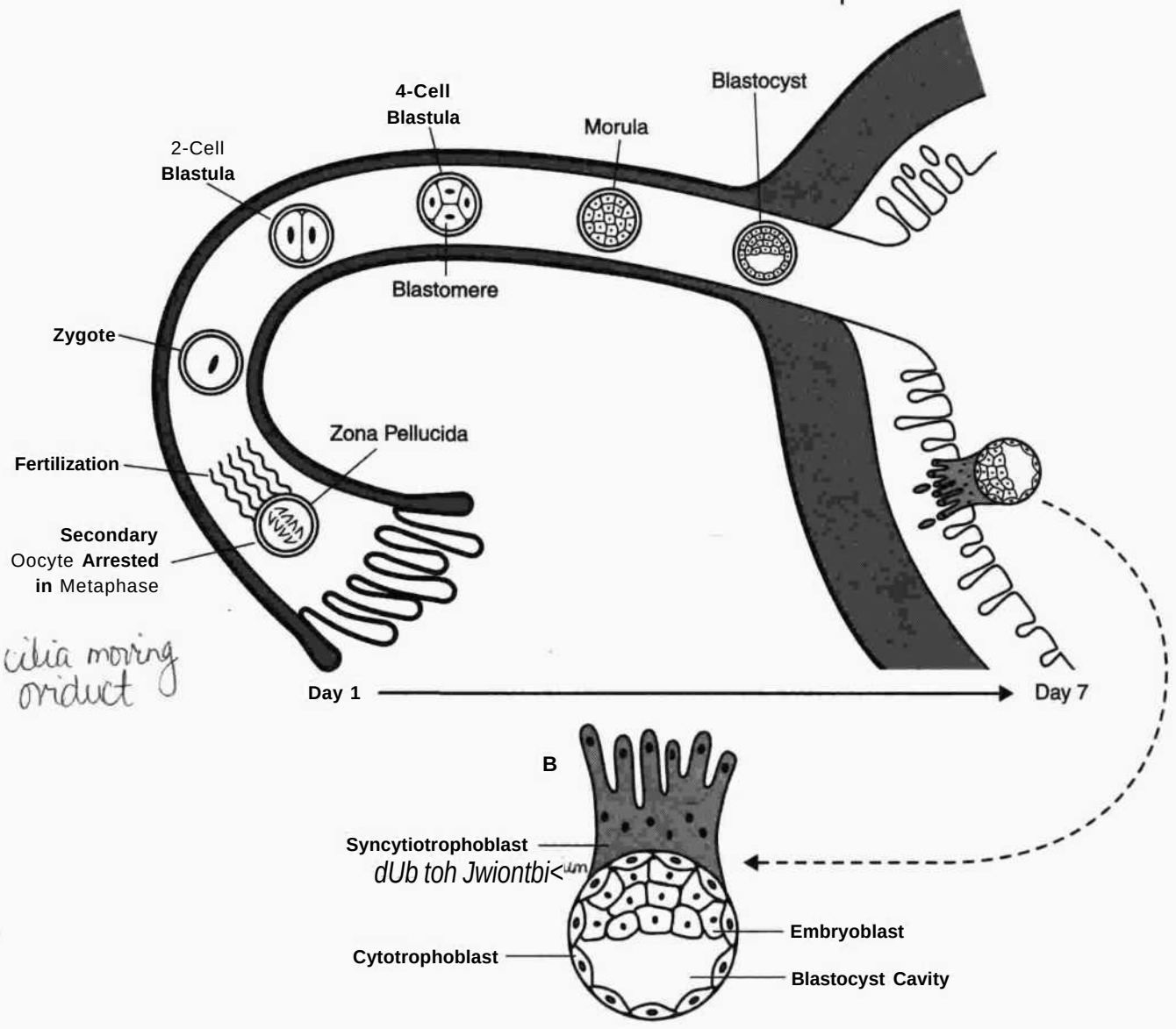


Figure 11-2-1. Week 1

Clinical Correlate

Ectoplc Tubal Pregnancy

This is the most common form of ectopic pregnancy. It most usually occurs when the blastocyst implants within the **ampulla of the uterine tube** because of **delayed transport.** Risk factors include endometriosis, pelvic inflammatory disease (PID), tubular pelvic surgery, or exposure to diethylsjjjbejtjpJUDES). Clinical signs include abnormal or brisk uterine bleeding, sudden onset of abdominal pain that may be confused with appendicitis, last mgnsesJaO days_ago, positive human chorionic gonadotropin (hCG) test, and culdocentesis showing intraperitoneal blood.

Ectoplc Abdominal Pregnancy

Ectopic abdominal pregnancy most commonly occurs in the **rectouterlne pouch (pouch of Douglas).**

ZYGOTE FORMATION

Fertilization occurs in the ampulla of the uterine tube. The male and female pronudei fuse to form a zygote.

CLEAVAGE

Cleavage is a series of **mitotic** divisions of the zygote.

Blastula

Zygote cytoplasm is successively cleaved to form a blastula consisting of increasingly smaller **blastomeres** (2-cell, 4-cell, 8-cell stage, etc.).

Morula

At the 32;cell stage, the blastomeres form a morula consisting of an **inner cell** mass and an outer cell mass.

BLASTOCYST

Blastocyst formation occurs when fluid secreted within the morula forms the **blastocyst cavity:**

The inner cell mass is now known as the **embryoblast** (becomes the embryo/fetus).

The outer cell mass is now known as the **trophoblast** (becomes part of the placenta).

IMPLANTATION

The **zona pellucida** must degenerate for implantation to occur.

The blastocyst usually implants within the **posterior wall of the uterus.**

The blastocyst implants within the **functional layer** of the endometrium during the progestational **phase** of the menstrual cycle.

The trophoblast differentiates into the **cytotrophoblast** and **syncytiotrophoblast**

Week 2: Formation of the Bilaminar Embryo

3

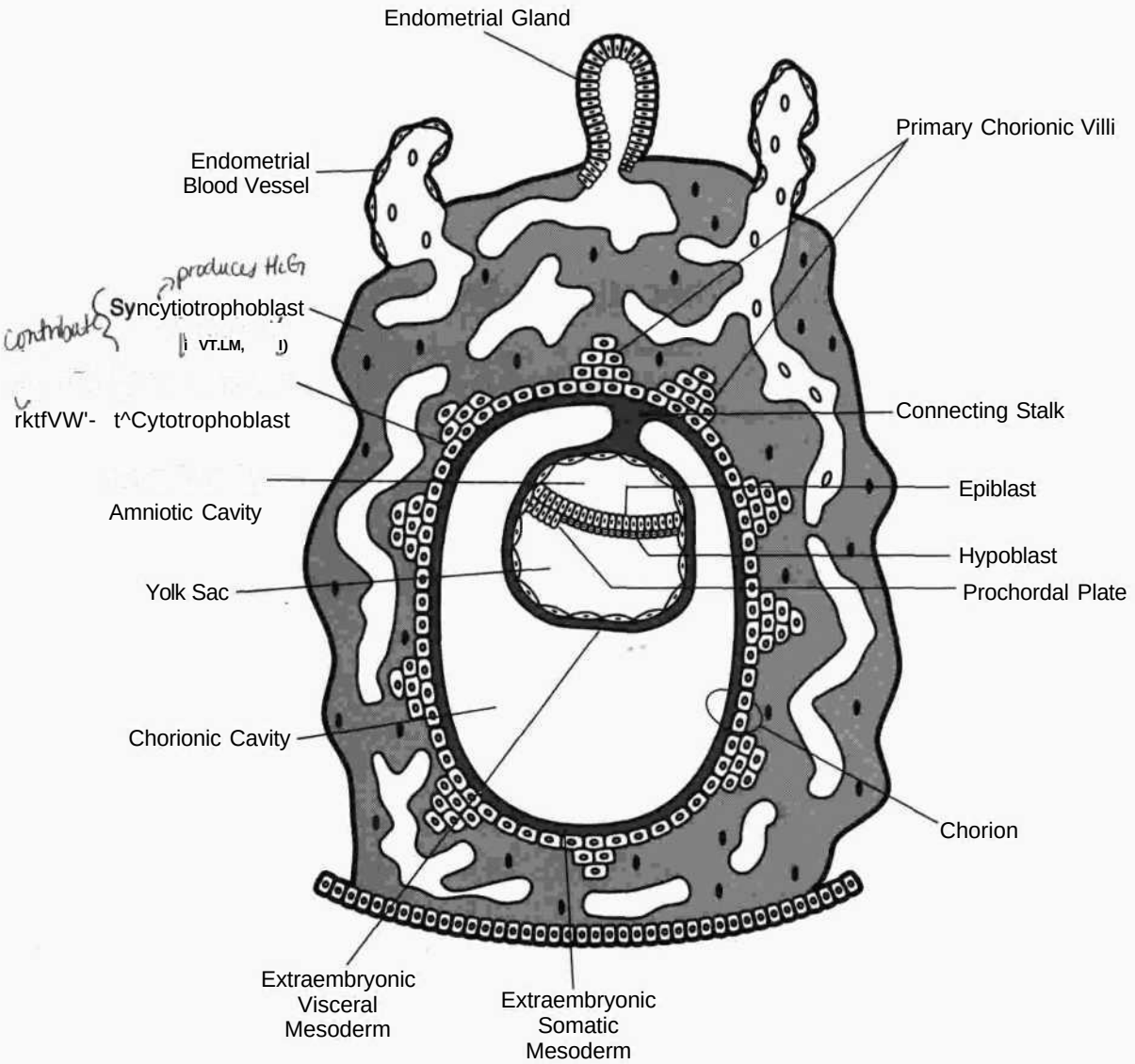


Figure 11-3-1. Week 2

Clinical Correlate

Human Chorionic Gonadotropln

hCG is a glycoprotein, produced by the syncytiotrophoblast, which stimulates the production of progesterone by the corpus luteum (i.e., maintains corpus luteum function).

hCG can be assayed in maternal blood at day 8 or maternal urine at day 10 and is the basis for early pregnancy testing. hCG is detectable throughout pregnancy. Low hCG levels may predict a spontaneous abortion or ectopic pregnancy. High hCG levels may predict a multiple pregnancy, hydatidiform mole, or gestational trophoblastic neoplasia.

Clinical Correlate

Hydatidiform Mole

A hydatidiform mole is a blighted blastbcysnembryo dies) followed by hyperplastic proliferation of the trophoblast within the uterine wall. Clinical signs are preeclampsia during the first trimester, hugh hCG levels (> 100,000 mIU/mL), and an enlarged uterus with bleeding. Five percent of moles develop into gestational trophoblastic neoplasia, so follow-up visits are essential.

Clinical Correlate

Gestational trophoblastic neoplasia (GTN; or chorlocarclnoma) is a malignant tumor of the trophoblast that may occur after a normal pregnancy, abortion, or hydatidiform mole. High hCG levels are diagnostic, with a high degree of suspicion.

Nonmetastatic GTN (confined to the uterus) is the most common form, and treatment is highly successful. However, prognosis of metastatic GTN is poor if it spreads to the liver or brain.

BILAMINAR EMBRYONIC DISK

The embryoblast differentiates into the **epiblast** and **hypoblast,** forming a bilaminar embryonic disk.

AMNIOTIC CAVITY AND YOLK SAC

The amniotic cavity and yolk sac form.

1 The **prochordal plate** marks the site of the future **mouth.**

GROWTH INTO THE ENDOMETRIUM

The syncytiotrophoblast continues its growth into the endometrium to make contact with endometrial blood vessels and glands. **No mitosis occurs in the syncytiotrophoblast.** The cytotrophoblast is mitotically active.

EXTRAEMBRYONIC MESODERM AND CHORION FORMATION

Extraembryonic mesoderm is a new layer of cells derived from the epiblast. **Extraembryonic somatic mesoderm** lines the cytotrophoblast, forms the connecting stalk, and covers the amnion. **Extraembryonic visceral mesoderm** covers the yolk sac.

The connecting stalk suspends the conceptus within the chorionic cavity. The wall of the chorionic cavity is called the chorion, which consists of extraembryonic somatic mesoderm, cytotrophoblast, and syncytiotrophoblast.

Embryonic Period (Weeks 3-8)

4

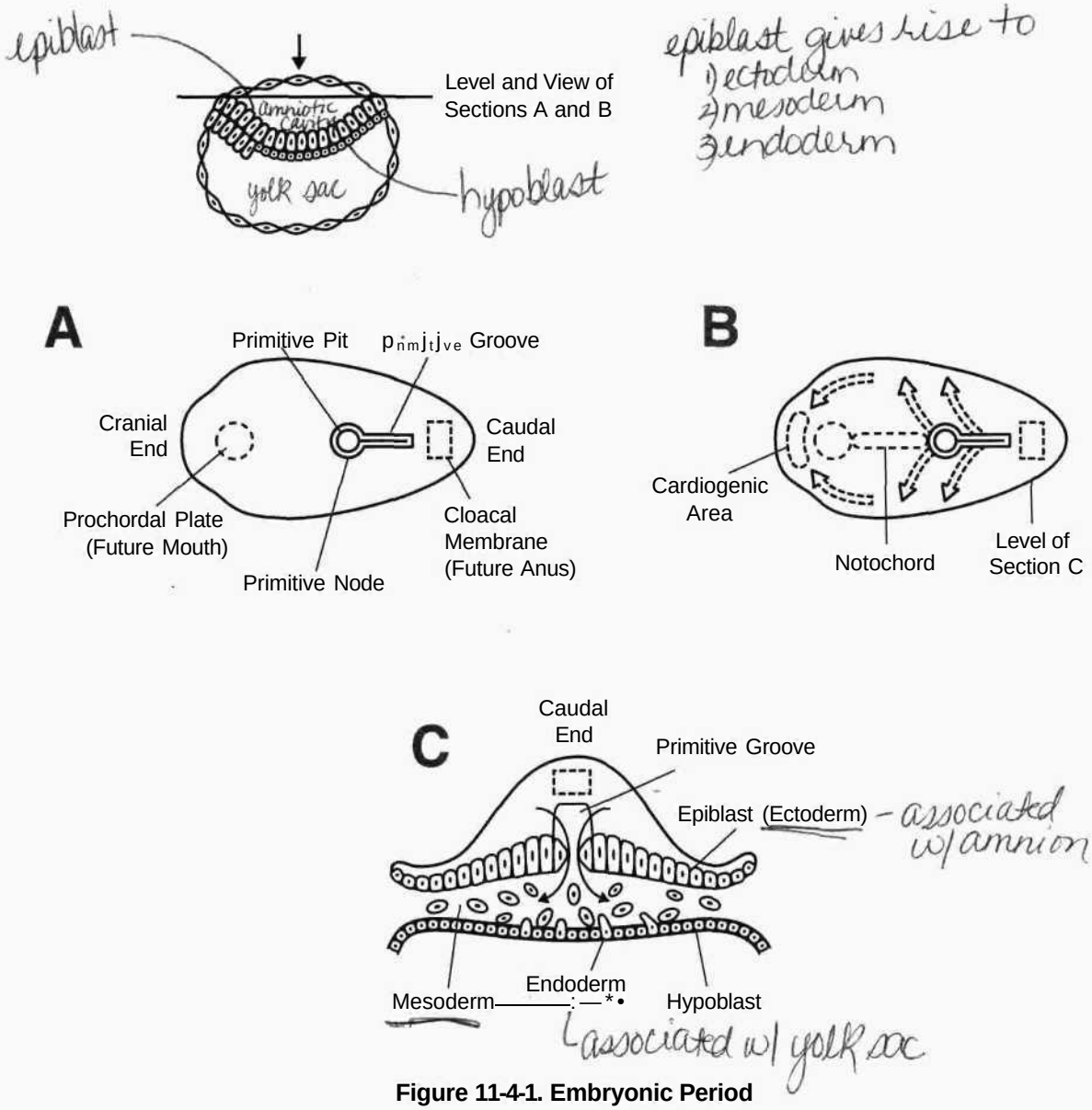


Figure 11-4-1. Embryonic Period

GASTRULATION

Gastrulation is a process that establishes the three primary germ layers: **ectoderm, mesoderm,** and endoderm. This process is first indicated by the formation of the **prjmjti¥e_streak** within the epiblast.

Ectoderm

Ectoderm gives further rise to neuroectoderm and **neural crest cells.**

Mesoderm

Mesoderm gives further rise to **paraxial mesoderm** (35 pairs of somites), **intermediate mesoderm,** and **lateral mesoderm.**

WEEK 3

Week 3 of embryonic development corresponds to the **first missed menstrual period.**

All cells and tissues of the adult can trace their origin back to the three primary germ layers.

ORGAN SYSTEMS DEVELOPMENT

All major organ systems begin to develop during the **embryonic period (weeks 3-8),** causing a craniocaudal and lateral body folding of the embryo. By the end of the embryonic period (week 8), the embryo has a distinct human appearance.

Clinical Correlate

Sacrococcygeal Teratoma

A sacrococcygeal teratoma is a tumor that arises from remnants of the primitive streak. It often contains various types of tissue (bone, nerve, hair, etc).

Chordoma

A chordoma is a tumor that arises from remnants of the notochord found either intracranially or in the sacral region.

Clinical Correlate

Caudal Dysplasfa (Sirenomella)

Caudal dysplasia refers to a constellation of syndromes ranging from minor lesions of the lower vertebrae to complete fusion of lower limbs as a result of **abnormal gastrulatlon** in which migration of mesoderm is disturbed. It is associated with **VATER** (vertebral defects, anal atresia, tracheoesophageal fistula, and renal defects) or **VACTERL** (vertebral defects, anal atresia, cardiovascular defects, tracheo esophageal fistula, renal defects, and upper limb defects).

Table II-4-1. Development of the Fetal Structures From the Three Germ Layers

Ectoderm	Mesoderm	Endoderm
Epidermis, hair, nails	I/Muscle (smooth, cardiac, skeletal)	Epithelial lining of:
Cochlear duct, semicircular ducts	Extraocular muscles (preotic somites)	Gastrointestinal tract
Enamel of teeth	Muscles of the tongue (occipital somites)	Trachea, bronchi, lungs
^denohypophysis' *hMtope****		Biliary apparatus
Lens of the eye	/Connective tissue, dermis of skin	Urinary bladder, urethra
"Tarotid gland	Bone, cartilage	Vagina
Mammary glands	i/Blood and lymph vessels	Auditory tube—-i *pL/jn^^AtaJQfJ]* •cL
Epithelial lining of lower anal canal	Heart	•-Middle ear cavity—' r o Q f
	Adrenal cortex	Parenchyma of:
	Spleen	Liver
	Kidney	Pancreas
	Dura mater	Submandibular gland
	Testes, ovaries	Sublingual gland
		Thyroid
		^Parathyroid- *dwiM'dU(Jt Mil/A*
Neuroectoderm		
All neurons within brain and spinal cord		
/Retina *cnaqcruHL H phMyvHtb^Ao^*		
^eurohypophysis		
Astrocytes, oligodendrocytes		
s^euralcresp		
^/Ganglia: dorsal root, cranial, autonomic		
V Schwann cells		
Pia and arachnoid		
/Adrenal medulla		
Parafollicular cells (calcitonin)		
i/Aorticopulmonary septum f-£ncto	rdial cushion cells	
Dilator and sphincter pupillae mm.		
Ciliary muscle		

Further detail of the development into adult structures is presented in the gross anatomy section.

think about inner lining of GI — and all things that excrete into respiratory

SECTION III

Gross Anatomy and Organogenesis

1 Back and Nervous System

VERTEBRAL COLUMN

Embryology

During the fourth week, sclerotome cells migrate medially to surround the spinal cord and notochord. After proliferation of the caudal portion of the sclerotomes, the v£rJtebxae_are-foFme4, each consisting of the caudal part of one sclerotome and the cephalic part of the next.

The nolochotd persists in the areas between the vertebral bodies, forming the -Wicleus pulposus. The latter, together with surrounding circular fibers of the anulus fibrosis, forms the intervertebral disc^

Cervical Vertebrae

There are sgy£fl cervical vertebrae of which the first two are atypical. All cervical vertebrae have openings in their transverse processes, the transverse foramina, which, when aligned, produce a canal that transmits the vertebraTartery and vein (FigIII-1-1).

Atlas

This is the first cervical vertebra (C1). It has no body and leaves a space to accommodate the dens of the second cervical vertebra.

Axis

This is the second cervical vertebra (C2). It has a tooth-shaped process, the dens (odontoid process), which articulates with the atlas as a pivot joint. Movement at this joint allows lateral rotation of the head.

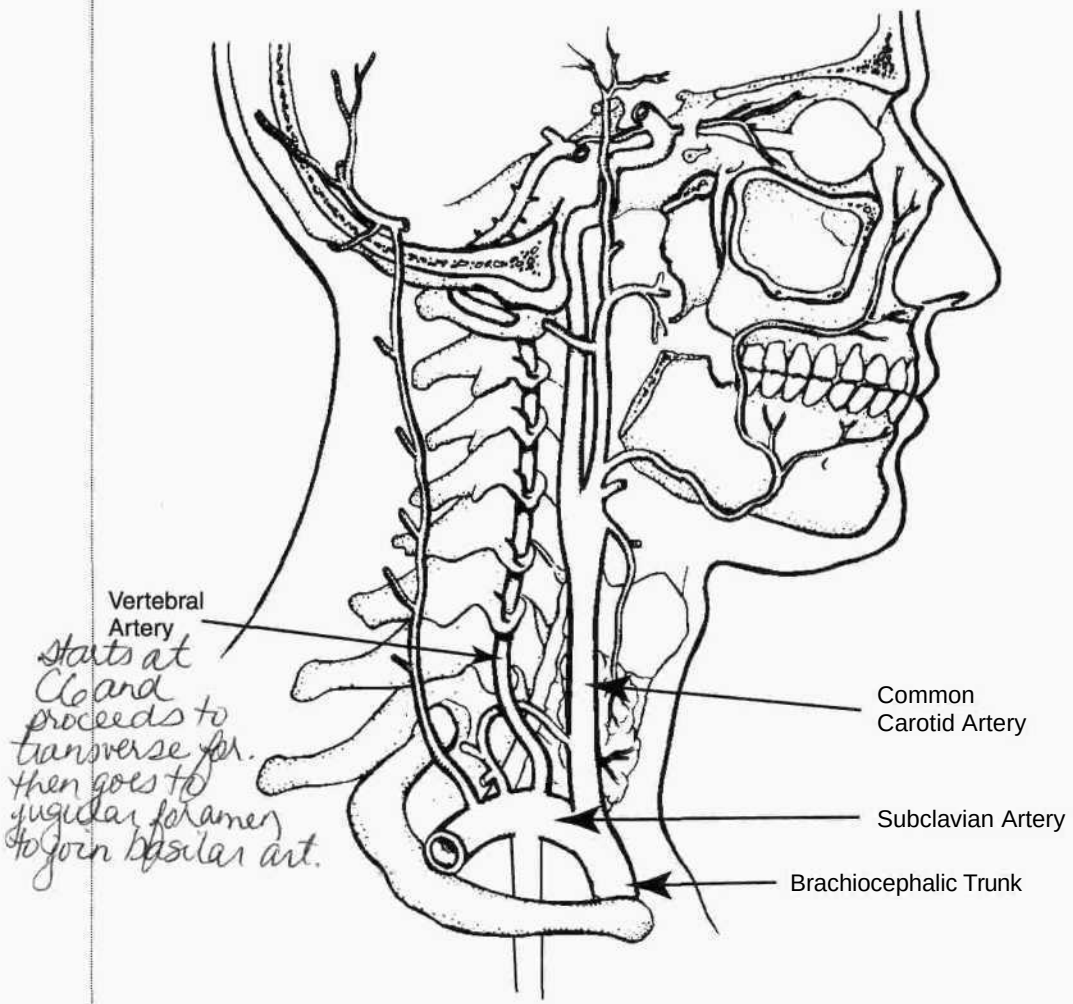


Figure II1-1-1. Arteries to the Head

Thoracic Vertebrae

There are 12 thoracic vertebrae (Fig III-1-2).

- The vertebrae have facets on their bodies to articulate with the heads of ribs; each rib head articulates with the body of the numerically corresponding vertebra and the one below it.
- The thoracic vertebrae have facets on their transverse processes to articulate with the tubercles of the numerically corresponding ribs.

Lumbosacral Vertebrae

Unlike the thoracic wall, the bony support of the abdomen is minimal, consisting only of the lumbar vertebrae and portions of the pelvis (the ilium and the pubis).

- There are five lumbar vertebrae, LI through L5.
- There are five sacral vertebrae, Si through S5, which are fused.

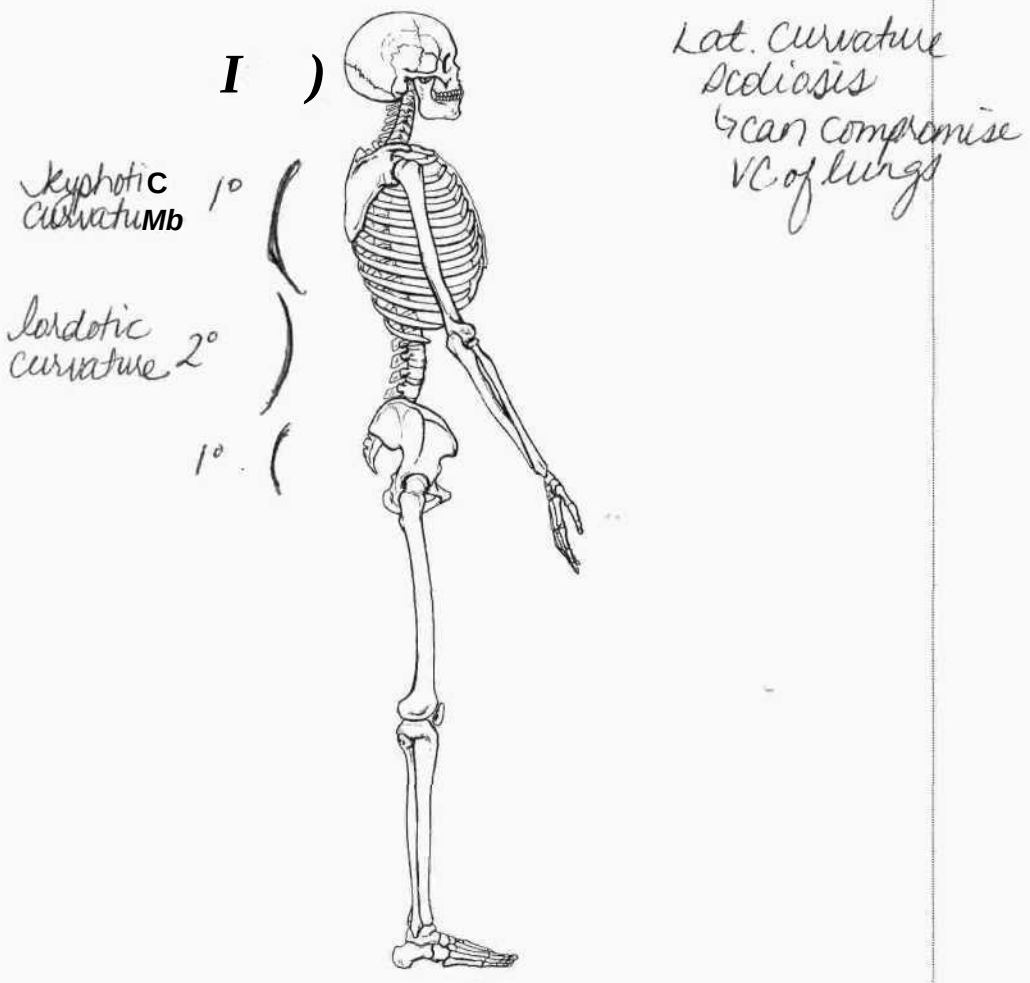


Figure IH-1-2

Intervertebral Disks

Each disk has an outer portion, the **anulus** fibrosus, which is composed of fibrocartilage and fibrous connective tissue, and an inner portion, the **nucleus pulposus,** which is a semigelatinous fluid with very few, if any, cells.

Herniation of a nucleus pulposus is almost always in a **posterolateral** direction, passing through a rupture of the anulus fibrosus.

> The herniated nucleus often comes to lie in the intervertebral foramen where it may compress a spinal nerve.

Ligaments

The intervertebral disk is reinforced anteriorly and anterolaterally by the **anterior longitudinal ligament.**

The posterior longitudinal ligament reinforces it posteriorly.

It is notjejnforce^ojterpkterally. this is why rupture occurs here

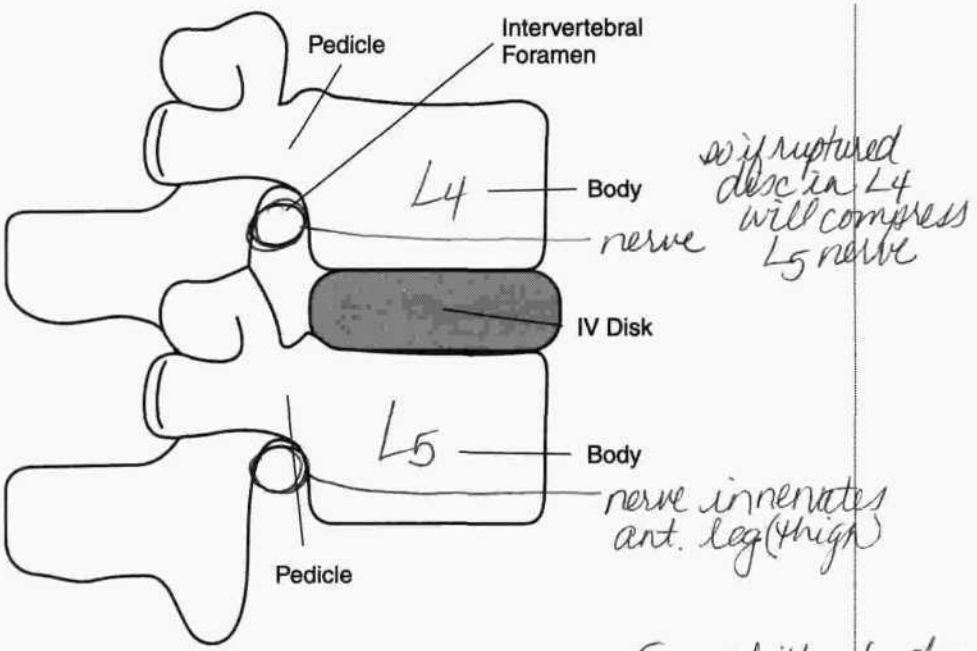
Intervertebral Foramen

The intervertebral foramen is bounded **superiorly and inferiorly** by the **pedicles** of the vertebrae (Fig III-1-3).

It is bounded **anteriorly** by parts of the **bodies** of the vertebrae and the **intervertebral disk.**

The articular processes and the zygapophyseal joint bound it posteriorly.

The **spinal nerve** contained within the intervertebral foramen may be compressed by herniation of the nucleus pulposus or zygapophyseal joint disease.



so if ruptured disc in L4 will compress L5 nerve

nerve innervates ant. leg (thigh)

S_1 – achilles tendon reflex post. leg

Figure 111-1-3. Intervertebral Foramen

SPINAL NERVES AND SPINAL CORD

Neuron and Spinal Cord

The basic functional unit of the nervous system is the neuron. Many different types of neurons are found in the nervous system, and most of them contain three elements: the sorna (cell body), dendrites, and an axon. A multipolar neuron is shown below to illustrate the main components of a neuron (Fig III-1-4).

Spinal nerves arise from the spinal cord by way of dorsal and ventral roots. The dorsal root contains sensory nerve fibers with their cell bodies in the dorsal root ganglion. The ventral root contains motor nerve fibers with their cell bodies in the gray matter of the spinal cord. The spinal nerve divides into a dorsal ramus and ventral ramus. Each ramus carries sensory and motor fibers to the dorsal and ventral parts of the body, respectively (Fig III-1-5).

spinal cord ends at L_2

OUMJ/ /)C ends d S,

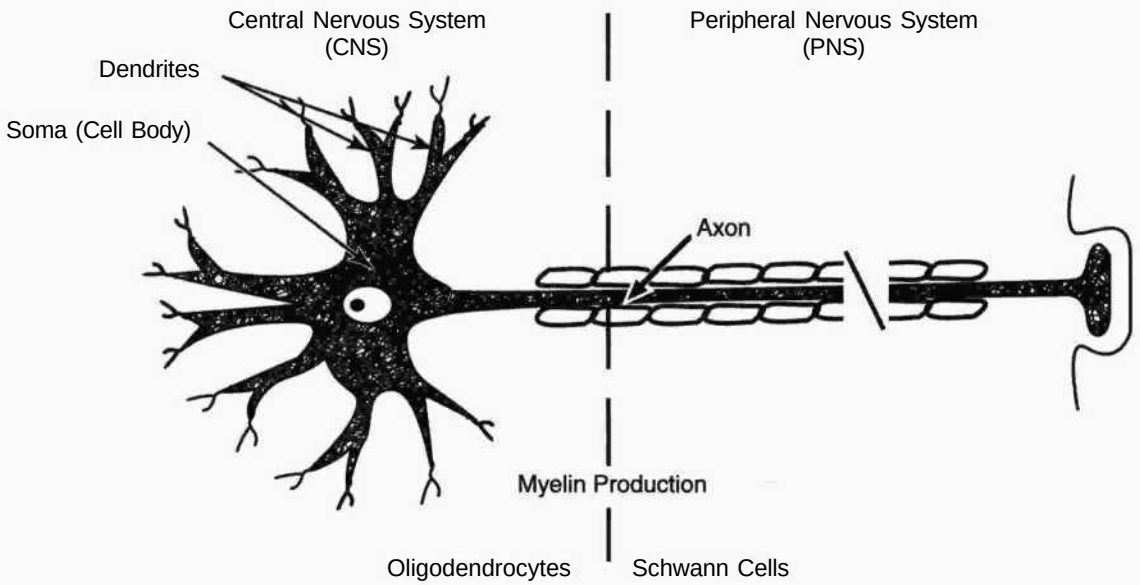


Figure III-1-4.The Neuron

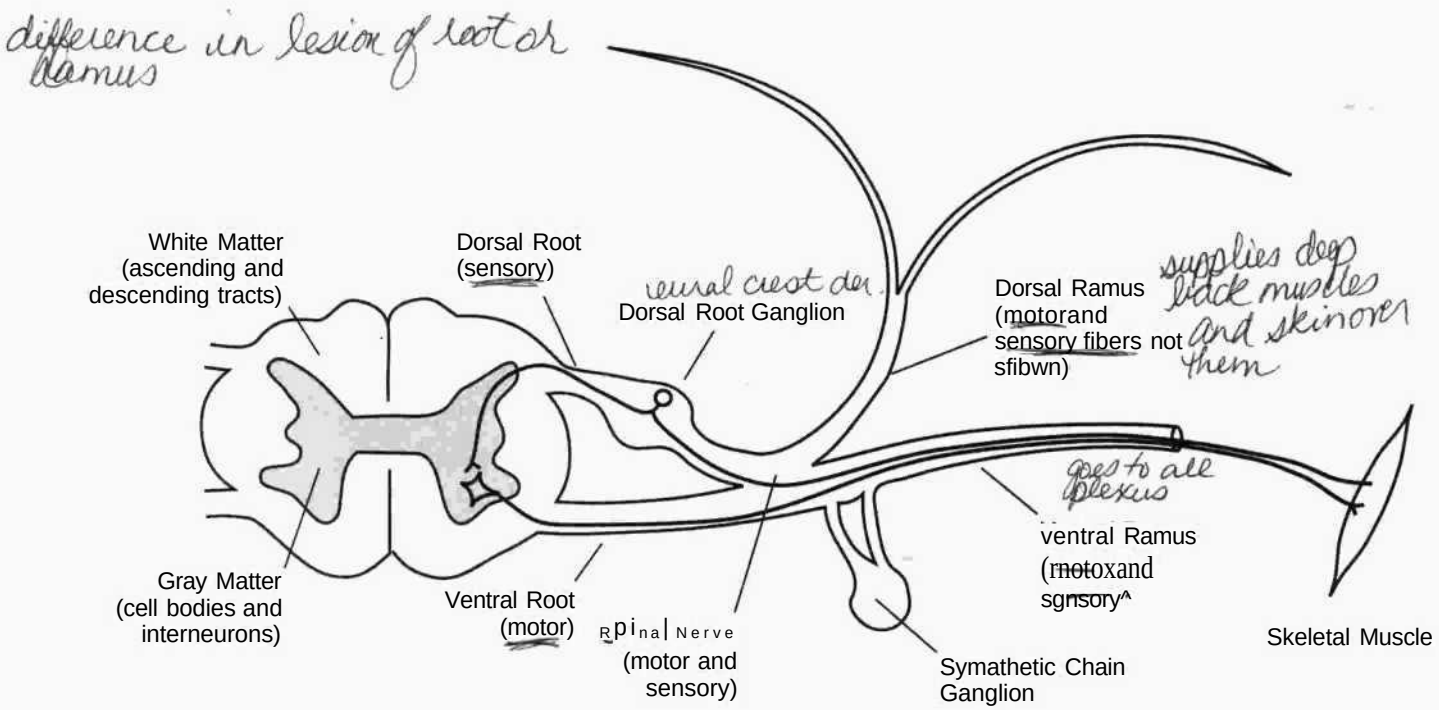


Figure 111-1-5. Cross Section of Spinal Cord and the Components of a Spinal Nerve

Meninges

Pia ***Mater***

The **pia mater** is fused to the surface of the spinal cord and cannot be separated from **it.**

External to this is the subarachnoid space, which is filled with **cerebrospinal fluid** (CSF).

The pressure of this fluid keeps the next layer, the **arachnoid,** away from the pia mater.

Dura ***Mater***

The outermost layer is the **dura mater.**

There normally is no subdural space, but such a space can be created when, for example, bleeding occurs into this space.

External to the dura is the **epidural space,** which contains fat and a plexus of veins.

The inferior limit of the dural sac and the subarachnoid space is at vertebral level S2.

Cauda *Equina*

Below the inferior limit of the spinal cord at the level of LI and L2, but within the subarachnoid space, is the cauda equina. This is composed of dorsal and ventral roots.

When a spinal **tap** is performed it is typically done at the level of L4 (top of the iliac crest). The cauda equina is at this level.

To perform a **lumbar puncture,** a needle is passed through the interlaminar space in the midline while the vertebral column is flexed. The layers that the needle must pass through are:

Skin
Superficial fascia
Deep fascia
Supraspinous ligament
Interspinous ligament
Interlaminar space
Epidural space
Dura
Arachnoid
Subarachnoid space

AUTONOMIC NERVOUS SYSTEM

General Organization

Definition

The autonomic nervous system (ANS) is responsible for the motor innervation of smooth muscle, cardiac muscle, and glands of the body. The ANS is composed of two divisions: (1) sympathetic and (2) parasympathetic.

In both divisions there are two neurons in the peripheral distribution of the motor innervation (Fig III-1-6).

Preganglionic neuron with the cell body in the central nervous system (CNS).

Postganglionic neuron with the cell body in a ganglion in the peripheral nervous system (PNS).

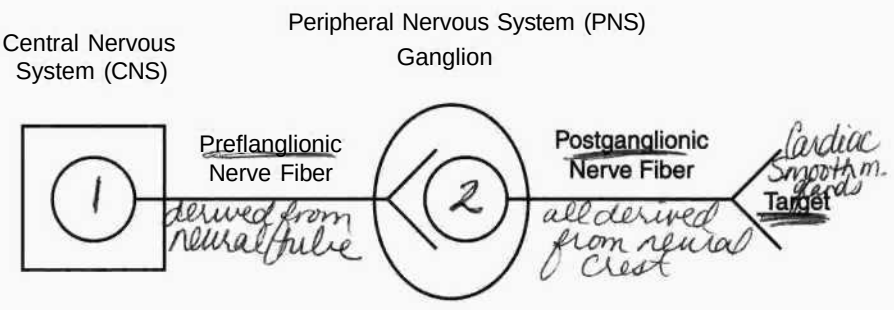


Figure 111-1-6. Autonomic Nervous System

Sympathetic System

Sympathetic = Thoracolumbar outflow (Figs III-1-7 and III-1-8).

preganglionic arise from T_1-L_2

ORIGIN	Site of Synapse	Innervation
Spinal Cord Levels T_1-L_2	sympathetic chain ganglia (paravertebral ganglia)	Smooth m. of modified cardiac m. and glands of body wall and limbs, head and thoracic viscera
Thoracic splanchnic nerves T5-12	prevertebral ganglia eg. celiac, aorticorenal, mesenteric ganglia	Smooth m. and glands of the foregut and midgut
Lumbar splanchnic nerves L1,2	prevertebral ganglia eg inf. mesenteric and pelvic ganglia	Smooth m. and glands of pelvic viscera and hindgut

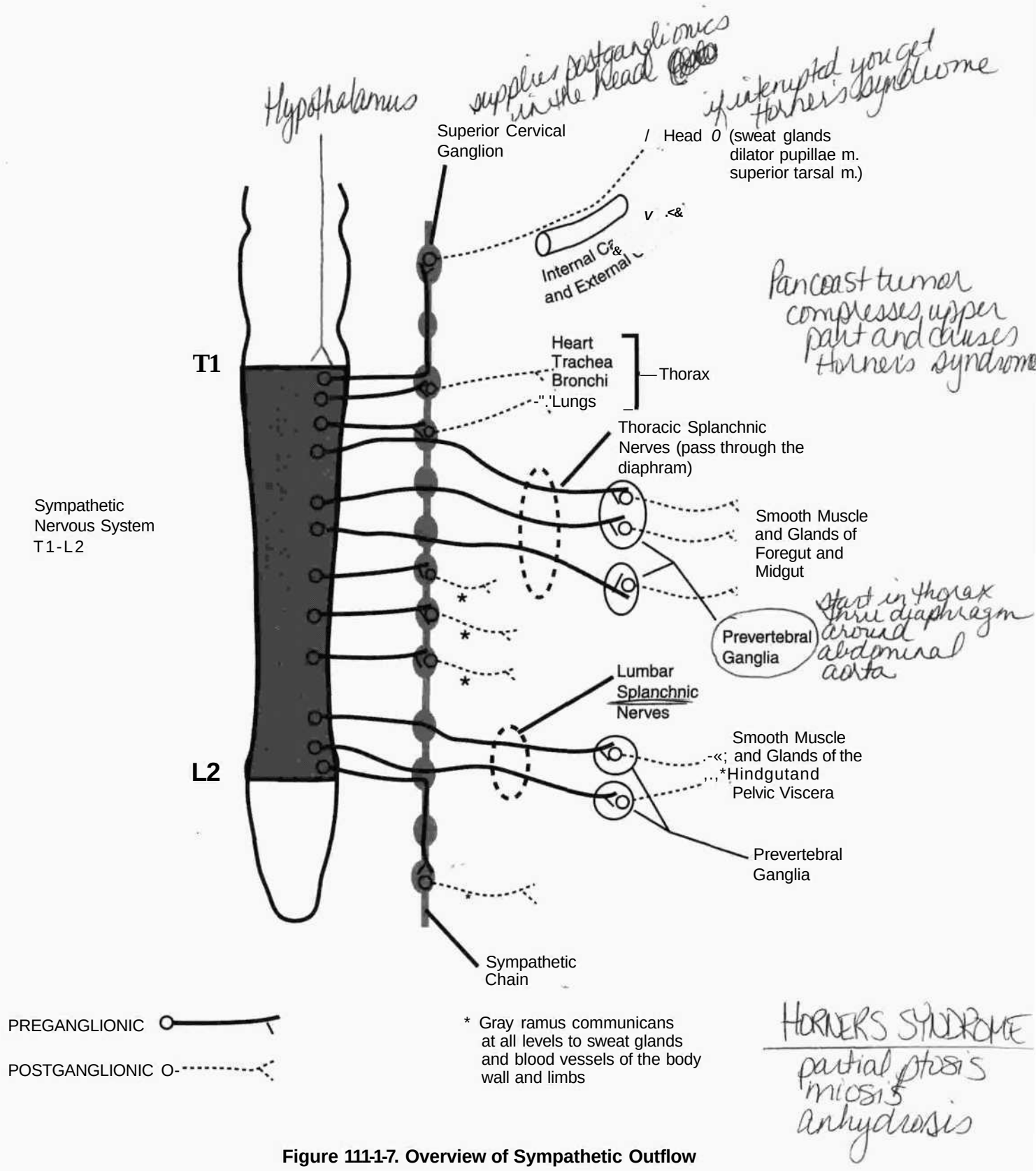


Figure 111-1-7. Overview of Sympathetic Outflow

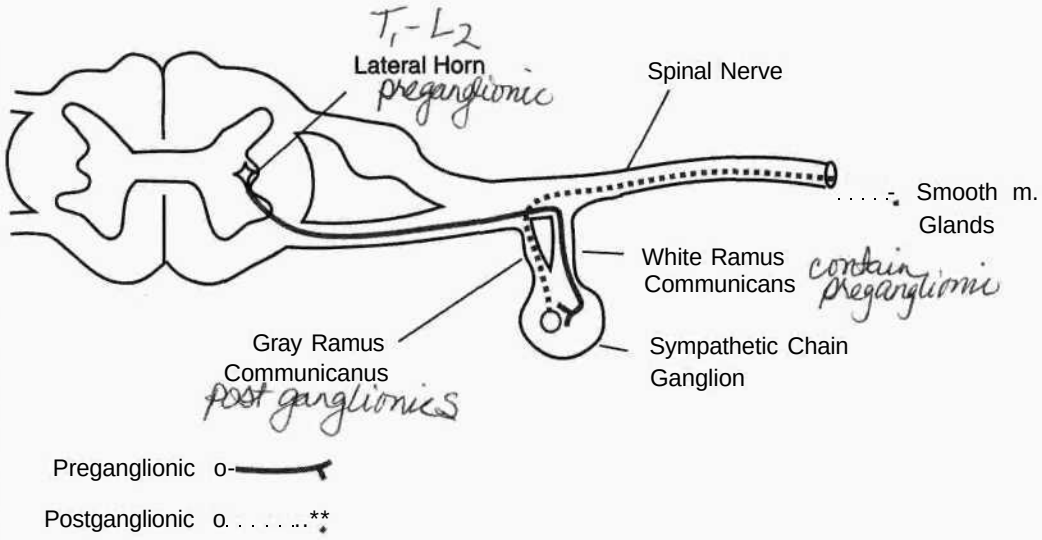


Figure 111-1-8. Cross Section of Spinal Cord Showing Sympathetic Outflow

Parasympathetic System

Parasympathetic = Craniosacral outflow (Fig III-1-9).

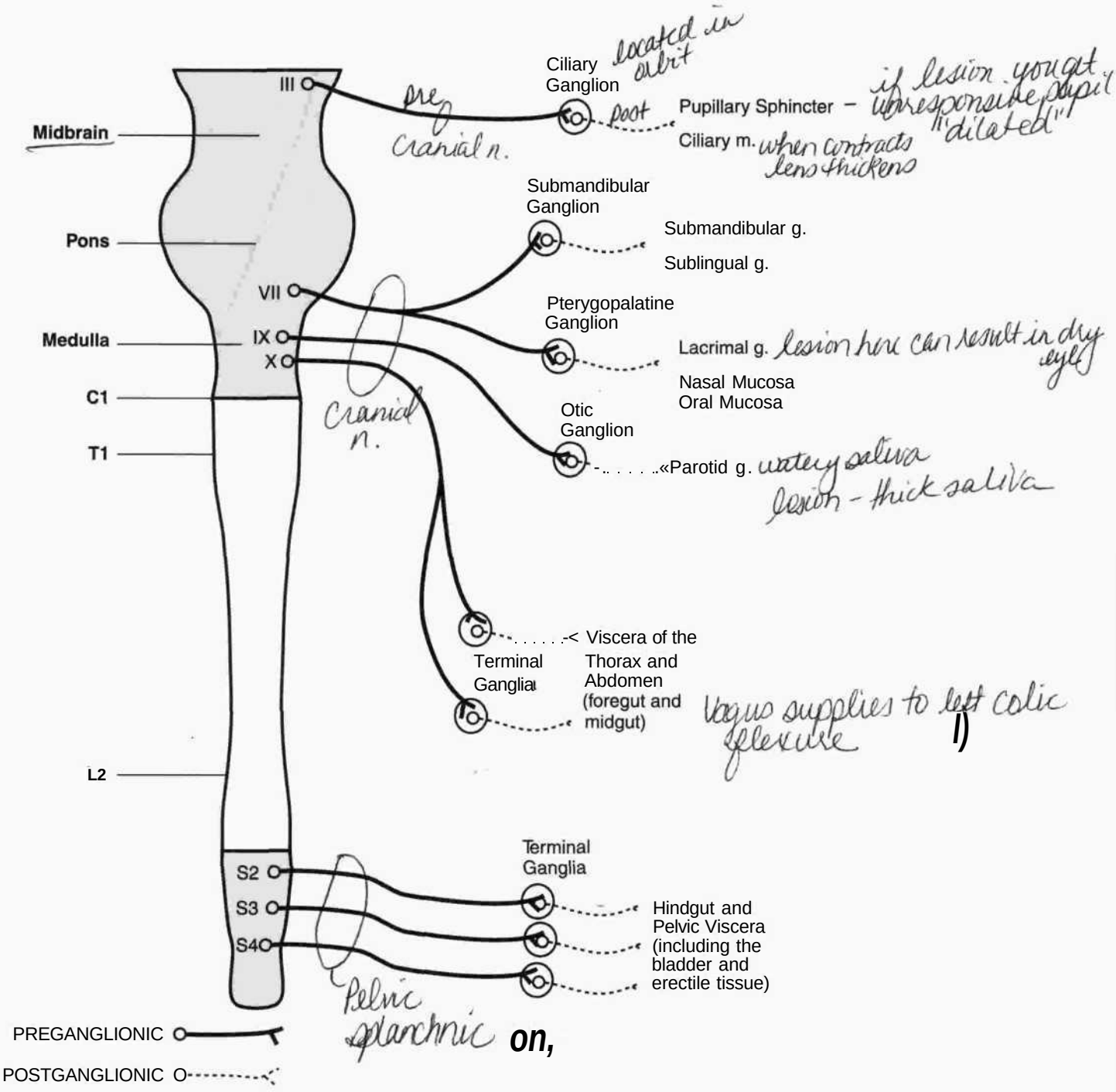


Figure III-1-9. Overview of Parasympathetic Outflow

Thorax

2

CHEST WALL

Breast

The breast (mammary gland) is a subcutaneous glandular organ of the superficial pectoral region. It is a modified sweat gland, specialized in women for the production and secretion of milk. A variable amount of fat surrounds the glandular tissue and duct system and is responsible for the shape and size of the female breast. *(jTTfplKd JLtff^Jyvuet' CCftacA-fofajUk.*

Nipple

The nipple contains the openings of the lactiferous ducts. It is located approximately at the level of the fourth intercostal space in nulliparous women and in men. It contains circular smooth muscle fibers that contract during emission (letdown) of milk from the ducts.

The areola is a variable area surrounding the nipple. It contains sebaceous glands.

There are 15 to 20 lactiferous ducts, each of which drains a glandular lobule of breast tissue. The ducts radiate outward from the nipple. The terminal portion of each duct, the lactiferous sinus, is dilated.

Cooper's Ligaments

Cooper's ligaments are suspensory ligaments, which attach the mammary gland to the skin and run from the skin to the deep fascia.

Arterial Supply

Most of the blood supply to the breast is derived from branches of the internal thoracic (internal mammary) artery. However, the lateral thoracic and thoracoacromial branches of the axillary artery and the intercostal arteries also contribute to the blood supply.

Venous Drainage

Venous blood from the breast drains primarily to tributaries of the axillary vein.

Lymphatic Drainage

Most of the lymph of the breast drains to axillary nodes (pectoral group). Lymphatics from the deep surface drain to the apical group of axillary nodes. From the medial surface, lymph drains to the parasternal nodes, which accompany the internal thoracic vessels.

Innervation

Sensory fibers from the breast contribute to intercostal nerves 2-6. These nerves also carry sympathetic fibers, which supply the smooth muscle of the areolae.

Skeletal Elements

Vertebrae

There are 12 thoracic vertebrae.

- The vertebrae have facets on their bodies to articulate with the heads of ribs; each rib head articulates with the body of the numerically corresponding vertebra and the one below it.
- The thoracic vertebrae have facets on their transverse processes to articulate with the tubercles of the numerically corresponding ribs.

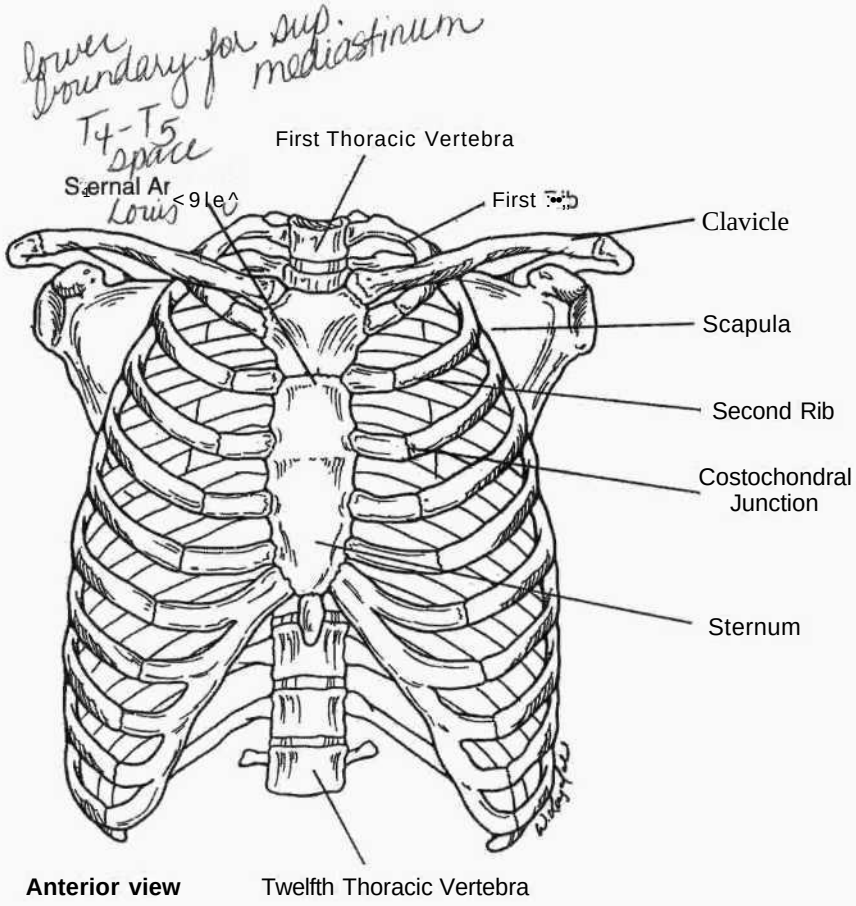


Figure 111-2-1, The Thoracic Wall

Sternum

The manubrium articulates with the clavicle and the first rib. It meets the body of the sternum at the sternal angle, **an important clinical** landmark.

The body articulates directly with ribs 2-7; it articulates inferiorly with the xiphoid process at the xiphisternal junction.

The xiphoid process is cartilaginous at birth and usually ossifies and unites with the body of the sternum around age 40.

Ribs and Costal Cartilages

There are 12 pairs of ribs, which are attached posteriorly to thoracic vertebrae.

- Ribs 1-7 are termed "true ribs" and attach directly to the sternum by costal cartilages.
- Ribs 8-10 are termed "false ribs" and attach to the costal cartilage of the rib above.
- Ribs 11 and 12 have no anterior attachments, and are therefore classified as both "floating ribs" and false ribs.

The costal groove is located along the inferior border of each rib and provides protection for the intercostal nerve, artery, and vein.

Muscles

ExternalIntercostalMuscles

There are 11 pairs of external intercostal muscles. Their fibers run anteriorly and inferiorly in the intercostal spaces from the rib above to the rib below.

These muscles fill the intercostal spaces from the tubercles of ribs posteriorly to the costochondral junctions anteriorly; external intercostal membranes replace them anteriorly.

InternalIntercostalMuscles

There are 11 pairs of internal intercostal muscles. Their fibers run posteriorly and inferiorly in the intercostal spaces deep to the external layer.

These muscles fill the intercostal spaces anteriorly from the sternum to the angles of the ribs posteriorly; internal intercostal membranes replace them posteriorly.

InnermostIntercostalMuscles

The deep layers of the internal intercostal muscles are the innermost intercostal muscles.

These muscles are separated from the internal intercostal muscles by intercostal nerves and vessels.

Intercostal Structures

IntercostalNerves

There are 12 pairs of thoracic nerves, 11 intercostal pairs, and 1 subcostal pair.

Intercostal nerves are the ventral primary rami of thoracic spinal nerves. These nerves supply the skin and musculature of the thoracic and abdominal walls and the parietal pleura and parietal peritoneum.

IntercostalArteries

There are 12 pairs of posterior and anterior arteries, 11 intercostal pairs, and 1 subcostal pair.

Anterior Intercostal Arteries

Pairs 1-6 are derived from the internal thoracic arteries.

Pairs 7-9 are derived from the musculophrenic arteries.

There are no anterior intercostal arteries in the last two spaces; branches of the posterior intercostal arteries supply these spaces.

Posterior Intercostal Arteries

The first two pairs arise from the superior intercostal artery, a branch of the costocervical trunk of the subclavian artery.

Nine pairs of intercostal and one pair of subcostal arteries arise from the thoracic aorta.

Intercostal Veins

Anterior branches of the intercostal veins drain to the internal thoracic and musculophrenic veins.

Posterior branches drain to the azygos system of veins.

Lymphatic Drainage of Intercostal Spaces

Anterior drainage is to the internal thoracic (parasternal) nodes.

Posterior drainage is to the para-aortic nodes of the posterior mediastinum.

EMBRYOLOGY OF THE RESPIRATORY SYSTEM

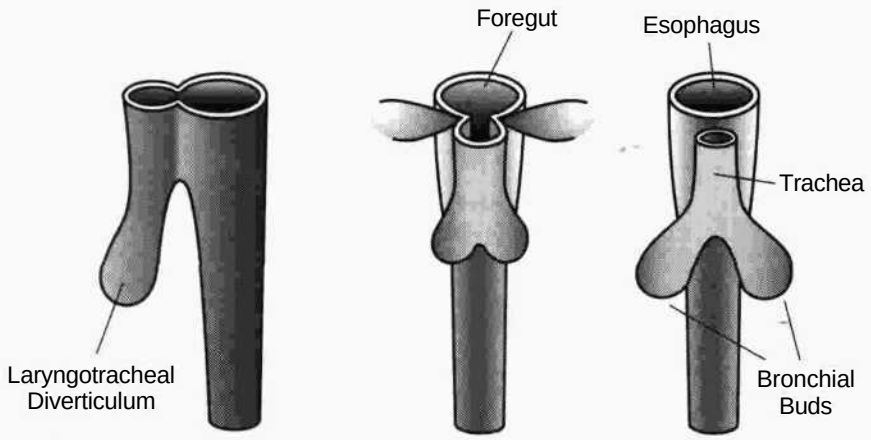


Figure 111-2-2. Development of the Respiratory System

Clinical Correlate

Tracheoesophageal Fistula

A tracheoesophageal fistula is an abnormal communication between the trachea and esophagus caused by a malformation of the tracheoesophageal septum. It is generally associated with **esgphagfiaLattggja** and **polyhydramnios.** This condition results m gauging and cyanosjs after feeding, excessive accumulation of saliva or mucus in the nose andjrjouth, abdominal distentio.n after crying, and reflux of gastric. contents into lungs causing pneumonitis. The fistula is most commonly (90% of all cases) located between the esophagus andJLs**tal third of the trachea.**

Foregut

The **Iaryngotracheal (respiratory) diverticulum** forms in the ventral wall of the foregut.

The **tracheoesophageal septum** divides the foregut into the esophagus and trachea.

Lung Bud

The distal end of the **Iaryngotracheal diverticulum** enlarges to form the lung bud.

The lung bud divides into two **bronchial buds,** which branch into the **main bronchi, lobar bronchi,** and **segmental bronchi.**

The tertiary bronchi are related to **bronchopulmonary segments** of the lungs.

The lungs undergo four stages of development. These are summarized in Table III-2-1.

Table III-2-1. The Four Stages of Lung Development

Stage	Characteristics
Glandular (weeks 5-17)	Respiration is not possible Premature fetuses cannot survive
Canalicular (weeks 13-25)	Respiration is not possible Premature fetuses rarely survive
Terminal sac (weeks 24-birth)	Type I and type II pneumocytes are present Respiration is possible Premature fetuses born between weeks 25 and 28 can survive with intensive care
ffilveolar(birth^ygars)*dhUClSU£kf>>nA-dlw^j^* Note: Lung development continues after birth	Respiratory bronchioles, terminal sacs, alveolar ducts, and alveoli increase in number Chest radiograph is more dense in children

PLEURA AND PLEURAL CAVITY

Parietal pleura lines the inner surface of the thoracic cavity; visceral pleura follows the contours of the lung itself (Fig III-2-3).

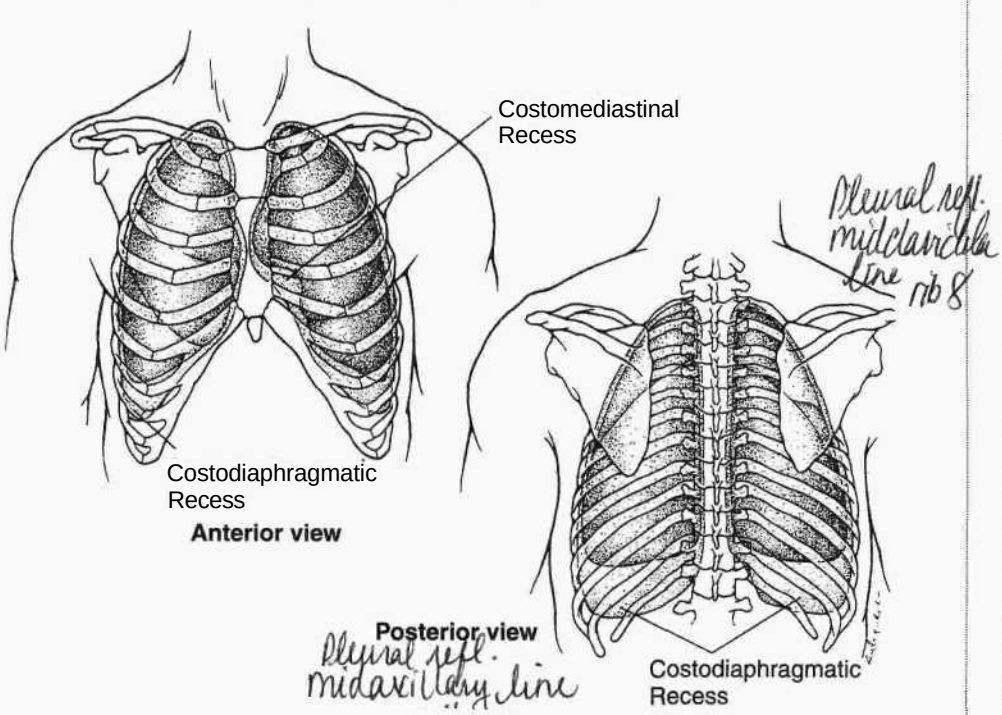


Figure III-2-3. Lungs and Pleura

Pleural Cavity

The pleural cavity is the space between the parietal and visceral layers of the pleura (Fig III-2-3). It is a sealed, blind space. The introduction of air into the pleural cavity may cause the lung to collapse (pneumothorax).

It normally contains a small amount of serous fluid elaborated by mesothelial cells of the pleural membrane.

Pleural Reflections

Pleural reflections are areas where the pleura change direction from one wall to the other.

- The sternal line of reflection is where the costal pleura is continuous with the mediastinal pleura behind the sternum (from costal cartilages 2-4). The pleural margin then passes inferiorly to the level of the sixth costal cartilage.

Clinical Correlate

Respiratory Distress Syndrome

Respiratory distress syndrome is caused by a deficiency of **surfactant** (composed of phos**phatidylcholine** [mainly dipalmi**toyl lecithin]** and proteins). This condition can be associated with premature infants, infants of diabetic mothers, and prolonged intrauterine asphyxia. **Thyroxine** and **cortisol** treatment increase the production of surfactant.

Hyaline Membrane Disease

Surfactant deficiency may lead to **hyaline membrane disease** whereby repeated gasping inhalations damage the alveolar lining. Hyaline membrane disease is characterized histologically by **collapsed alveoli (atelectasis)** and eosinophilic **(pink) fluid** covering the alveoli.

Clinical Correlate

Pulmonary Hypoplasia

Pulmonary hypoplasia occurs when lung development is stunted. This condition can be associated with congenital diaphragmatic hernia (herniation of abdominal contents into the thorax, which compresses the lung) or **withjrilateral renal agenesis** (this causes oligohydramnios, which increases the pressure on the fetal thorax).

- The costal line of reflection is where the costal pleura becomes continuous with the diaphragmatic pleura from rib 8 in the midclavicular line, to rib 10 in the midaxillary line, and to rib 12 lateral to the vertebral column.

Pleural Recesses

Pleural recesses are potential spaces not occupied by lung tissue except during deep inspiration (Fig III-2-3).

- Costodiaphragmatic recesses are spaces below the inferior borders of the lungs where costal and diaphragmatic pleura are in contact.
- The costomediastinal recess is a space where the left costal and mediastinal parietal pleura meet, leaving a space caused by the cardiac notch of the left lung. This space is occupied by the lingula of the left lung during inspiration.

Innervation of Parietal Pleura

The intercostal nerves supply the costal and peripheral portions of the diaphragmatic pleura.

The phrenic nerve supplies the central portion of the diaphragmatic pleura and the mediastinal pleura.

LUNGS

Regions

The costal surface is a large convex area related to the inner surface of the ribs.

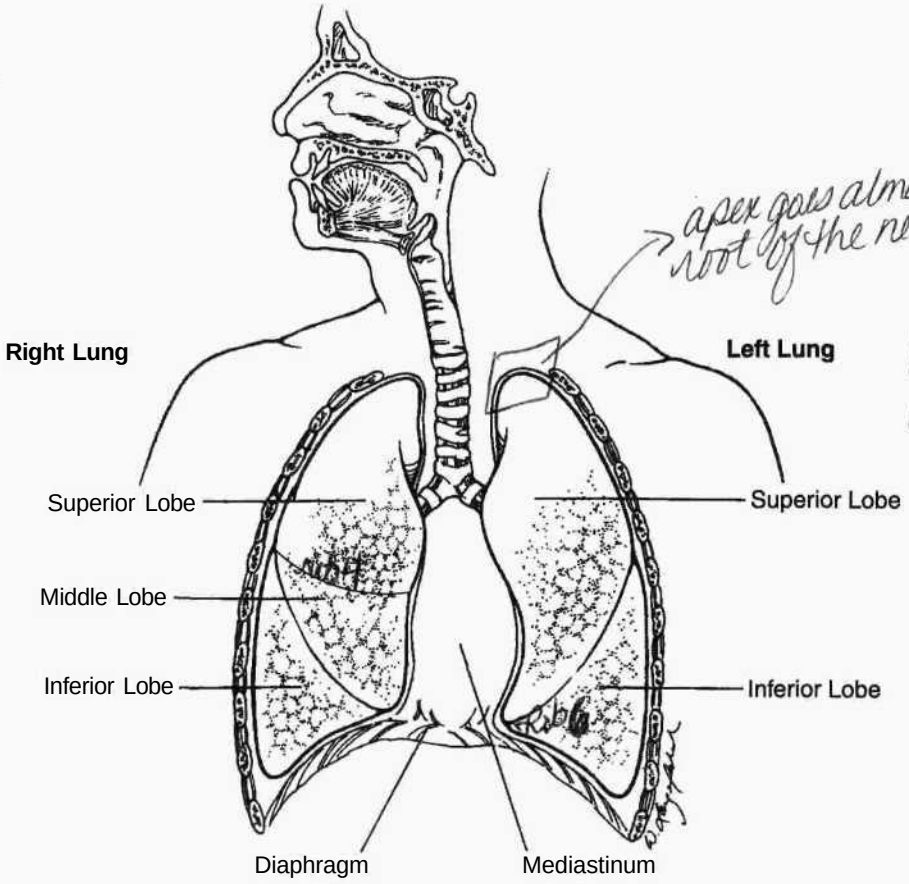
The mediastinal surface is a concave medial surface:

- The left lung has a deep cardiac impression.
- The mediastinal surface contains the root, or hilus, of the lung.
- The pulmonary ligament is a double fold of pleura hanging inferior to the root of the lung.

The diaphragmatic surface (base) is related to the convex surface of the diaphragm. It is more concave on the right owing to the presence of the liver.

The apex (cupola) protrudes into the root of the neck. It is crossed by the subclavian artery and vein anteriorly.

The hilus is the point of attachment for the root of the lung. It contains the bronchi, pulmonary and bronchial vessels, lymphatics, and nerves.



apex goes almost to T1
root of the neck
percussion
post. T4 - lower lobe
ant. - upper lobe
Left give CT scan
cross section in
ant. part it is sup.
lobe. If at post.
then inf. lobe.
Rt side

Figure IH-2-4. Pleural Cavities and Mediastinum

Lobes and Fissures

The right lung is divided by the oblique and horizontal fissures into three lobes: superior, middle, and inferior.

The left lung has only one fissure, the oblique, which divides the lung into upper and lower lobes. The lingula of the upper lobe corresponds to the middle lobe of the right lung.

Bronchopulmonary Segments

Bronchopulmonary segments of the lung are supplied by the segmental (tertiary) bronchus, artery, and vein. There are 10 on the right and 8 on the left.

Arterial Supply

The right and left pulmonary arteries arise from the pulmonary trunk. The pulmonary arteries deliver deoxygenated blood to the lungs from the right side of the heart.

The bronchial arteries supply the bronchi and nonrespiratory portions of the lung. They are usually branches of the thoracic aorta.

Venous Drainage

There are four pulmonary veins: superior right and left and inferior right and left.

- The pulmonary veins carry oxygenated blood to the left atrium of the heart.

The bronchial veins drain to the azygos system. They share drainage from the bronchi with the pulmonary veins.

Lymphatic Drainage

Superficial drainage is to the bronchopulmonary nodes; from there, drainage is to the tracheobronchial nodes.

Deep drainage is to the pulmonary nodes; from there, drainage is to the bronchopulmonary nodes.

Bronchomediastinal lymph trunks drain to the right lymphatic duct and the thoracic duct.

Innervation of Lungs

Anterior and posterior pulmonary plexuses are formed by vagal (parasympathetic) and sympathetic fibers.

Parasympathetic stimulation has a bronchoconstrictor effect.

Sympathetic stimulation has a bronchodilator effect.

EMBRYOLOGY OF THE HEART

Formation of Heart Tube

Endocardium

Lateral plate mesoderm fuses in the midline to form the **primitive heart tube,** which becomes the endocardium of the adult heart (Fig III-2-5).

Myocardium

Mesoderm surrounding the primitive heart tube secretes **cardiac jelly** and forms the myocardium of the adult heart.

Epicardium

Mesoderm from the coelomic wall forms the epicardium of the adult heart.

Dextral Looping

The primitive heart tube undergoes dextral looping (bends to the right).

Adult Structures Derived From the Dilatations of the Primitive Heart

The primitive heart forms five dilatations, the fates of which are shown in Table III-2-2.

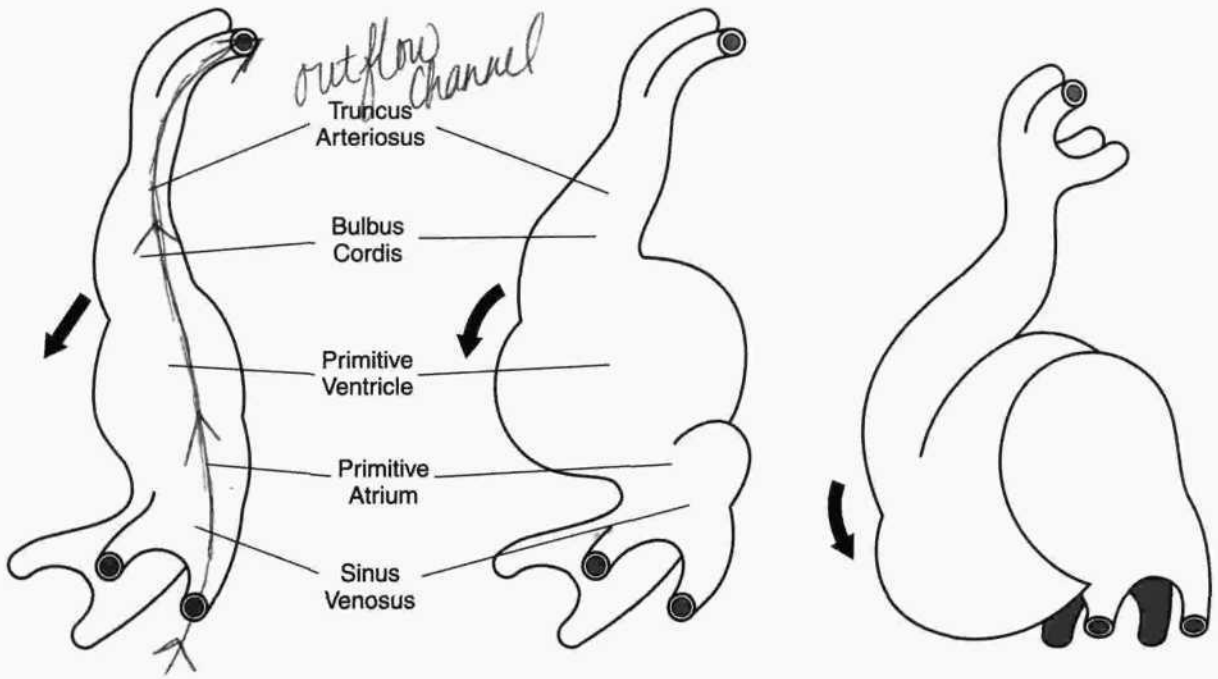


Figure III-2-5. Development of the Heart Tube

*Know formation of rt. atrium — { rough RA; ridge b/t crista terminalis; smooth RA

Table III-2-2. Adult Structures Derived From the Dilatations of the Primitive Heart

Embryonic Dilatation	Adult Structure
Truncus arteriosus	Aorta Pulmonary trunk
Bulbus *cordisgrcUcuYjZ- uJd-o a^f^* V /	Smooth part of right ventricle **(conus arteriosus)** *p^M ^7-* Smooth part of left ventricle **(aortic vestibule)** *cwt'J^*
Primitive ventricle	Trabeculated part of right ventricle Trabeculated part of left ventricle
Primitive atrium	Trabeculated part of right atrium Trabeculated part of left atrium
Sinus venosus	Smooth part of right atrium **(sinus venarum)** Coronary sinus Oblique vein of left atrium

Note

The smooth part of the left atrium is formed by incorporation of parts of the pulmonary veins into its wall.

The junction of the trabeculated and smooth parts of the right atrium is called **crista terminalis.**

Atrial Septum

The septum primum (SP) grows toward the atrioventricular (AV) septum (Fig III-2-6).

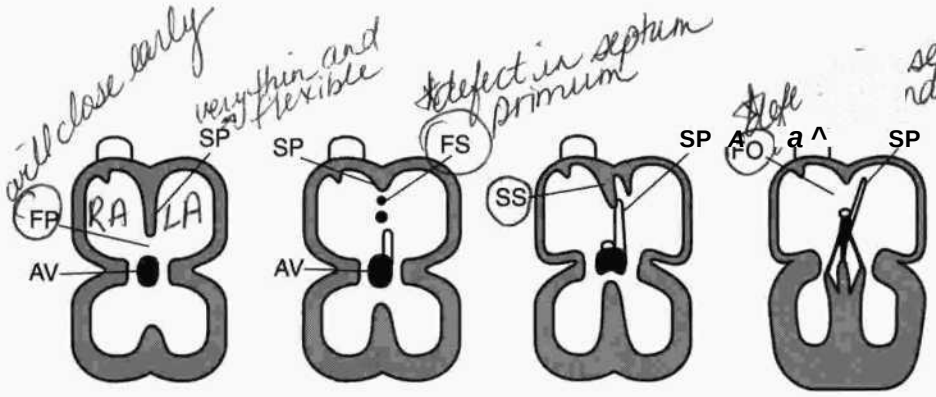
The foramen primum (FP) is located between the edge of the SP and the AV septum; it is obliterated when the SP fuses with the AV septum.

The foramen secundum (FS) forms in the center of the SP. The septum secundum (SS) forms to the right of the SP and fuses (after birth) with the SP to form the atrial septum.

The foramen ovale (FO) is the opening between septum primum (SP) and septum secundum (SS).

During fetal life, blood is shunted from the right atrium to the left atrium via the FO and FS (right-to-left shunt).

Closure of the FO normally takes place soon after birth and is facilitated by the increased left atrial pressure that results from changes in the pulmonary circulation.



SP = Septum Primum, AV = Atrioventricular Septum, FP = Foramen Primum, SS = Septum secundum, FO = Foramen Ovale, FS = Foramen Secundum.

Figure 111-2-6. Formation of Atrial Septum

Interventricular Septum

The **muscular interventricular (IV) septum** develops in the floor of the ventricle and grows toward the AV cushions but stops short, leaving the **IV foramen** (FigIH-2-7).

The **membranous IV septum** (closes the IV foramen) forms by the fusion of the:

(a) Right bulbar ridge
(b) Left bulbar ridge
(c) AV cushions

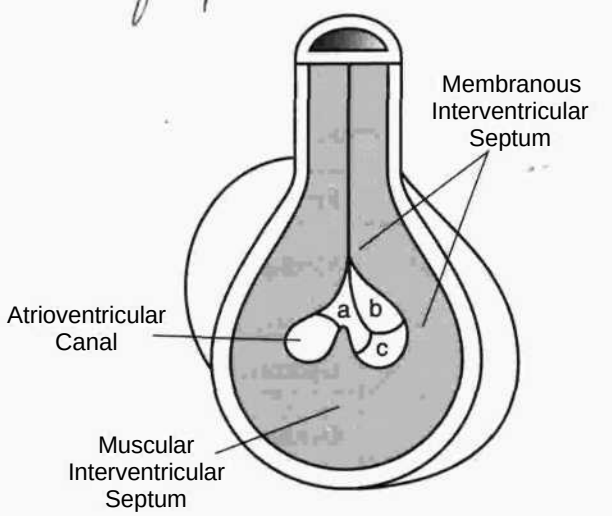


Figure 111-2-7, Formation of Interventricular Septum

Clinical Correlation

Atrial septal defects are called **ASDs.**

FS defects are caused by excessive resorption of the SP, SS, or both. This results in an opening between the right and left atria (patent FO). If the ASD is small, clinical symptoms may be delayed as late as age 30. This is the most clinically significant ASD.

Premature closure **of the** FO is the closure of the FO during prenatal life. This results injiyeertrophy of the right side of the heart and underdevelopment of the left side.

Clinical Correlation

Membranous Ventricular Septal Defect (VSD)

A membranous VSD is caused by the failure of the membranous IV septum to develop, and it results in **left-to-rlght shunting** of blood through the IV foramen. Patients with left-to-right shunting complain of **excessive fatigue upon exertion.** Left-to-right shunting of blood causes increased blood flow and pressure to the lungs (pulmonaryhypertension). Pulmonary hypertension causes marked proliferation of the tunica intima and media of pulmonary muscular arteries and arterioles. Ultimately, the pulmonary resistance becomes higher than systemic resistance and causes **right-to-left shunting** of blood and **cyanosis.** At this stage, the condition fs called **Elsenmenger complex.**

Clinical Correlations

Transposition of Great Vessels

Transposition of the great vessels occurs when the AP septum fails to develop in a spiral fashion and results in the aorta opening into the right ventricle and the pulmonary trunk opening into the left ventricle. This causes **right-to-left** shunting of blood with resultant **cyanosis.**

Tetralogy of Fallot

Tetralogy of Fallot occurs when the AP septum fails to align properly and results in (1) pulmonary stenosis, (2) overriding aorta, (3) interventricular septal defect, and (4) right ventricular hypertrophy. This causes **right-to-left** shunting of blood with resultant **cyanosis.**

Persistent Truncus Arteriosus

Persistent truncus arteriosus occurs when there is only partial development of the AP septum. This results in a condition in which only one large vessel leaves the heart and it receives blood from both the right and left ventricles. The causes **right-to-left** shunting of blood with resultant **cyanosis.**

Aorticopulmonary Septum

Neural crest cells migrate into the truncal and bulbar ridges, which grow in a spiral fashion and fuse to form the aorticopulmonary (AP) septum. The AP septum divides the truncus arteriosus into the **aorta** and **pulmonary trunk** (Fig III-2-8).

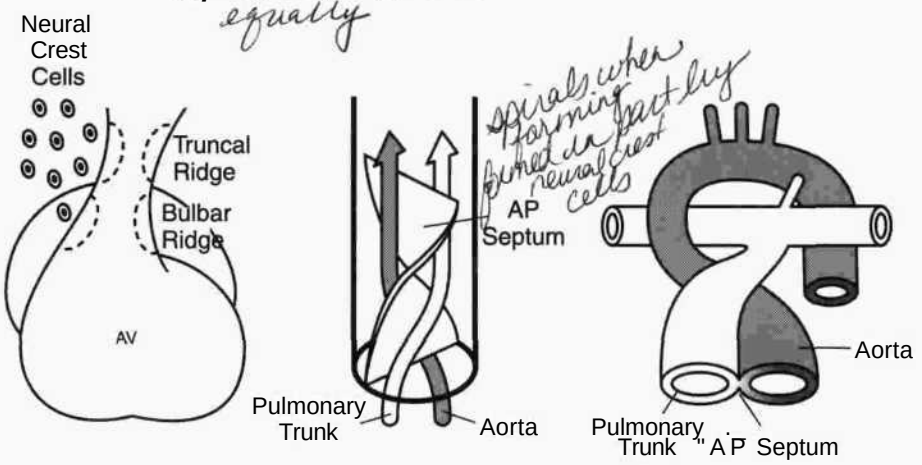


Figure III-2-8. Formation of the Aorticopulmonary Septum

Fetal Circulation

Fetal circulation involves three shunts: **ductus venous, ductus arteriosus,** and **foramen** ovale (Fig III-2-9). After birth, a number of changes occur in the circulatory system because of the cessation of placental blood flow and start of lung respiration (Table III-2-3).

Table III-2-3. Adult Vestiges Derived From the Fetal Circulatory System

Changes After Birth	Remnant in Adult
Closure of right and left umbilical arteries	Medial umbilical ligaments
Closure of left umbilical vein	Ligamentum teres
Closure of ductus venosus	Ligamentum venosum
Closure of foramen ovale	Fossa ovale
Closure of ductus arteriosus	Ligamentum arteriosum

Vasculogenesis starts in the mesoderm surrounding the yolk sac.

Hematopoiesis occurs initially in the mesoderm surrounding the yolk sac and later in the fetal liver, spleen, thymus, and bonemarrow.

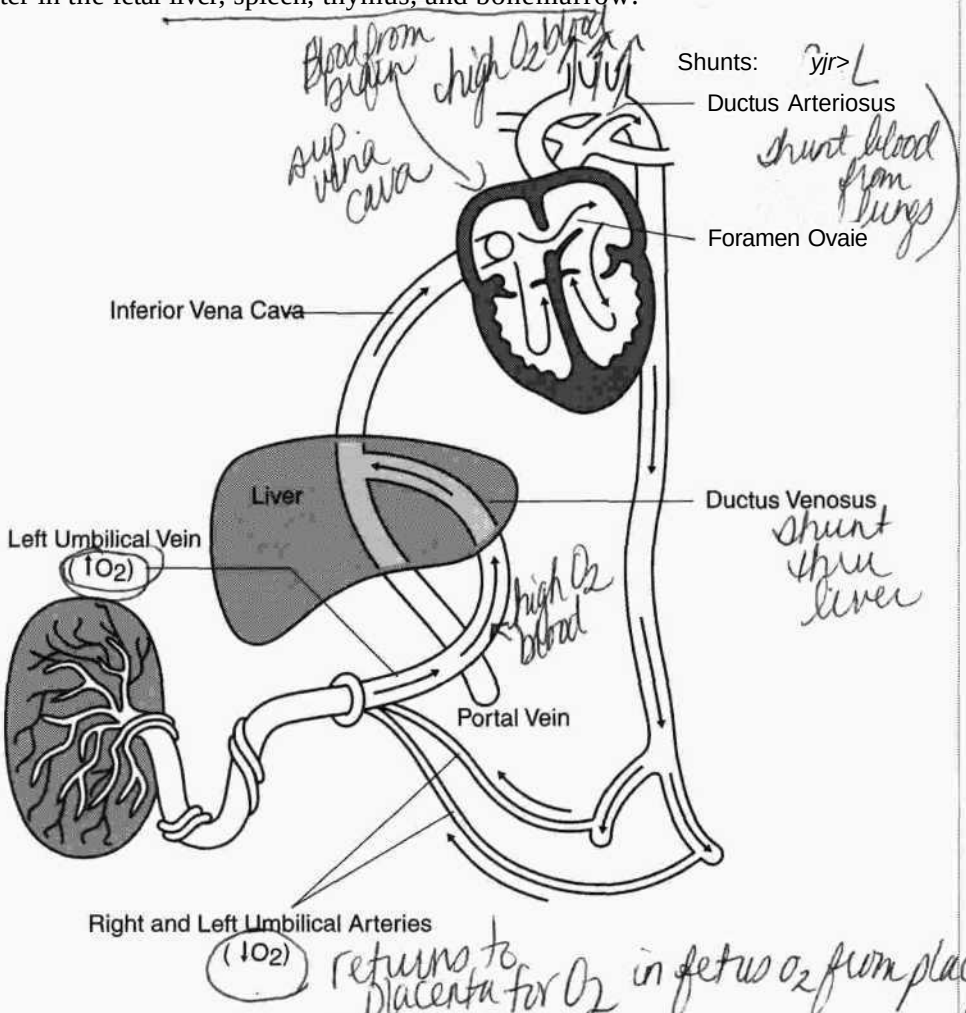


Figure III-2-9. Fetal Circulation

MEDIASTINUM

General Features

Located between the pleural cavities, the mediastinum is divided into inferior and superior parts by a plane passing from the sternal angle anteriorly to the intervertebral disc between T4 and T5 posteriorly. The inferior mediastinum is classically subdivided into middle, anterior, and posterior parts (Fig III-2-10).

Clinical Correlate

Patent Ductus Arteriosus

Patent ductus arteriosus (PDA) occurs when the ductus arteriosus (a connection between the pulmonary trunk and aorta) fails to close after birth. Normally, the ductus arteriosus closes within a few hours after birth via smooth muscle contraction to form the ligamentum arteriosum.

Prostaglandin E and intrauterine or neonatal asphyxia sustain patency of the ductus arteriosus.

Prostaglandin inhibitors (e.g., indomethacin), acetylcholine, histamine, and catecholamines promote closure of the ductus arteriosus.

PDA is common in premature infants and cases of maternal rubella infection. It causes a left-to-right shunting of blood (Note: the ductus arteriosus during fetal development is a right-to-left shunt).

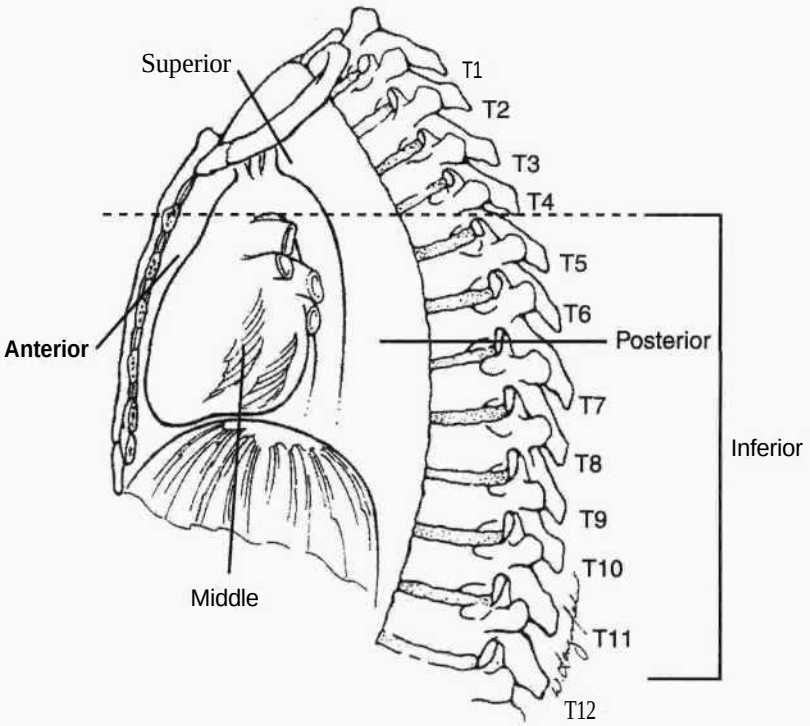


Figure 111-2-10. Eivisions of the Mediastinum

Middle Mediastinum

This section contains the pericardium, phrenic nerves, and heart.

Pericardium

The pericardium is the outer fibrous sac; it is a double-layered serous membrane that encloses the pericardial cavity between its parietal and visceral layers.

The transverse pericardial sinus is a space posterior to the ascending aorta and pulmonary trunk and anterior to the superior vena cava and left atrium.

- The oblique pericardiahsinus is a blind, inverted, U-shaped space posterior to the heart and bounded by reflection of serous pericardium around the four pulmonary veins and the inferior vena cava as they enter the heart.

PhrenicNerves

Phrenic nerves arise from the ventral rami of cervical nerves 3, 4, and 5.

They are the sole motor supply of the diaphragm and convey sensory information from the central portion of both the superior and inferior portions of the diaphragm.

Both phrenic nerves pass through the middle mediastinum lateral to the fibrous pericardium and anterior to the root of the lung.

Heart (discussed separately below)

Anterior Mediastinum

This section contains fat and areolar tissue.

Posterior Mediastinum

Thoracic (Descending) Aorta

The most important branches of the thoracic aorta are the bronchial, esophageal, and posterior intercostal arteries.

It terminates at vertebral level T12, where it passes through the aortic hiatus of the diaphragm.

Esophagus

The esophagus is related anteriorly to the jinterior esophageal plexus, which is derived mainly from the left vagus.

The esophagus is related goslexiedy- to the posterior esophageal plexus, which is derived mainly from the right vagus.

The thoracic esophagus terminates at vertebral level T10 by passing through the esophageal hiatus of the diaphragm.

Thoracic Duct

The thoracic duct lies behind the esophagus and between the thoracic aorta and azygos vein.

It arises from the cisterna chyli in the abdomen at vertebral level LI through L2 and enters the thorax through the aortic hiatus of the diaphragm.

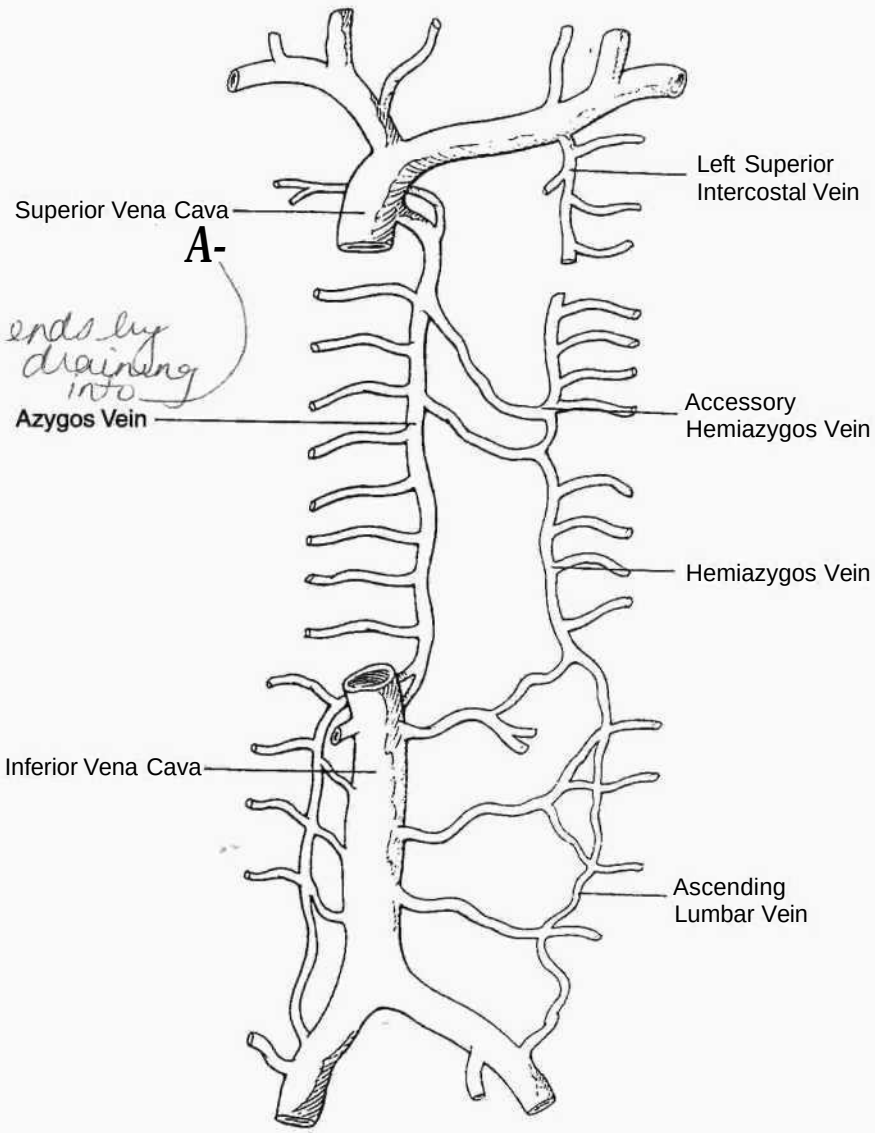
Azygos System of Veins

The posterior thoracic and abdominal walls are drained by the azygos system of veins (Fig III-2-11).

The azygos vein usually arises from the posterior aspect of the inferior vena cava in the abdomen; the hemiazygos vein often arises from the left renal vein. These veins ascend to the thorax through the aortic orifice of the diaphragm.

The azygos vein terminates by arching over the root of the right lung to empty into the superior vena cava.

It receives blood directly from the right posterior intercostal veins and indirectly via the left-sided tributaries of the hemiazygos and accessory hemiazygos veins and the left posterior intercostal veins.



Modified with permission from AgurA: Grants Atlas of Anatomy, 9th ed. Williams & Wilkins, Baltimore, MD, 1992, p 75.

Figure 111-2-11 .The Azygos System of Veins

Sympathetic Trunks

The sympathetic trunks are located paravertebrally, just outside the posterior mediastinum.

Greater, lesser, and least splanchnic nerves, which convey preganglionic sympathetic fibers to the preaortic ganglia of the abdomen, enter the posterior mediastinum as branches of the sympathetic trunks.

splanchnic nerves run through mediastinum

Superior Mediastinum

Thymus

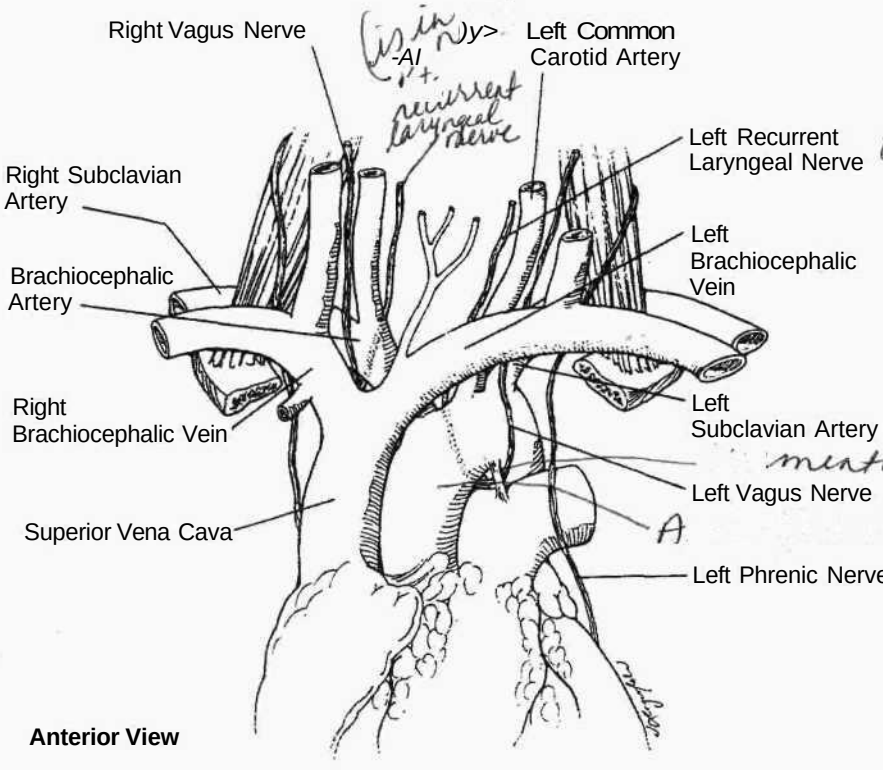
The thymus usually atrophies in the adult. The remains of the thymus may be found as a fatty mass. ^<sQjrf. fl&tf- M -Ol(J. mediastinum

Superior Vena Civa

The superior vena cava is formed behind the right first costal cartilage by the union of the right and left brachiocephalic veins (Fig III-2-12).

It returns blood from the head, neck, and upper extremities to the right atrium of the heart

originates in thorax



mediastinum arteriosum

Figure 111-2-12. Structures of the Superior Mediastinum

Arch of Aorta

The aortic arch begins and ends at the level of the sternal angle.

There are three branches: the brachiocephalic trunk, the left common carotid artery, and the left subclavian artery.

Vagus

Right and left vagus nerves contribute to the pulmonary and cardiac plexuses.

- In the neck, the right vagus nerve gives rise to the right recurrent laryngeal nerve, which passes under the right subclavian artery to ascend in the groove between the esophagus and the trachea to reach the larynx. **Note:** The right recurrent laryngeal nerve is not in the thorax.
- The left vagus nerve gives rise to the left recurrent laryngeal nerve, which passes under the aortic arch and ligamentum arteriosum to ascend to the larynx (Fig III-2-12).

Trachea

The trachea extends from below the cricoid cartilage (vertebral level C6) to its bifurcation (behind the sternal angle) to form the primary bronchi.

At the bifurcation is a ridge called the carina whose mucosa is very sensitive to external stimuli.

Esophagus

The esophagus extends from the cricoid cartilage (vertebral level C6) and passes through the esophageal hiatus of the diaphragm (T10).

It lies posterior to the trachea.

Thoracic Duct

The thoracic duct is the largest lymphatic channel in the body.

It returns lymph to the venous circulation at the junction of the left internal jugular vein and the left subclavian vein.

HEART

Borders of the Heart

The right border is formed by the right atrium (Fig III-2-13).

The left ventricle and the auricle of the left atrium form the left border.

The superior border is formed by the right and left auricles plus the conus arteriosus of the right ventricle.

The apex is the tip of the left ventricle.

The base is opposite the apex, formed mainly by the surface where the pulmonary veins enter the heart (left atrium) and by part of the right atrium.

The anterior wall is formed primarily by the right ventricle.

The posterior wall is formed by the left atrium.

The diaphragmatic wall is formed primarily by the left ventricle.

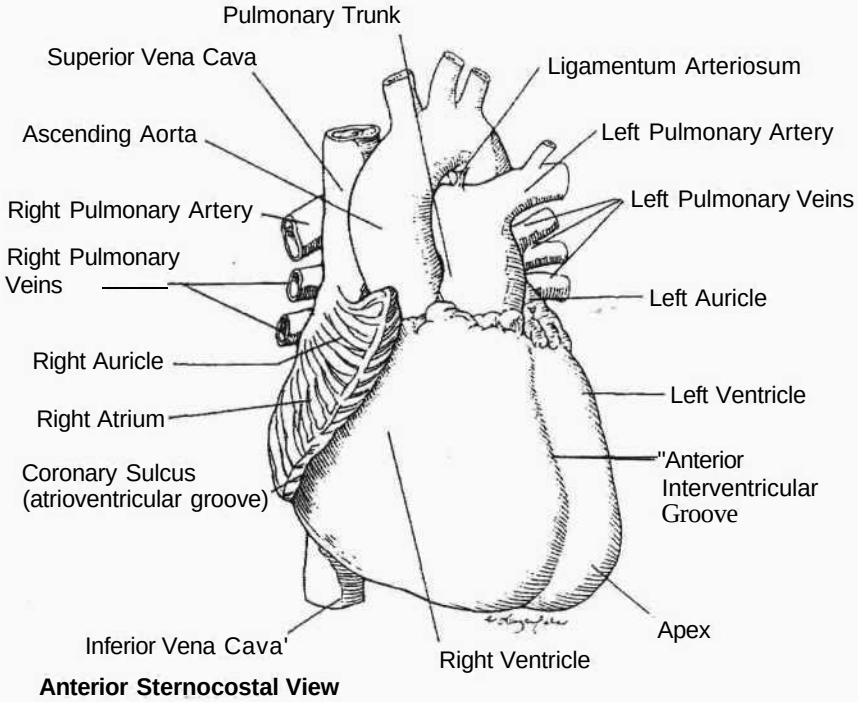


Figure III-2-13. Sternocostal View of the Heart

Surface Projections

Surface projections of the heart may be traced on the anterior chest wall (Fig III-2-14).

- The right border extends from the margin of the third right costal cartilage to the sixth right costal cartilage just to the right of the sternum.
- The inferior border extends from the sixth right costal cartilage to the fifth left intercostal space at the middavicular line.
- The left border extends from the fifth left intercostal space to the second left costal cartilage.
- The superior border extends from the inferior margin of the second left costal cartilage to the superior margin of the third right costal cartilage.

Chambers of the Heart

RightAtrium

The right atrium receives venous blood from the entire body with the exception of blood from the pulmonary veins.

Auricle

The auricle is derived from the fetal atrium; it has rough myocardium known as pectinate muscles.

Sinus Venarum

The sinus venarum is the smooth-walled portion of the atrium, which receives blood from the superior and inferior venae cavae.

Crista Terminalis

The crista terminalis is the vertical ridge that separates the smooth from the rough portion of the right atrium; it extends longitudinally from the superior vena cava to the inferior vena cava.

Foramen Ovale

In the fetus, the FO is an opening in the interatrial septum, which allows blood entering the right atrium from the inferior vena cava to pass directly to the left side of the heart.

Tricuspid Valve

The right AV (tricuspid) valve communicates with the right ventricle.

RightVentricle

The right ventricle receives blood from the right atrium via the tricuspid valve; outflow is to the pulmonary trunk via the pulmonary semilunar valve.

What is function of valves? to prevent regurgitation

Trabeculae Carneae

The trabeculae carneae are ridges of myocardium in the ventricular wall.

Papillary Muscles

The papillary muscles project into the cavity of the ventricle and attach to cusps of the AV valve by the strands of the chordae tendineae.

Chordae Tendineae

The chordae tendineae control closure of the valve during contraction of the ventricle.

Infundibulum

The infundibulum is the smooth area of the right ventricle leading to the pulmonary valve.

Left Atrium

The left atrium receives oxygenated blood from the lungs via the pulmonary veins.

- There are four openings: the upper right and left and the lower right and left pulmonary veins.

Bicuspid Valve (Mitral) most frequently diseased valve of heart → pulm. congestion rheumatic fever

The left AV orifice is guarded by the mitral (bicuspid) valve; it allows oxygenated blood to pass from the left atrium to the left ventricle.

Left Ventricle

Blood enters from the left atrium through the mitral valve and is pumped out to the aorta through the aortic valve.

Aortic valve stenosis → enlarged lft. ventricle

Trabeculae Carneae

The trabeculae carneae, or ridges of myocardium in the ventricular wall, are normally three times thicker than those of the right ventricle.

Pulm. valve stenosis → ↑ size of rt heart

Papillary Muscles

The papillary muscles, usually two large ones, are attached by the chordae tendineae to the cusps of the bicuspid valve.

Aortic Vestibule

The aortic vestibule leads to the aortic semilunar valve and ascending aorta; the right and left coronary arteries originate from the right and left aortic sinuses at the root of the ascending aorta.

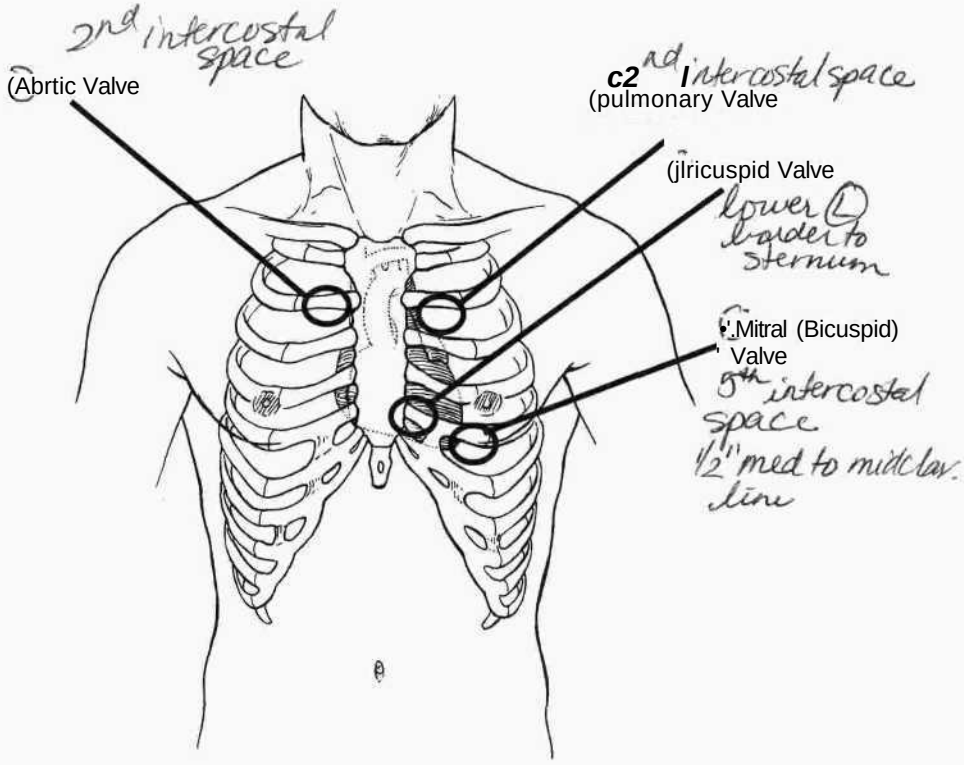


Figure 111-2-14. Projection of Heart Valve Sounds on Anterior Chest Wall

Arterial Supply of the Heart

Right Coronary Artery

The right coronary artery arises from the ascending aorta and runs in the coronary (AV) sulcus (Fig III-2-15).

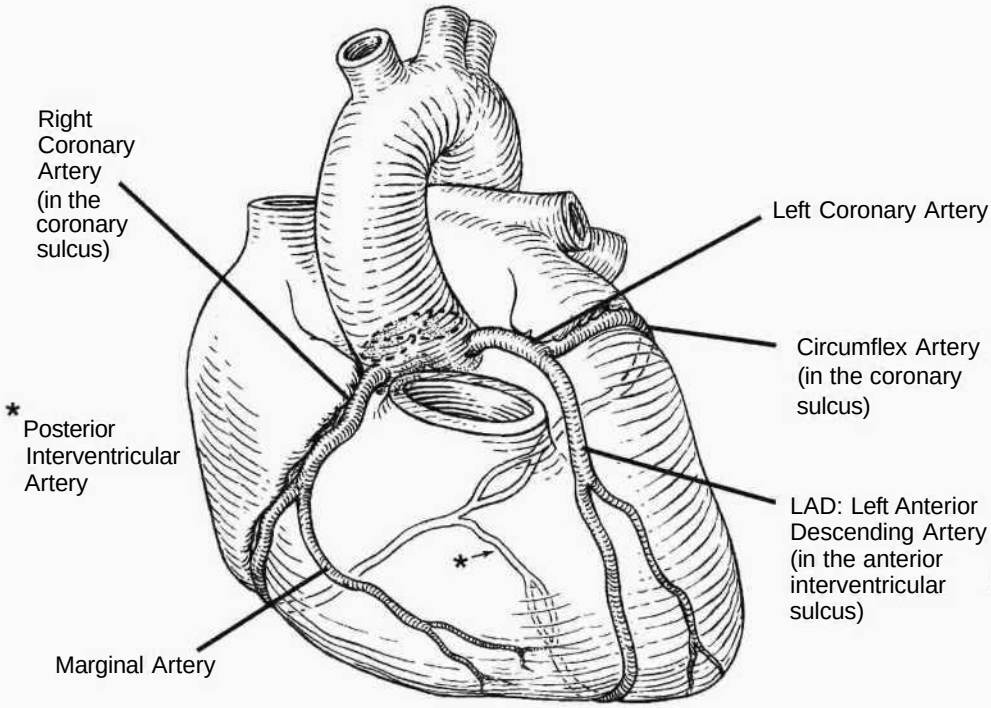
The right coronary artery supplies the right atrium, the right ventricle, the sinoatrial (SA) and AVjiodes, and parts of the left atrium and left ventricle.

Important branches are the SA nodal artery, the right marginal artery, and the posterior interventricular artery.

Left Coronary Artery

The left coronary artery arises from the ascending aorta. It divides into two branches, the anterior interventricular (descending) artery and the circumflex artery.

The left coronary artery supplies most of the left ventricle, the left atrium, and the interventricular septum.



if blocked can cause bundle branch block

Figure 111-2-15. Arterial Supply of the Heart

Venous Drainage of the Heart

Coronary Sinus *WJSVJ CUJUA^J inh> C<r. ^nu^; ffiwf c*uwf*

middle card., small card V.

The coronary sinus is the main vein of the coronary circulation; it travels in the posterior coronary sulcus. It drains to an opening in the right atrium (Fig III-2-16).

GreatCardiacVein

The great cardiac vein travels in the anterior interventricular sulcus. It is the main tributary of the coronary sinus.

MiddleCardiacVein

The middle cardiac vein travels in the posterior interventricular sulcus. It joins the coronary sinus.

VenaeCordisMinimae(ThebesianVeins)andAnteriorCardiacVeins

The venae cordis minimae and anterior cardiac veins open directly to the chambers of the heart.

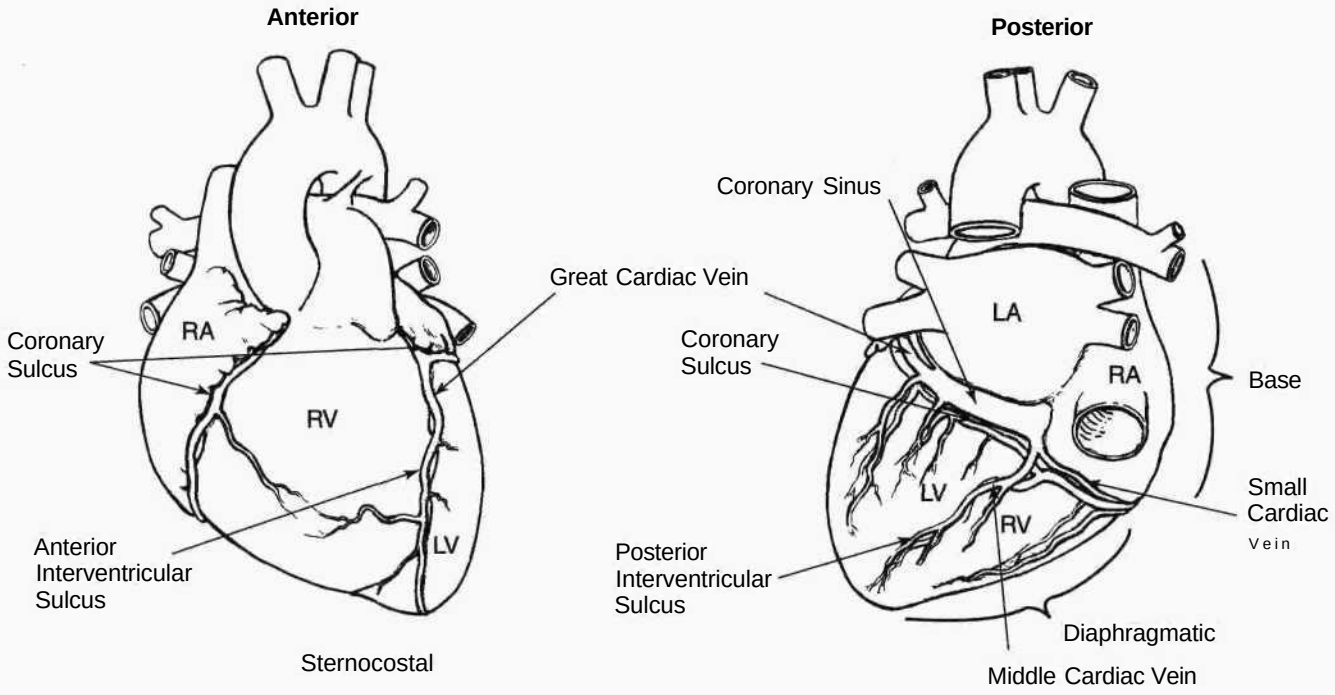


Figure Iii-2-16. Venous Drainage of the Heart

Conducting System of the Heart

SA Node

The SA node initiates the impulse for contraction of heart muscle (and is therefore termed the "pacemaker" of the heart). It is located at the superior end of the crista terminalis, where the superior vena cava enters the right atrium (Fig III-2-17).

The SA node is supplied by the SA nodal branch of the right coronary artery.

Impulse production is speeded up by sympathetic nervous stimulation; it is slowed by parasympathetic (vagal) stimulation.

AV Node

The AV node received impulses from the SA node. The AV node is located in the interatrial septum near the opening of the coronary sinus.

The **bundle of His** originates in the AV node. It conducts impulses to the right and left ventricles.

In the right ventricle, the moderator band (septomarginal trabecula) contains the right bundle branch.

Impulses pass from the right and left bundle branches to the papillary muscles and ventricular myocardium.

Innervation

The cardiac plexus is a combination of sympathetic and parasympathetic (vagal) fibers.

- Sympathetic stimulation increases the heart rate.
- Parasympathetic stimulation slows the heart rate.

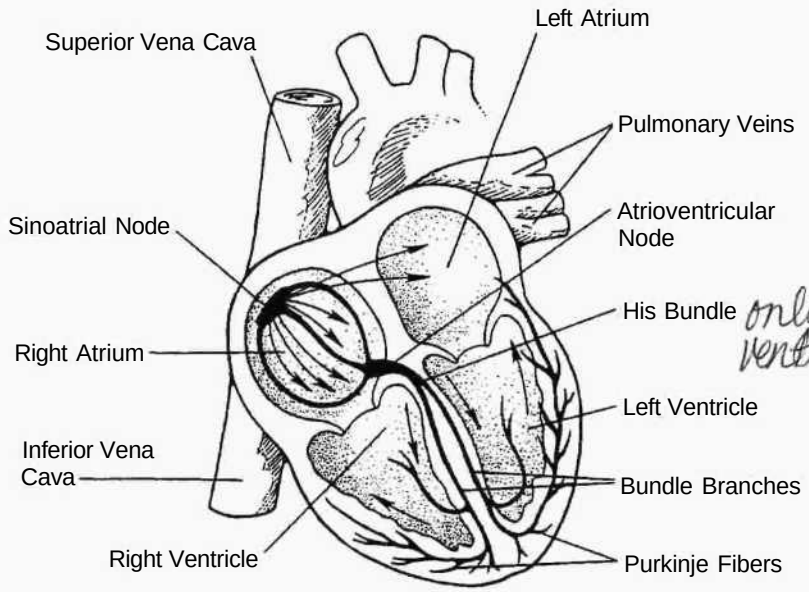


Figure III-2-i7.The Cardiac Conduction System

DIAPHRAGM

Composition

The diaphragm is composed of a **muscular portion** and a **central tendon.** It is dome shaped, and upon contraction of its muscular portion, it descends. It is innervated by the **phrenic nerves** arising from spinal cord segments **C3 through C5.** The muscular portion has three regions of origin.

Lumbar Origin

- **Two crura**—each crus takes its origin from the bodies of the upper two (left) or three (right) lumbar vertebral bodies.

- **Medial** arcuate ligament—a thickening of the deep fascia covering the anterior surface of the psoas major. Some muscle of the diaphragm arises from this thickening.
- **Lateral arcuate ligament**—a thickening of the deep fascia covering the anterior surface of the quadratus lumborum. Some muscle of the diaphragm arises from this thickening.

Costal Origin

From muscle fibers arising from the inner surfaces of the lower six ribs.

SternalOrigin

From muscle fibers arising from the inner surface of the xiphoid process.

Apertures in the Diaphragm

Caval Hiatus

Located to the right of the midline at the level of T8, within the central tendon (Fig III-2-18). Transmits the inferior vena cava and some branches of the right phrenic nerve.

EsophagealHiatus

Located to the left of the midline at the level of **TIO,** within the muscle of the right crus. Transmits the esophagus and the anterior and posterior vagus nerves.

AorticHiatus

Located in the midline at the level of T12, behind the two crura. Transmits the aorta, the azygos vein, and the thoracic duct.

SternocostalHiatuses

Located at the level of **TIO,** between the muscle of the sternal origin and the costal origin. Transmits the superior epigastric vessels.

Note

Structures that pass through the diaphragm without a specific hiatus include the sympathetic trunk, the thoracic splanchnic nerves, the hemiazygos vein, and most branches of the phrenic nerves.

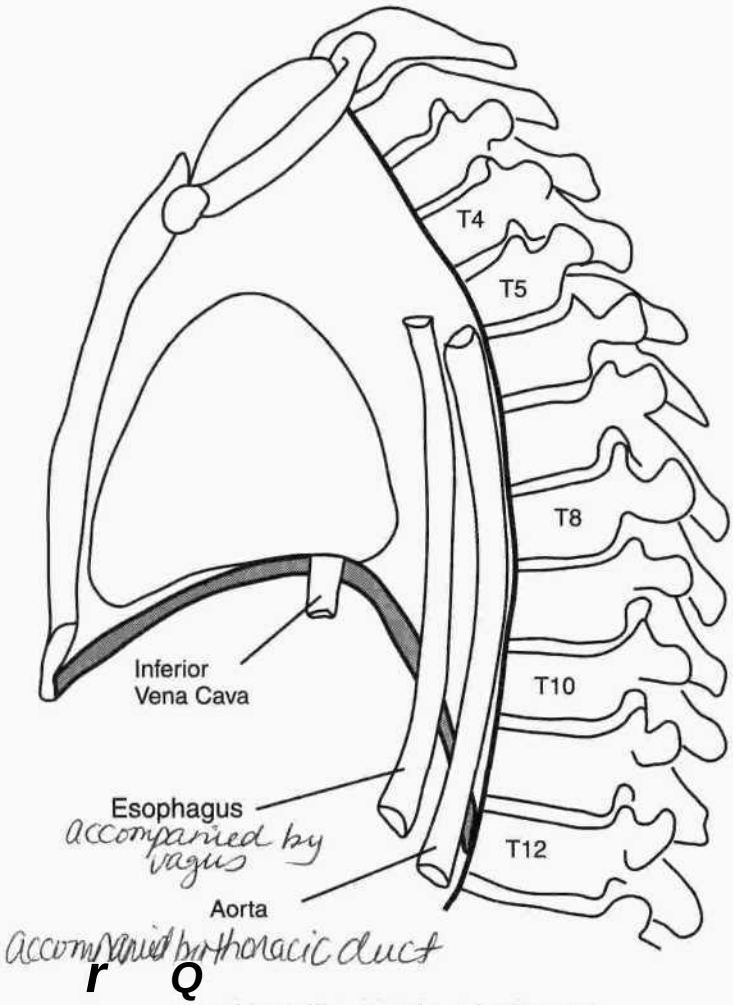


Figure III-2-18.The Diaphragm

Clinical Correlate

Pain Referra).

Because the innervation to the diaphragm (motor and sensory) is primarily from C3 through C5 spinal nerves, pain arising from the diaphragm (e.g., subphrenic access) is referred to these dermatomes in the shoulder region.

Table III-2-4. Important Landmarks in the Thorax

Level	Landmark
T2	Jugular notch
T3	Base of scapular spine
	Top of aortic arch
T4	Sternal angle (manubriosternal junction)
	Second costal cartilage
	Tracheal bifurcation
	Upper end of ascending aorta
	Beginning of descending aorta
	Arch of azygos vein and its entrance into superior vena cava
	Fusion of right and left mediastinal pleurae in anterior midline
T7	Inferior angle of scapula
T8	Caval hiatus
T9	Xiphoid process
T10	Esophageal hiatus
T12	Aortic hiatus

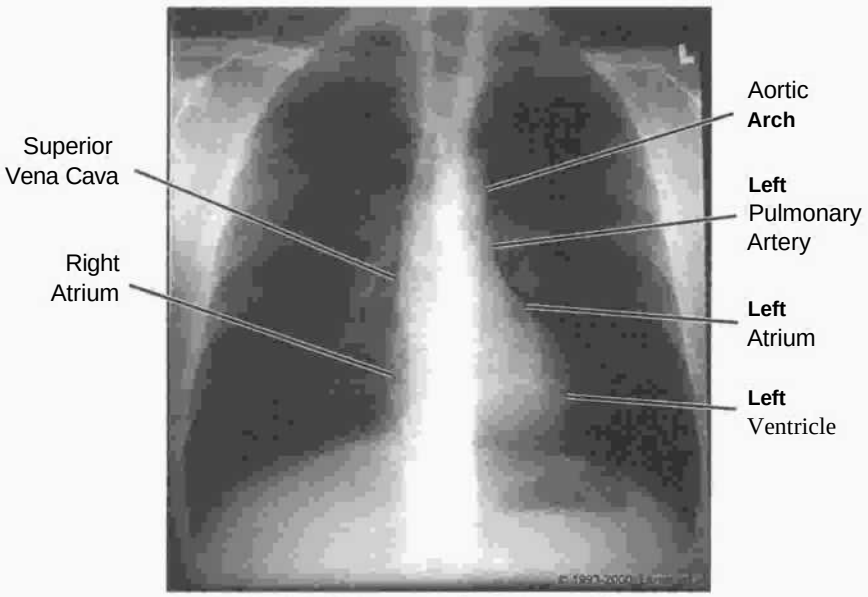


Figure 111-2-19. Postanterlor View of Chest, Male

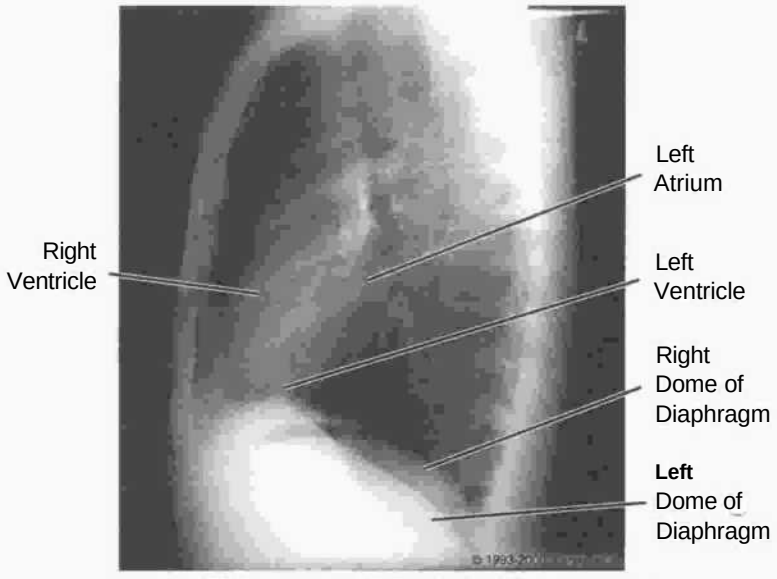


Figure HI-2-20. Lateral View of Chest, Male

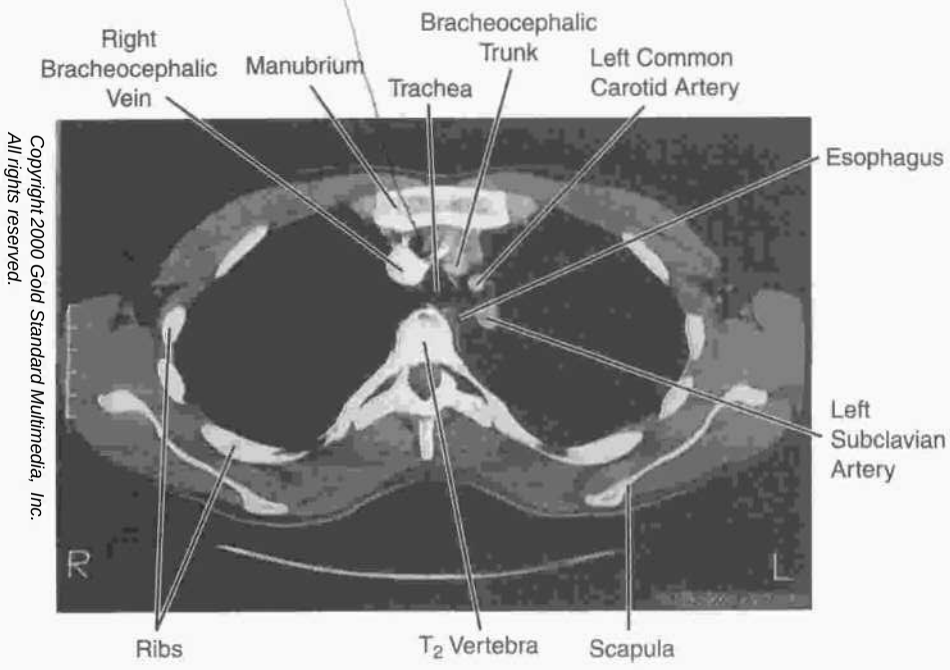


Figure III-2-21. Chest: CT, T_2

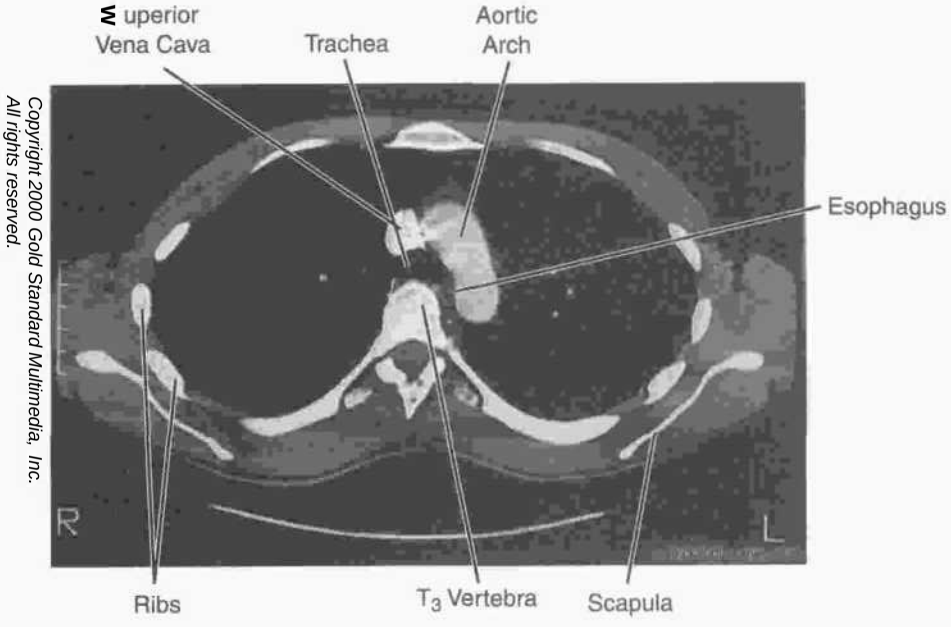


Figure III-2-22. Chest: CT, T_3

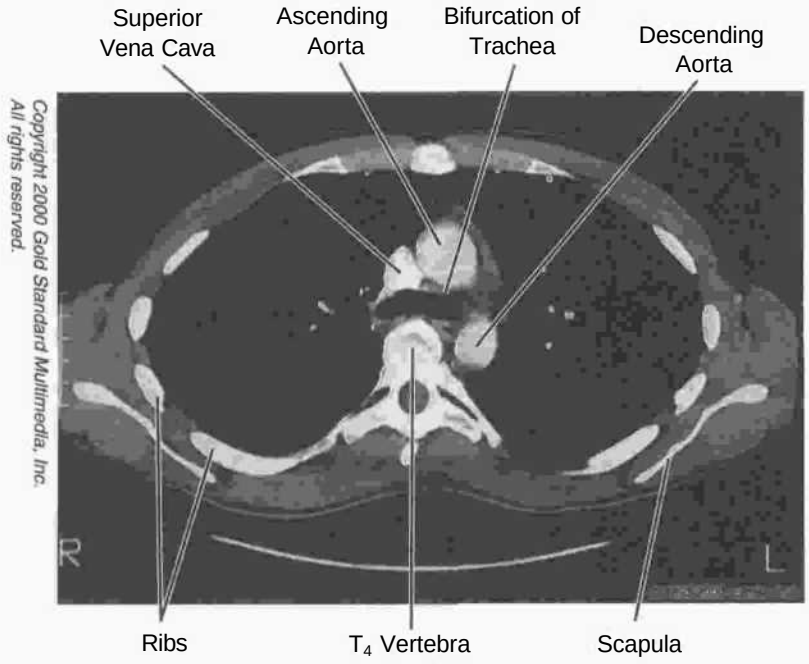


Figure ill-2-23. Chest: CT, T_4

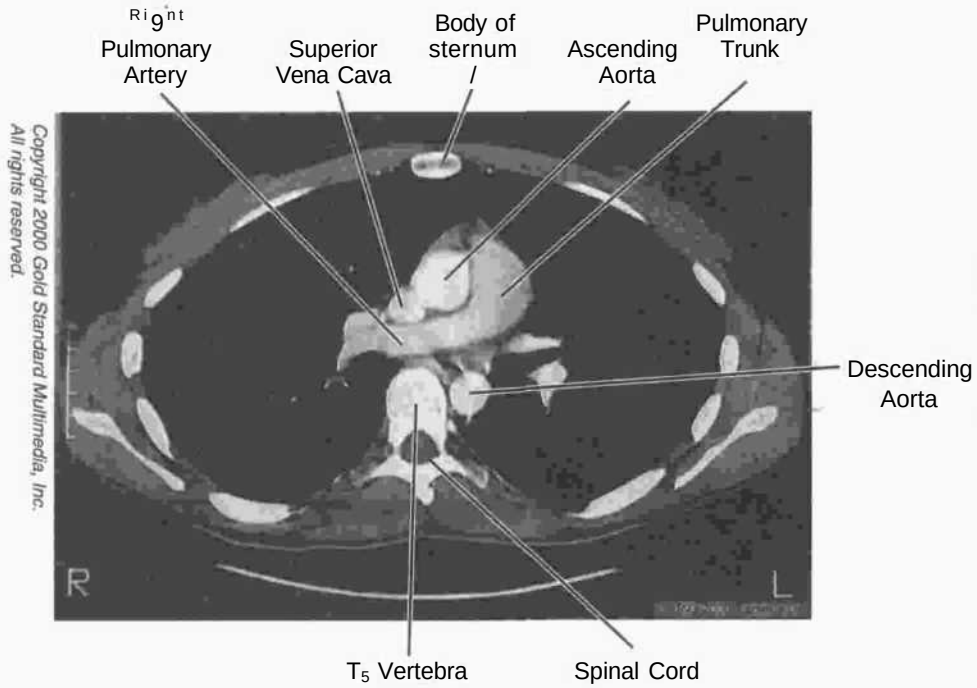


Figure 111-2-24. Chest: CT, T_5

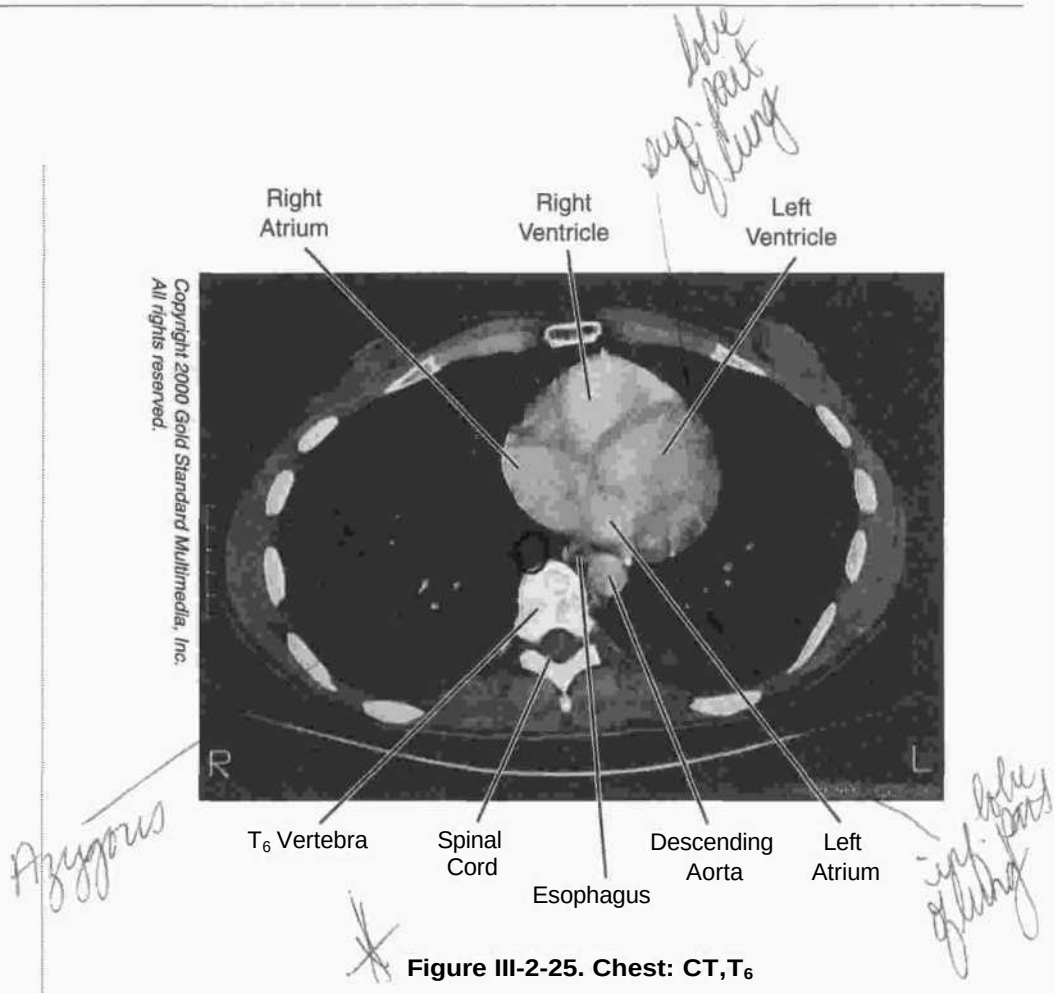


Figure III-2-25. Chest: CT, T_6

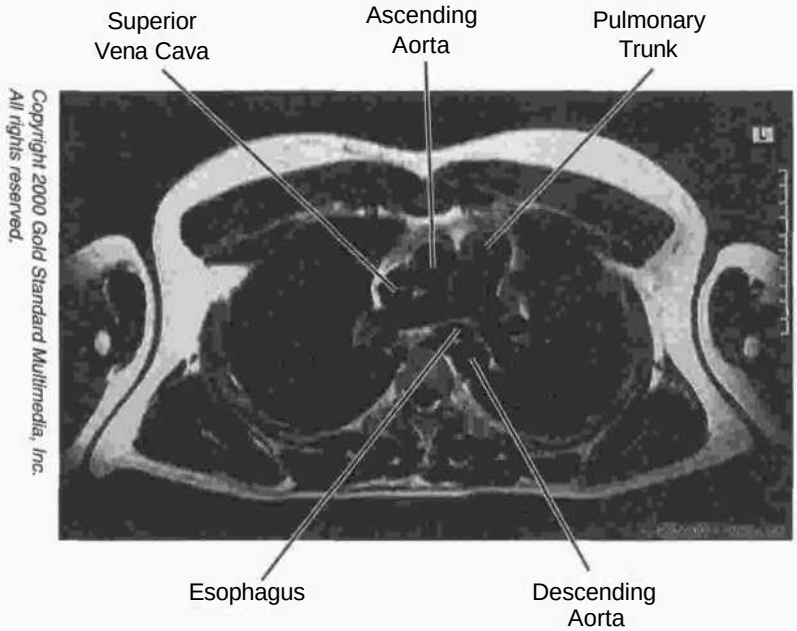
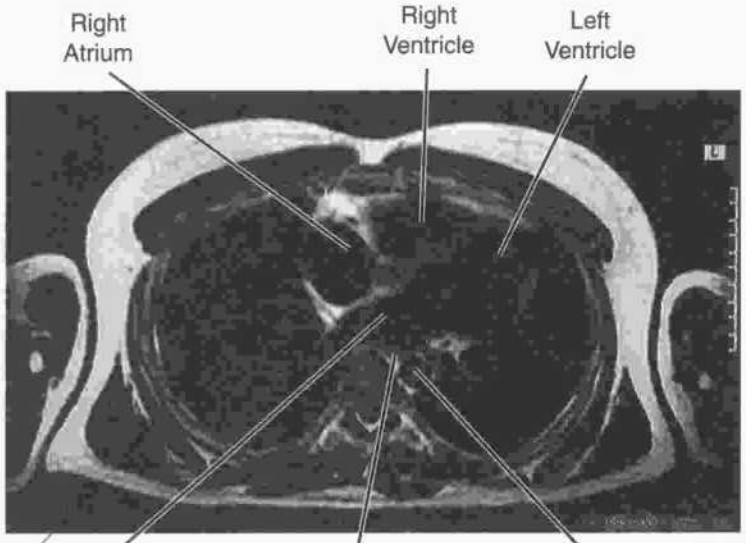
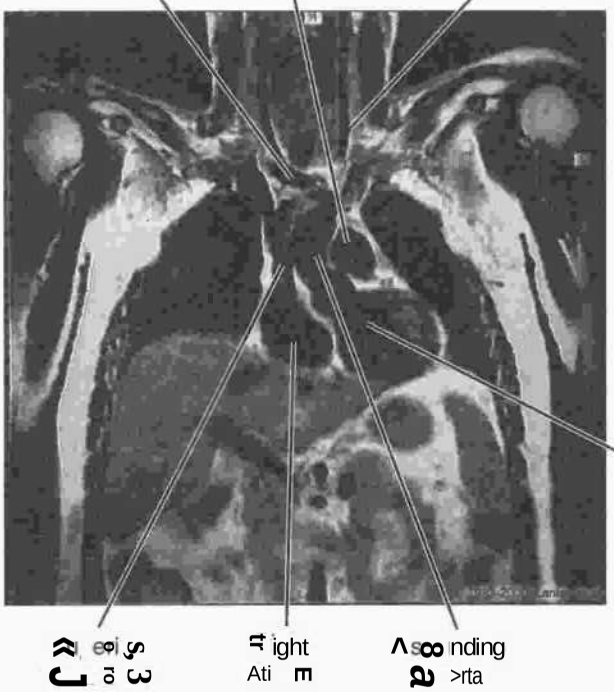


Figure III-2-26. Chest: MRI, Axial T_4



know dome of diaphragm can be seen here Not tumor

Figure III-2-27. Chest: MRI, Axial T_6



Fi re III-2-28. hest: m, oron l

Abdomen, Pelvis, and Perineum

3

ANTERIOR ABDOMINAL WALL

Abdominopelvic Cavity

Osteology

Unlike the thoracic wall, the bony support of the abdomen is minimal, consisting only of the lumbar vertebrae and portions of the pelvis (the ilium and the pubis).

Lumbar Vertebrae

There are five lumbar vertebrae, LI through L5 (Fig III-3- L).

Ilium

The ilium is part of the hipbone or os coxae. The osteology of this bone is presented in detail in the section on the pelvis. Only the landmarks pertinent to the anterior abdominal wall are listed here.

- Anterior superior iliac spine (ASIS)
- Iliac fossa
- Iliac crest
- Iliac tubercle

Pubis (part of os coxae)

- Pubic tubercle
- Pubic crest
- Pubic symphysis

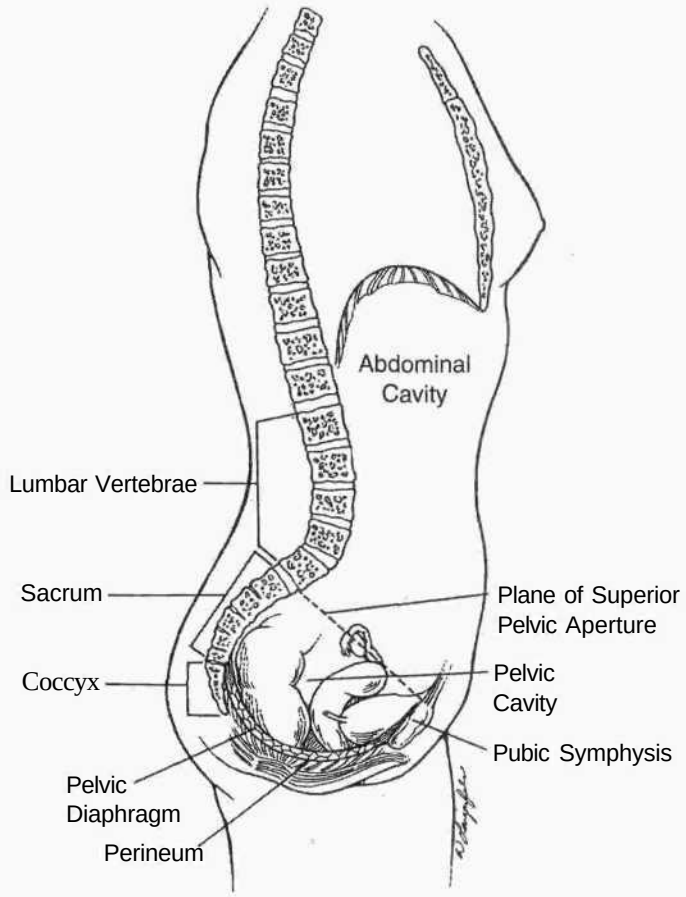


Figure 111-3-1. The Abdominopelvic Cavity

Surface Anatomy

Linea Alba *juorwi £u*J-//)Uj/^tx /^ u^J^ WotiJloM'^i^o* bad healing

The linea alba is a shallow groove that runs vertically in the median plane from the xiphoid to the pubis. It separates the right and left rectus abdominis muscles.

Linea Semilunaris

The linea semilunaris is a curved line defining the lateral border of the rectus abdominis, a bilateral feature.

Inguinal Groove

The inguinal groove indicates the site of the inguinal ligament, the rolled-over, free border of the external oblique aponeurosis. It separates the abdomen superiorly from the lower extremity inferiorly. The inguinal ligament extends from the ASIS to the pubic tubercle (Fig III-3-2).

PlanesandRegions

There are four planes to define nine regions of the abdomen (Fig III-3-2).

Subcostal Plane

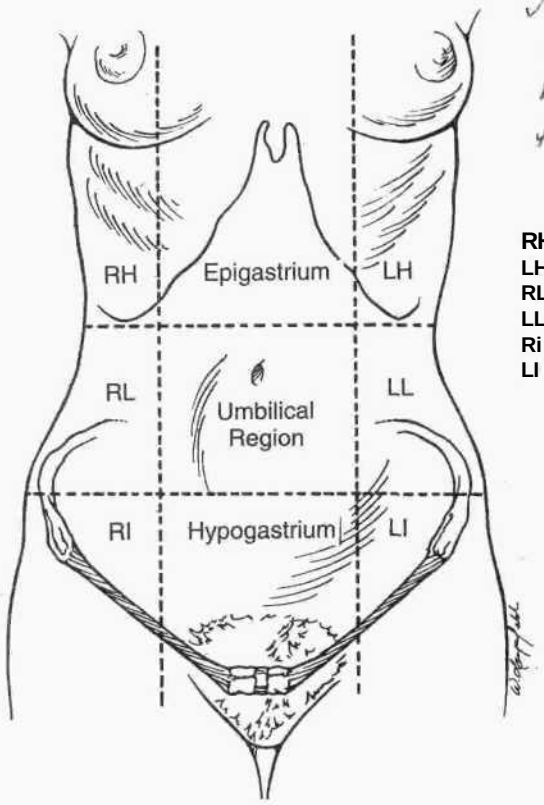
The subcostal plane (horizontal) passes through the inferior margins of the 10th costal cartilages.

Transtubercular Plane

The transtubercular plane (horizontal) passes through the iliac tubercles.

Middavicular lines

The midclavicuJar lines (vertical) are the two planes that pass from the midpoint of the clavicle to the midpoint of the inguinal ligament on each side.



referred pain:
foregut → epigastrium
midgut → umbilical, periumbilical
hindgut → hypogastrium

RH = **right** hypochondrium
LH = left hypochondrium
RL = right lumbar
LL = left lumbar
Ri = right inguinal
LI = left inguinal

Modified with permission from Moore K.L.: Clinically Oriented Anatomy, 3rded. Williams & Wilkins. Baltimore, MD, 1992, p 131.

Figure MI-3-2. Regions of the Abdomen.

Fascial Layers

Superficial Fascia

Camper's fascia is subcutaneous and variable in thickness owing to the presence of fat.

Scarpa's fascia is a deeper membranous layer devoid of fat and is continuous with the fascia lata of the thigh below the inguinal ligament, the dartos fascia of the scrotum or the labia majora, and Colles' fascia of the perineum.

Deep Fascia

The deep fascia is the investing fascia of the abdominal musculature.

Muscles

External Oblique

The fibers run anteriorly and inferiorly (i.e., the hands-in-pockets direction like the external intercostal layer in the thorax; Fig III-3-3).

As fibers pass medially, they become aponeurotic and contribute to the anterior layer of the rectus sheath.

Inferiorly, the free border of the external oblique aponeurosis forms the inguinal ligament.

The superficial inguinal ring is an opening in the external oblique aponeurosis just superior and lateral to the pubic tubercle.

In men, the external oblique fascia gives rise to the external spermatic fascia of the spermatic cord.

Internal Oblique

The fibers run posteriorly and inferiorly at right angles to those of the external oblique like those of the internal intercostal layer in the thorax.

As the fibers pass medially, they become aponeurotic and split to contribute to the rectus sheath.

Inferiorly, these fibers contribute to the formation of the conjoint tendon.

In men, the internal oblique layer gives rise to the middle spermatic fascia and the cremaster muscle of the spermatic cord.

Transversus Abdominis

The muscle fibers run horizontally. As the fibers pass medially, they become aponeurotic and contribute to the posterior rectus sheath.

Inferiorly, the fibers join with those of the internal oblique to form the conjoint tendon.

Rectus Abdominis

The fibers run vertically between the pubic symphysis and the xiphoid process.

The **right** and **left** recti muscles are separated medially by the linea alba.

The rectus sheath is formed by aponeurotic fibers of three lateral muscle layers.

- The arcuate line is located midway between the umbilicus and pubis. It is a landmark for the change in disposition of the aponeurotic fibers. Above the arcuate line, posterior and anterior layers of the rectus sheath have equal thickness; below it, all aponeurotic fibers run anterior to the rectus abdominis.
- Superior and inferior epigastric vessels travel in the posterior layer of the rectus sheath.

Transversalis Fascia

The transversalis fascia lines the abdominal cavity. It forms the posterior layer of the rectus sheath below the arcuate line and the internal spermatic fascia of the spermatic cord.

The deep inguinal ring begins as an outpouching of transversalis fascia just lateral to where the inferior epigastric vessels intersect the inguinal ligament.

The transversalis fascia is separated from the peritoneum by a layer of fatty areolar connective tissue.

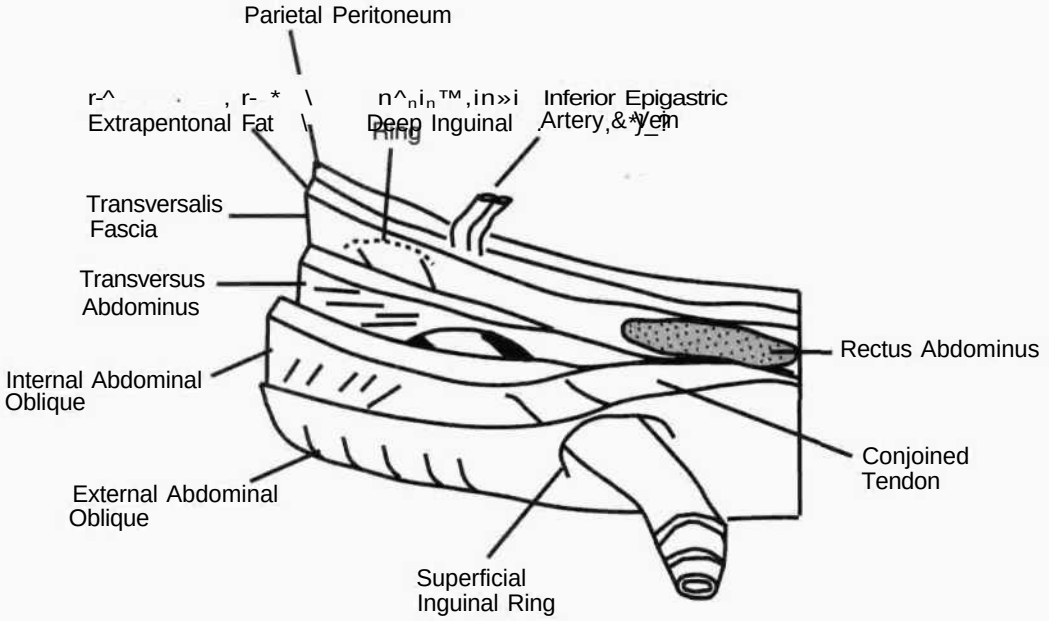


Figure 111-3-3. Layers of Anterolateral Abdominal Wall

Nerves, Blood Vessels, and Lymphatics

Innervation of the skin and musculature of the anterior abdominal wall is via branches of the ventral primary rami of the lower six thoracic spinal nerves (includes the subcostal nerve), plus the iliohypogastric and ilioinguinal branches of the ventral primary rami of LI.

The major arterial blood supply to the anterior wall is derived from the superior epigastric branch of the internal thoracic artery as well as the inferior epigastric and the deep circumflex iliac branches of the external iliac artery.

Venous drainage from the anterior wall is to the superficial epigastric, the lateral thoracic veins superiorly, and the great saphenous vein inferiorly.

Lymph from tissues of the anterior wall drains to axillary nodes superiorly and to superficial inguinal nodes inferiorly.

Inguinal Canal

Contents

Female:

- Round ligament and ilioinguinal nerve

Male:

- Spermatic cord and ilioinguinal nerve

Spermatic cord includes:

Spermatic fascias
Testicular artery
Pampiniform venous plexus
Vas deferens (ductus deferens)

Boundaries of the Inguinal Canal

Roof

Internal abdominal oblique and the transverse abdominus muscles (Fig III-3-4).

Anterior Wall

Aponeurosis of the external abdominal oblique and the internal abdominal oblique muscle.

Floor

Inguinal ligament (part of the aponeurosis of the external oblique).

Posterior Wall

Transversalis fascia (weak area) and conjoined tendon.

The conjoined tendon reinforces the medial part of the posterior wall.

The conjoined tendon is formed by the aponeuroses of the internal oblique and transversus abdominus muscles.

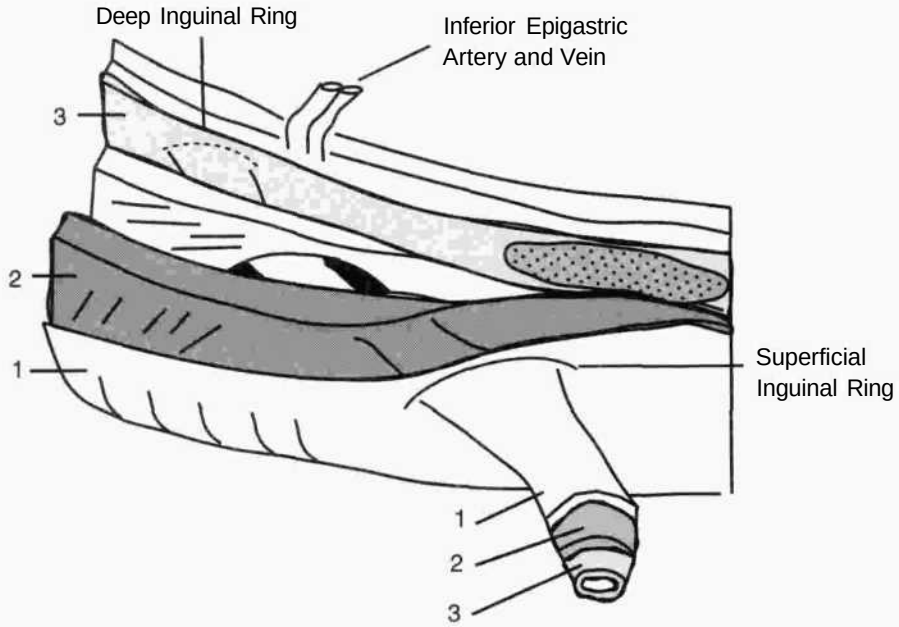


Figure 111-3-4. Inguinal Canal

Descent of the Testis

The tunica vaginalis is a remnant of parietal peritoneum (Fig III-3-5):

Spermatic fascia—an abdominal wall derivative

- **External spermatic fascia**—external abdominal oblique fascia
- **Cremasteric fascia—**internal abdominal oblique fascia
- **Internal spermatic fascia**—transversalis fascia

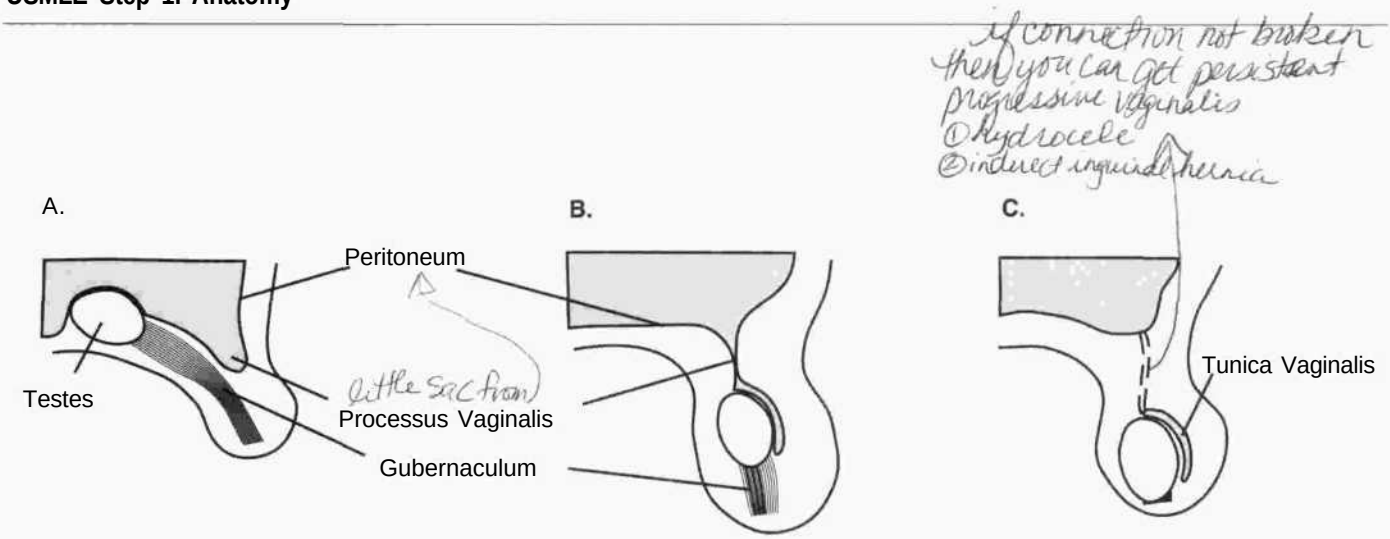


Figure III-3-5. Decent of the Testis

Groin Hernias

InguinalHernias

The most commorrtype of hernia in men and women (Fig III-3-6):

- Direct emerges through the posterior wall of the inguinal canal medial to the inferior epigastric vessels.
- Indirect: passes through the deep ring lateral to the inferior epigastric vessels, courses through the inguinal canal. A persistent process vaginalis often results in a congenital indirect inguinal hernia.

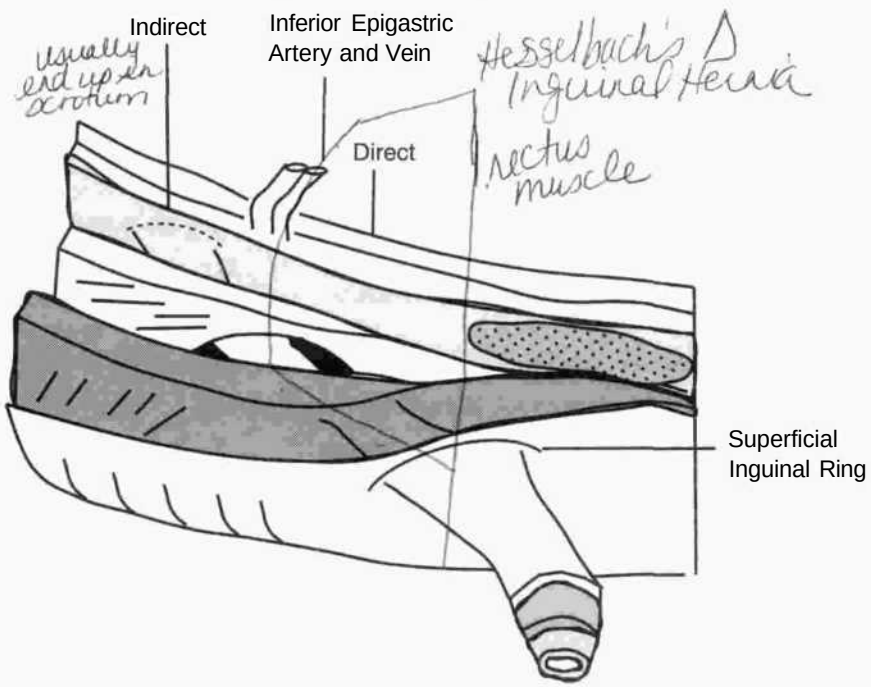


Figure III-3-6. Inguinal Hernia

Femoral Hernias

Most often occur in women (Fig III-3-7).

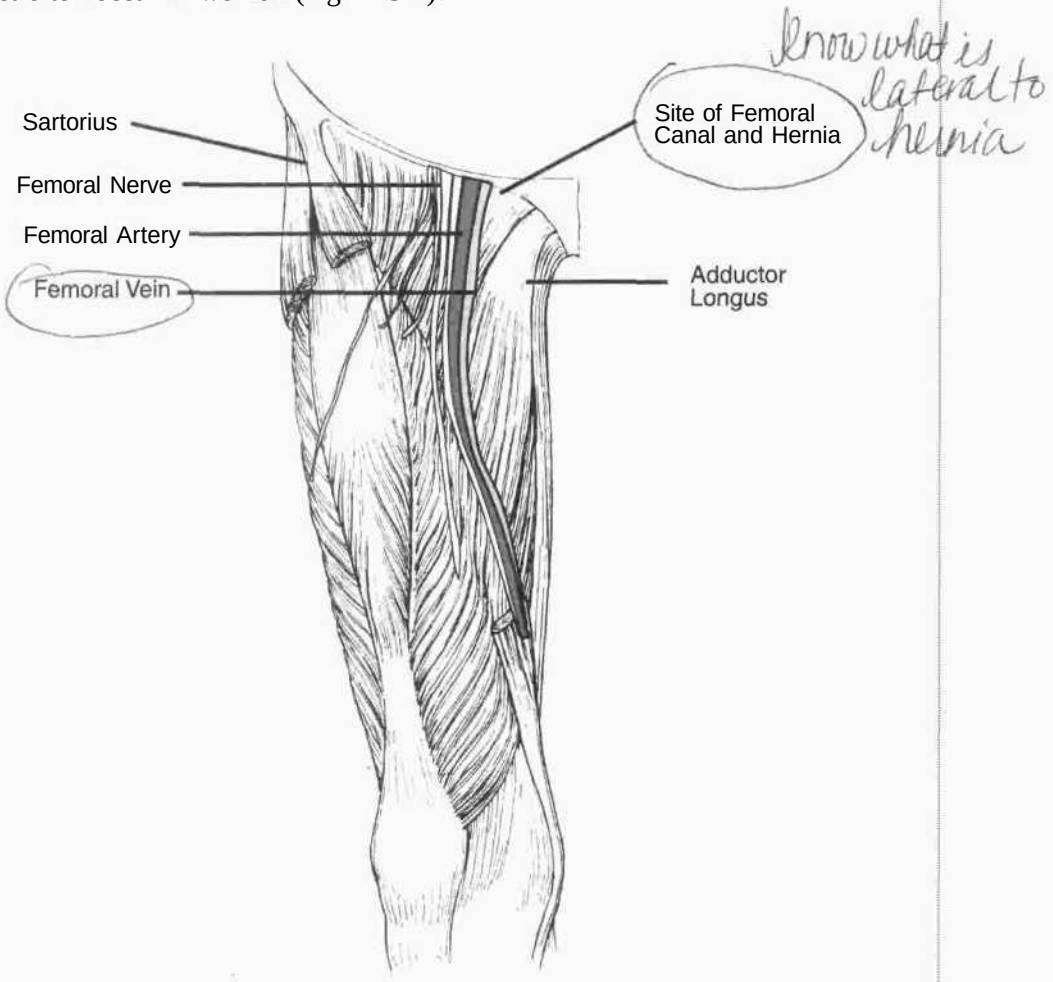


Figure **111-3-7.** Femoral Hernia

POSTERIOR ABDOMINAL WALL

The posterior abdominal wall is located behind the posterior layer of the parietal peritoneum.

Osteology

The bony structure of the posterior wall includes many of the same features as the anterior wall of the abdomen and bony landmarks from the thorax and the lower Limb.

- Five lumbar vertebrae (LI through L5)
- Iliac crest
- Iliac fossa
- Twelfth pair of ribs
- Lesser trochanter of femur

Muscles

Quadratus Lumborum

The quadratus lumborum extends upward from the iliac crest to the inferior border of the 12th rib. It stabilizes the 12th rib during inspiration.

Psoas Major

The psoas major arises from the transverse processes of the lumbar vertebrae.

Insertion, along with iliacus, is on the lesser trochanter of the femur.

It is the chief flexor of the hip.

Iliacus

The iliacus originates from the iliac fossa.

It joins with the psoas major to insert on the lesser trochanter.

Together with psoas major, it is known as the iliopsoas.

EMBRYOLOGY OF THE GASTROINTESTINAL SYSTEM

Primitive Gut Tube

The primitive gut tube is formed by incorporation of the yolk sac into the embryo during cranial-caudal and lateral folding (Fig III-3-8).

- The epithelial lining and glands of the mucosa are derived from **endoderm.**
- The lamina propria, muscularis mucosae, submucosa, muscularis externa, and adventitia/serosa are derived from **mesoderm.**

The epithelial lining of the gut tube proliferates rapidly and obliterates the lumen followed by recanalization.

The primitive gut tube is divided into the foregut, midgut, and hindgut, each supplied by a specific artery (Table III-3-1).

Table III-3-1. Adult Structures Derived From Each of the Three Divisions of the Primitive Gut Tube

Foregut (Celiac Trunk)	Midgut wt^AsW^-iiZUuii/ (Superior Mesenteric Artery)	Hindgut (Inferior Mesenteric Artery)
Esophagus Stomach	Duodenum 2nd, 3rd, 4th part Jejunum	Transverse colon (distal third) Descending colon
Duodenum 1st part	Ileum	Sigmoid colon
Liver	Cecum	Rectum
Pancreas	Appendix	Anal canal (upper part)
Biliary apparatus	Ascending colon	
Gall bladder	Transverse colon (proximal two thirds)	
Pharyngeal pouches*		
Lungs*		
Thyroid*		

* These are derivatives of the primitive gut tube but not part of the gastrointestinal tract per se.

Remnants of ventral mesentery attach to liver
1. lesser omentum b/t liver & stomach
a. Hepatoduodenal lig.
b. Hepatogastric lig.
2. falciform ligament
3. coronary ligaments
4. triangular ligaments
→ liver-diaphragm/body wall

dorsal mesentery
1. greater omentum
a. gastrosplenic lig
b. gastrocolic lig
a. gastrophrenic lig.
vi. Splenorenal lig.
3. The mesentery
4. Mesoappendix
5. Transverse mesocolon
6. Sigmoid mesocolon

AL: allantois
AM: amniotic cavity
CA: celiac artery
CL: cloaca
DP: dorsal pancreatic bud
E: esophagus
GB: gall bladder
HD: hepatic diverticulum
IMA: inferior mesenteric artery
LB: lung bud
SMA: superior mesenteric artery
ST: stomach
TD: thyroid diverticulum
VD: vitelline duct
VP: ventral pancreatic bud
YS: yolk sac

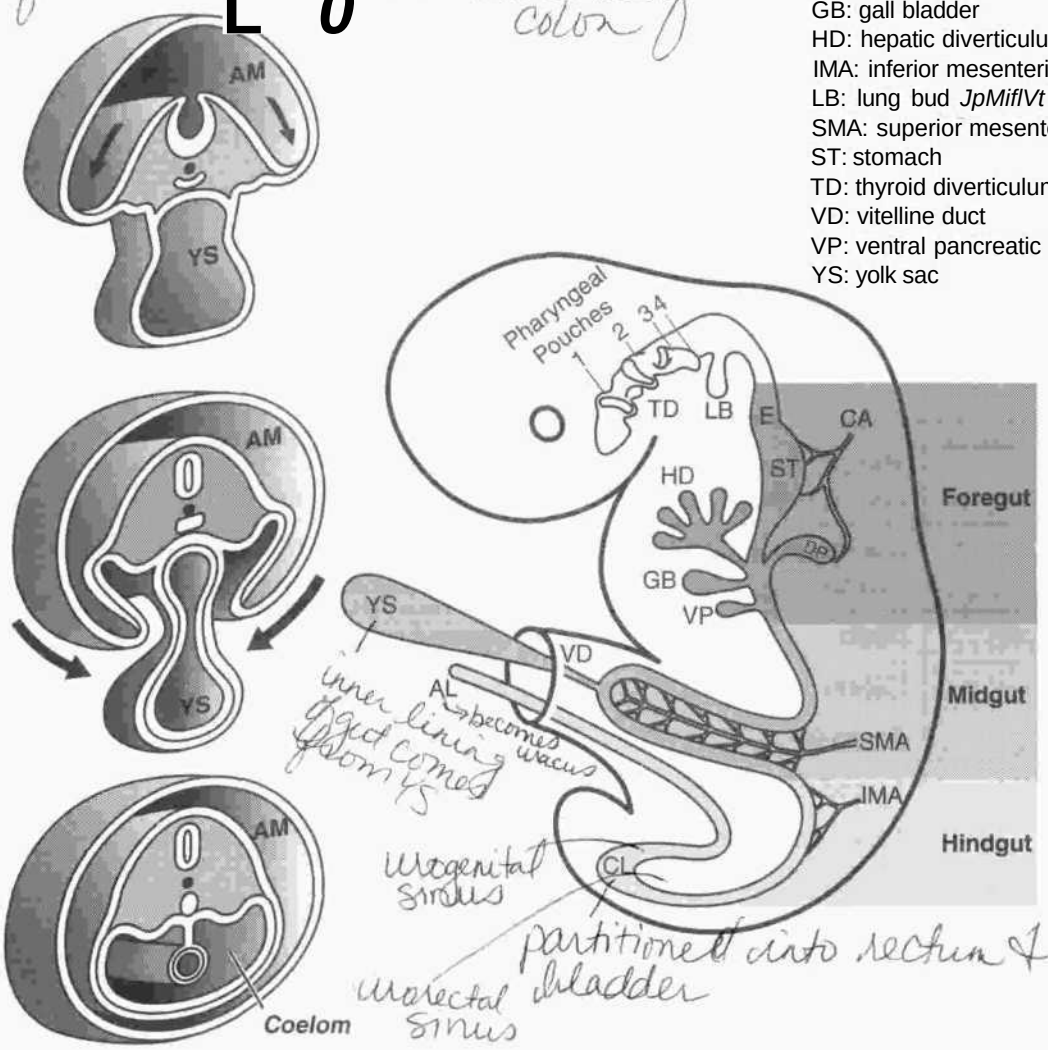


Figure 111-3-8. Development of the GI Tract

Hypertrophic Pyloric Stenosis

Occurs when the muscularis externa hypertrophies, causing a narrow pyloric lumen. This condition is associated with projectile, nonbilious vomiting and a small knot at the right costal margin.

Extrahepatic Biliary Atresia

Occurs when the lumen of the biliary ducts is occluded owing to incomplete recanalization. This condition is associated with jaundice, white-colored stool, and dark-colored urine.

Annular Pancreas

Occurs when the ventral and dorsal pancreatic buds form a ring around the duodenum, thereby causing an obstruction of the duodenum.

Duodenal Atresia

Occurs when the lumen of the duodenum is occluded owing to failed recanalization. This condition is associated with polyhydramnios, bile-containing vomitus, and a distended stomach. *ducdlAjUSH s/jh^S^D CMjE /£ 0k :tL*

Omphalocele

Occurs when the midgut loop fails to return to the abdominal cavity, forming a light gray shiny sac at the base of the umbilical cord filled with loops of small intestine.

Heal (Meckel's) Diverticulum

Occurs when a remnant of the vitelline duct persists, thereby forming a blind pouch on the antimesenteric border of the ileum. This condition is often asymptomatic but occasionally becomes inflamed if it contains ectppic gastric, pancrg; atic, or endometrial tissue, which may produce ulceration. *^E^^3^P/S)*

Vitelline Fistula

Occurs when the vitelline duct persists, thereby forming a direct connection between the intestinal lumen and the outside of the body at the umbilicus. This condition is associated with diainage of meconium from the umbilicus.

Malrotation of Midgut

Occurs when the midgut undergoes only partial rotation and results in abnormal position of abdominal viscera. This condition may be associated with **volvulus** (twisting of intestines).

Colonic Aganglionosis (Hirschsprung's Disease)

Results from the failure of neural crest cells to form the myenteric plexus in the sigmoid colon and rectum. This condition is associated with loss of peristalsis, fecal retention, and abdominal distention.

utonomic Inn. of GI

Sympathetic

pot	Ganglia	Target
or. Splanch. n. T5-12	prevertebral (coll) eg. celiac, aorticorenal ganglia	foregut midgut GI
nferior Splanch. n. L1-2	prevertebral (coll) eg. intermesenteric ganglia	hindgut GI

Parasympathetic

out	Ganglia	Target
gus n.	terminal (submucosal + myenteric plexus)	esoph. to 1/3 transverse colon foregut + midgut
ric Splanchnic rves 2, 3, 4 (autonomic)	terminal (submucosal + myenteric plexus)	1/3 colic flexure to anal canal: hindgut

idenal (somatic) $S_{2,3,4}$

ABDOMINAL VISCERA AND PERITONEUM

Gastrointestinal (GI) System

Peritoneum

The serous membrane related to the viscera of the abdominal cavity. It is divided into two layers (Fig III-3-9).

Parietal Layer

The parietal layer lines the body wall and covers the retroperitoneal organs.

Visceral Layer

The visceral layer is composed of two parts:

- Covering of the surface of the peritoneal organs.
- Mesentery—a double layer of peritoneum that suspends a part of the GI tract from the body wall. Allows for the passage of vessels, nerves, and lymphatics. Includes the terms *amentum, meso,* and *ligament.*

Peritoneal Cavity

The peritoneal cavity is the potential space located between the parietal and visceral layers.

'that is normally found in peritoneal cav. = serous fluid

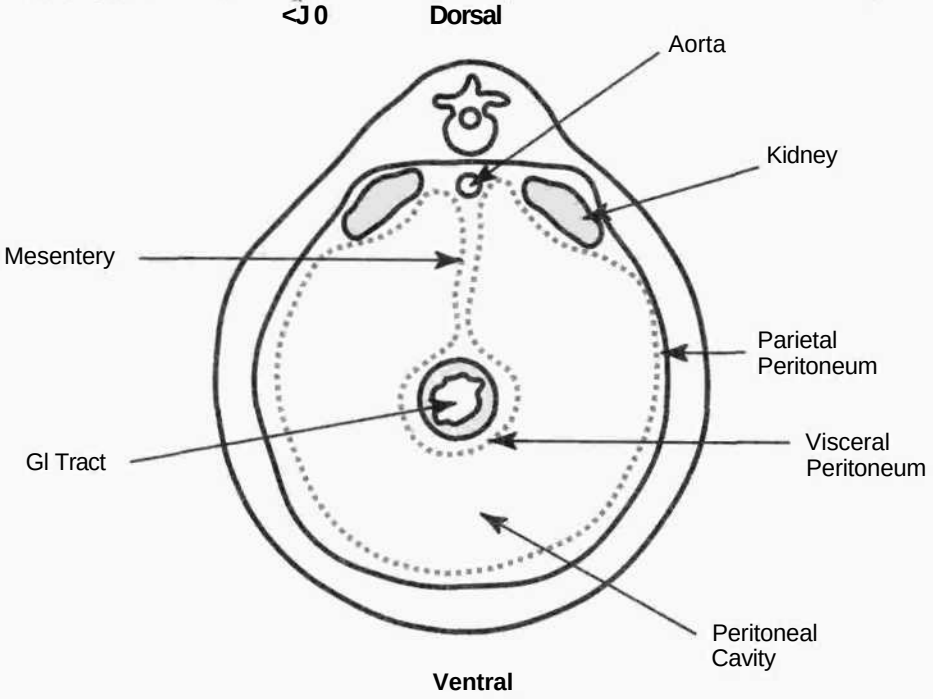


Figure III-3-9. Cross-Sectional View of the Abdominal Viscera

Viscera

Viscera are classified as:

Peritoneal organs—have a mesentery and are almost completely enclosed in peritoneum. These organs are mobile.

Retroperitoneal organs—are partially covered with peritoneum and are immobile or fixed organs.

Peritoneal Cavity and Mesenteries

Epiploic Foramen of Winslow

An opening into omental bursa (Figs III-3-10 and III-3-11).

A finger in the epiploic foramen that presses:

- Anteriorly—touches hepatoduodenal ligament and the portal vein
- Posteriorly—touches inferior vena cava

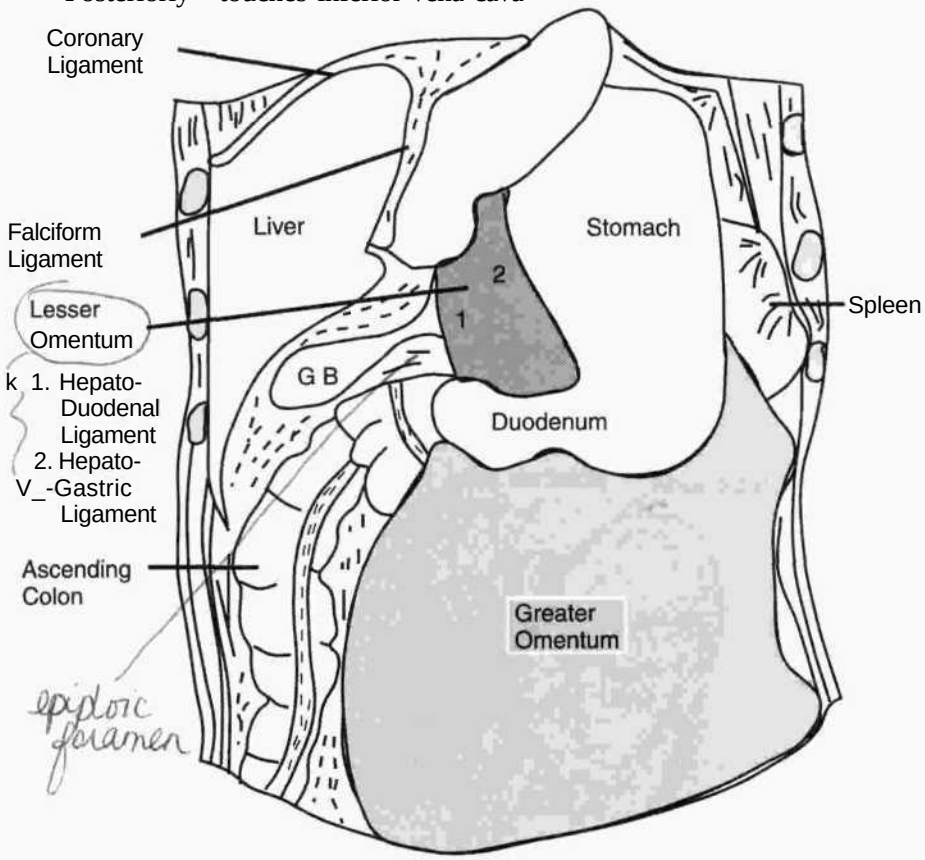


Figure III-3-10. Peritoneal Membranes

(mobile) Intraperitoneal
Stomach
Less. Omen.
Great. Omen.
Duodenum (1st part)
Jejunum
Ileum
Cecum
Appendix
Transverse colon
Sigmoid colon
Spleen (gr. omen)
Liver and gall bladder (ventral mesentery)
pancreas (tail)
uterus
uterine tubes
Ovaries (broad lig)

(fixed) Retroperitoneal
Duodenum parts 2, 3, 4
Ascending colon
Descending colon
Rectum
Pancreas (head, neck, body)
Kidneys
Ureters
Suprarenal glands
Aorta
Inf. vena cava

Lesser Omentum
Hepatoduodenal ligament contains portal vein, hepatic artery, common bile duct, lymphatic vessels, and nerves.

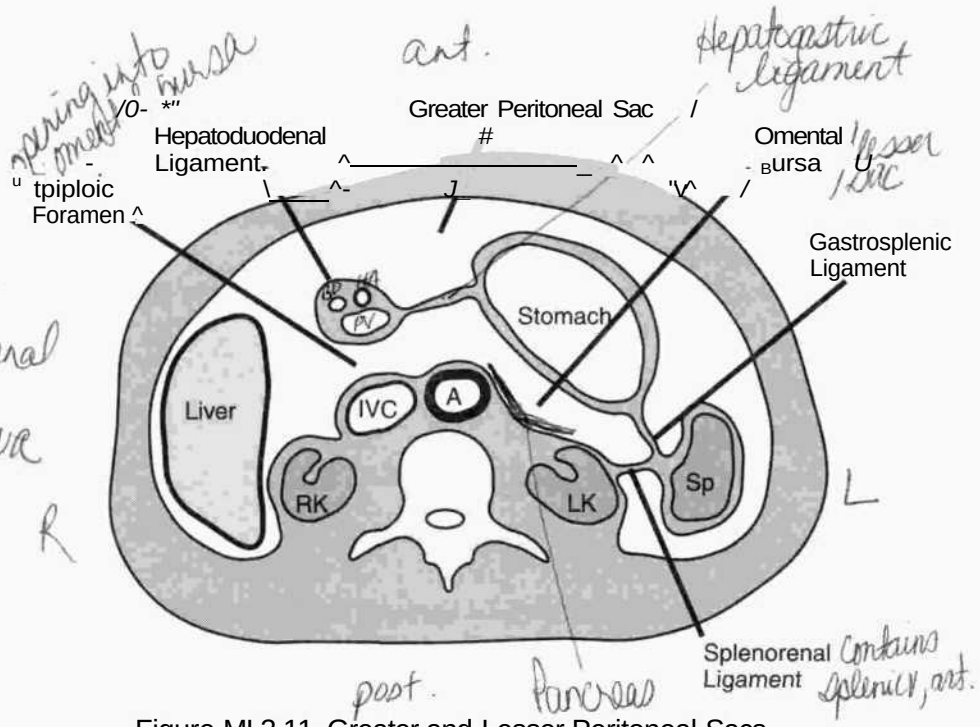


Figure MI-3-11. Greater and Lesser Peritoneal Sacs

Liver

The liver is invested by peritoneum (i.e., the coronary ligament and the right and left triangular ligaments) except over the bare area that lies in direct contact with the diaphragm. It lies mostly in the right hypochondrium and is protected by the rib cage.

The liver has two surfaces: a superior, diaphragmatic surface and an inferior, visceral surface (Fig III-3-12).

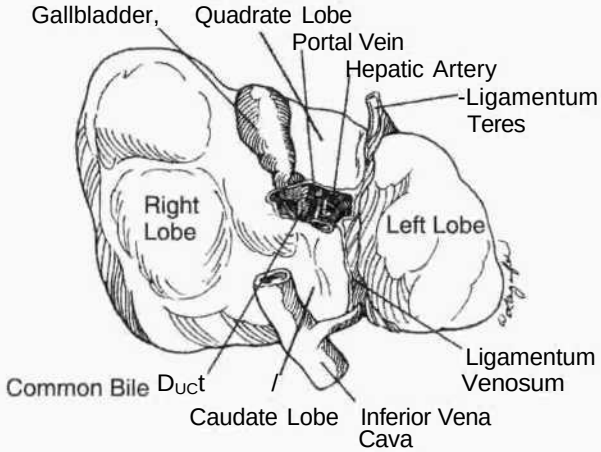


Figure III-3-12. Visceral Surface of the Liver

The liver is divided into two lobes of unequal size by the falciform ligament.

- Fissures for the ligamentum teres and the ligamentum venosum, the porta hepatis, and the fossa for the gallbladder further subdivide the right lobe into the right lobe proper, the quadrate lobe, and the caudate lobe.
- The quadrate and caudate lobes are anatomically part of the right lobe but functionally part of the left. They receive their blood supply from the left branches of the portal vein and hepatic artery and secrete bile to the left hepatic duct.

The liver has a central hilus, or porta hepatis, which receives venous blood from the GI system via the portal vein and arterial blood from the hepatic artery.

- The central hilus also transmits the common bile duct, which collects bile produced by the liver.
- These structures, known collectively as the portal triad, are located in the hepatoduodenal ligament, which is the right free border of the lesser omentum.

The hepatic veins drain the liver by collecting blood from the liver sinusoids and returning it to the inferior vena cava.

Gallbladder

The gallbladder lies in a fossa on the visceral surface of the liver to the right of the quadrate lobe.

It scores and concentrates bile, which enters and leaves through the cystic duct. The cystic duct joins the common hepatic duct to form the common bile duct.

Pancreas

The ventral pancreatic diverticulum becomes the major pancreatic duct (of Wirsung), and the dorsal pancreatic diverticulum becomes the minor pancreatic duct (of Santorini) (Figs III-3-13 and III-3-14).

The inferior portion of the head of the pancreas and the uncinate process develop from the ventral bud, and the superior portion of the head and the neck, body, and tail of the pancreas develop from the dorsal bud.

Most of the pancreas is secondarily retroperitoneal, but the distal part of the tail of the pancreas remains peritoneal in the splenorenal ligament. The tip of the tail of the pancreas reaches the hilus of the spleen.

Both pancreatic ducts open into the second portion of the duodenum.

The head of the pancreas receives its blood supply from the superior and inferi-

Art. supply of GI:
Celiac art. (supplies embryonic foregut)
esophagus
stomach
duodenum (1/2)
Liver and gallbladder
Pancreas
Spleen (not a foregut der. from mesoderm)
Sup. Mesenteric art (midgut)
duodenum (last 1/2)
jejunum
ileum
cecum
appendix
ascending colon
transverse colon (prox. 2/3)
Inf. Mesenteric Art.
transverse colon (distal 1/3)
descending colon
^iqnrmcL Colon
Mdtvum (upper portion)

Common Bile Duct reaches the second part of the duodenum by passing through the head of the pancreas
tumor → jaundice
Signs of cholecystitis: pain in upper rt. quadrant of abdomen; nausea & vomiting after heavy meal
Stones in comm. bile duct → jaundice
Acute pancreatitis: pt. will have severe and acute pain radiating from the center of abd. to back

or pancreaticoduodenal arteries. This region is an important region for **collateral circulation** because there are anastomoses between these branches of the celiac trunk and superior mesenteric artery.

The body and tail of the pancreas receive their blood supply from the splenic artery.

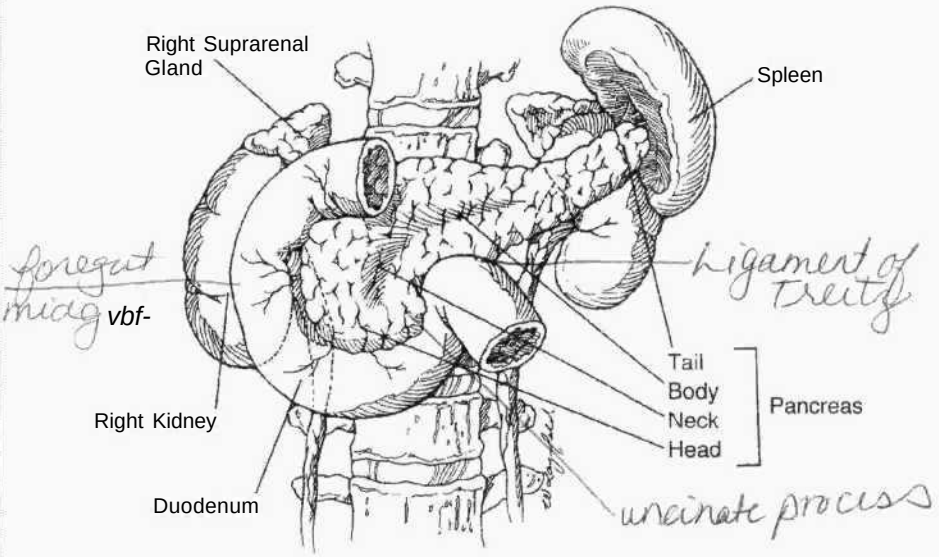


Figure 111-3-13. Adult Pancreas

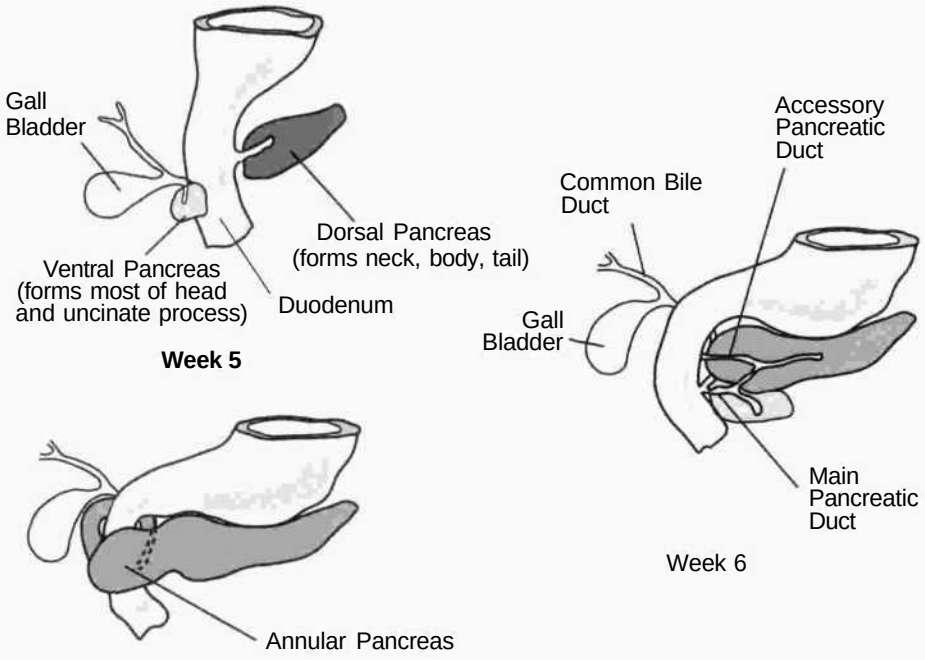


Figure 1(1-3-14. Development of the Pancreas and Duodenum

Spleen

The spleen is a peritoneal organ in the upper left quadrant that is related to the left 9th, 10th, and 11th ribs. Fracture of these ribs may lacerate the spleen.

Inasmuch as the spleen lies above the costal margin, a normal-sized spleen is not palpable. An enlarged spleen may be palpated below the left costal margin.

The splenic artery and vein reach the hilus of the spleen by traversing the splenorenal ligament.

Stomach

The stomach has a lesser curvature, which is connected to the porta hepatis of the liver by the lesser omentum, and a greater curvature from which the greater omentum is suspended.

The cardiac region receives the esophagus.

The dome-shaped upper portion of the stomach, which is normally filled with air, is the fundus.

The main center portion of the stomach is the body.

The pyloric portion of the stomach has a thick muscular wall and narrow lumen that leads to the duodenum.

Duodenum

The duodenum is C-shaped, has four parts, and is located retroperitoneally except at the beginning.

It receives the common bile duct and pancreatic duct in its second (descending) part. The common opening for these structures is the hepatopancreatic ampulla (of Vater). Smooth muscle in the wall of the ampulla is known as the sphincter of Oddi. Note that the foregut terminates at the point of entry of the common bile duct or the anterior intestinal portal; the remainder of the duodenum is part of the midgut.

Celiac and Superior Mesenteric Arteries

Branches of the celiac and superior mesenteric arteries form a collateral circulation around the duodenum and the head of the pancreas (Fig III-3-15).

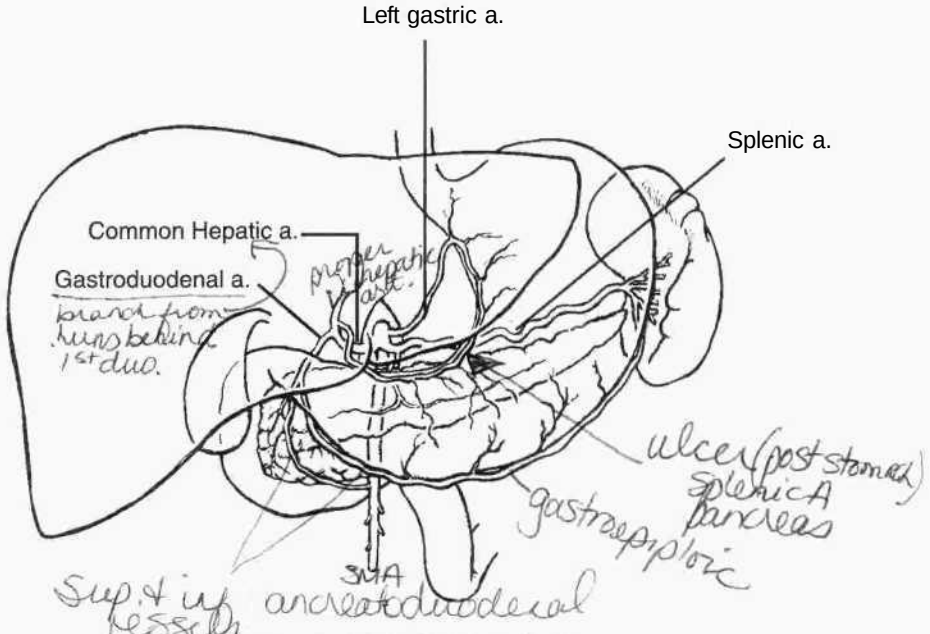


Figure III-3-15. Celiac Artery

Jejunum and Ileum

The jejunum begins at the duodenojejunal junction and comprises two fifths of the remaining small intestine. The beginning of the ileum is not clearly demarcated; it consists of the distal three fifths of the small bowel.

The jejunoileum is suspended from the posterior body wall by the mesentery proper. Although the root of the mesentery is only 9 inches long, the mobile part of the small intestine is approximately 22 feet in length.

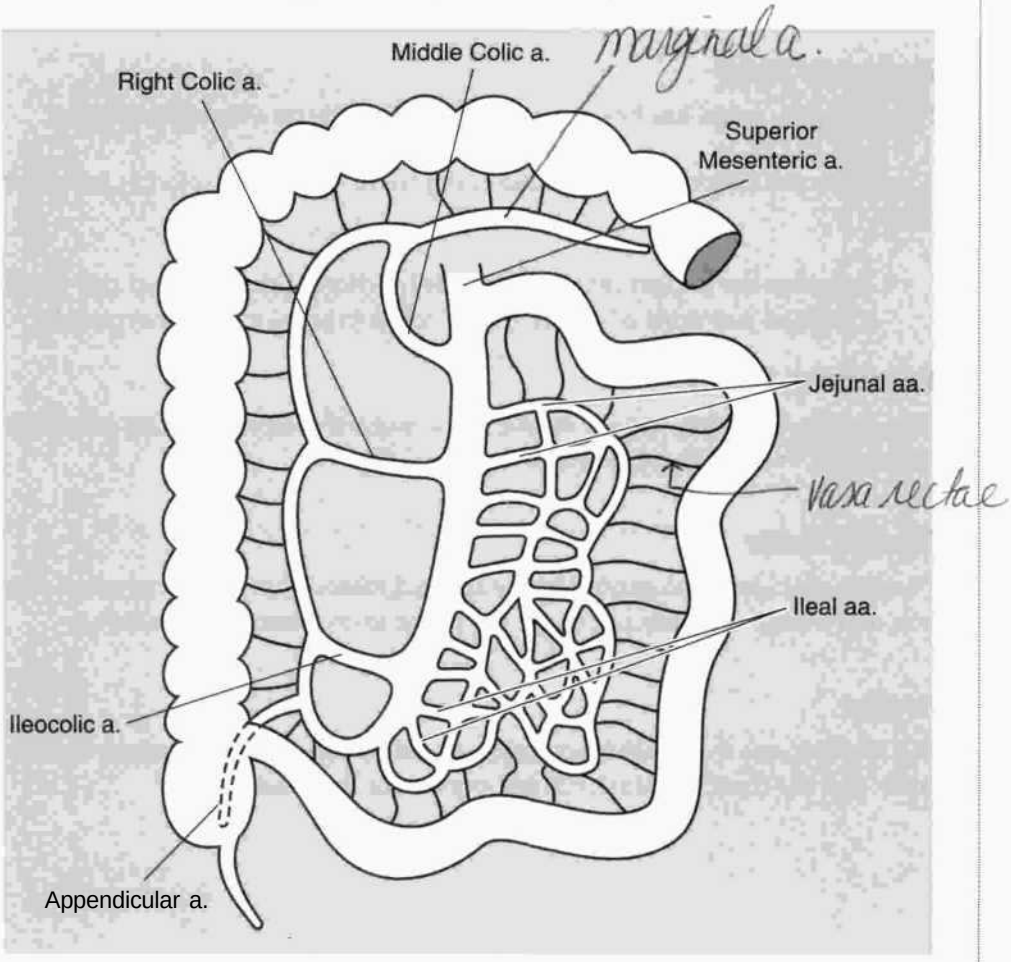


Figure 111-3-16. Distribution of Superior Mesenteric Artery

Colon

Cecum

The cecum is the first part of the colon, or large intestine, and begins at the ileocecal junction (Fig III-3-16).

It is a blind pouch, which has a mesentery, and gives rise to the vermiform appendix. The appendix has its own mesentery, the mesoappendix.

Ascending Colon

The ascending colon lies retroperitoneally and lacks a mesentery. It is continuous with the transverse colon at the right (hepatic) flexure of colon.

Transverse Colon

The transverse colon has its own mesentery called the transverse mesocolon.

It becomes continuous with the descending colon at the left (splenic) flexure of colon.

- Note that the midgut terminates at the junction of the proximal two thirds and distal one third of the transverse colon (posterior intestinal portal).

Descending Colon

The descending colon lacks a mesentery. It joins the sigmoid colon where the large bowel crosses the pelvic brim.

Sigmoid Colon

The sigmoid colon is suspended by the sigmoid mesocolon. It is the terminal portion of the large intestine and enters the pelvis to continue as the rectum.

Rectum

The superior one third of the rectum is covered by peritoneum anteriorly and laterally. It is the fixed, terminal, straight portion of the hindgut.

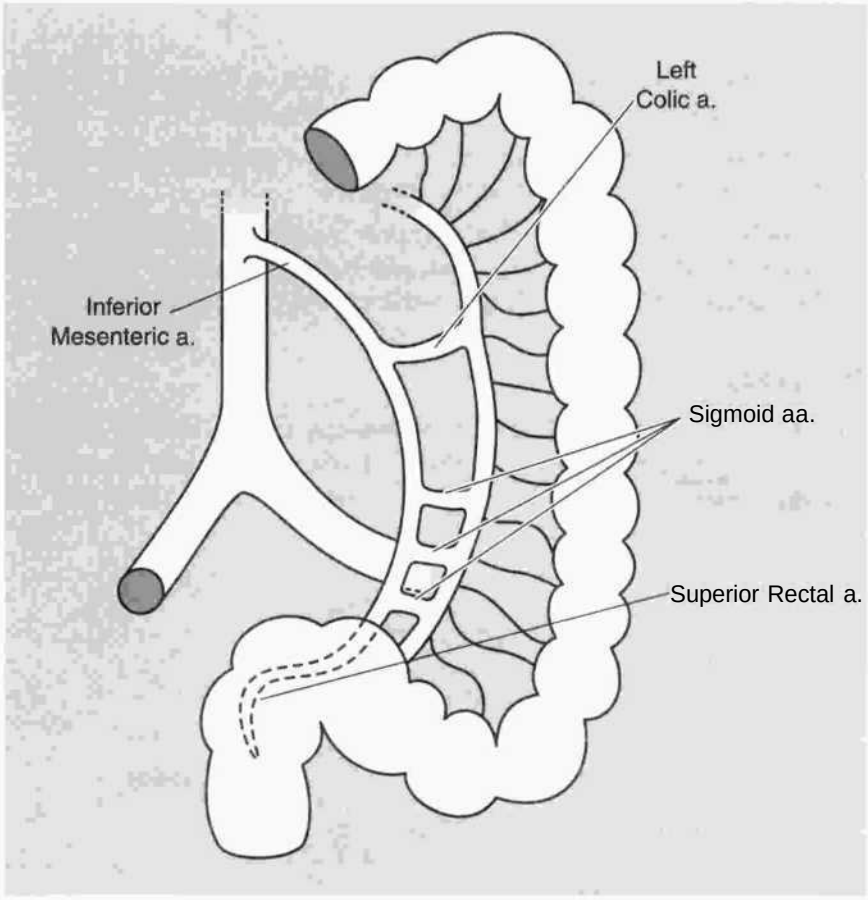


Figure 111-3-17. **Distribution of Inferior Mesenteric Artery**

EMBRYOLOGY OF KIDNEYS AND URETER

Renal development is characterized by three successive, slightly overlapping kidney systems (Fig III-3-18).

Pronephros

During week 4, segmented nephrotomes appear in the cervical intermediate mesoderm of the embryo. These structures grow laterally and canalize to form nephric tubules. Successive tubules grow caudally and unite to form the pronephric duct, which empties into the cloaca. The first tubules formed regress before the last ones are formed. By the end of the fourth week, the pronephros disappears.

Mesonephros

In week 5, the mesonephros appears as S-shaped tubules in the intermediate

mesoderm of the thoracic and lumbar regions of the embryo.

- The medial end of each tubule enlarges to form a Bowman's capsule into which a tuft of capillaries, or glomerulus, invaginates.
- The lateral end of each tubule opens into the mesonephric (Wolffian) duct, an intermediate mesoderm derivative.
- Mesonephric tubules function temporarily and degenerate by the beginning of the third month. The mesonephric duct persists in the male as the ductus epididymidis, ductus deferens, and the ejaculatory duct.

Metanephros

During week 5, the metanephros, or permanent kidney, develops from two sources: the **ureteric bud,** a diverticulum of the mesonephric duct, and die mgtanetuiric-inass, from intermediate mesoderm of the lumbar and sacral regions.

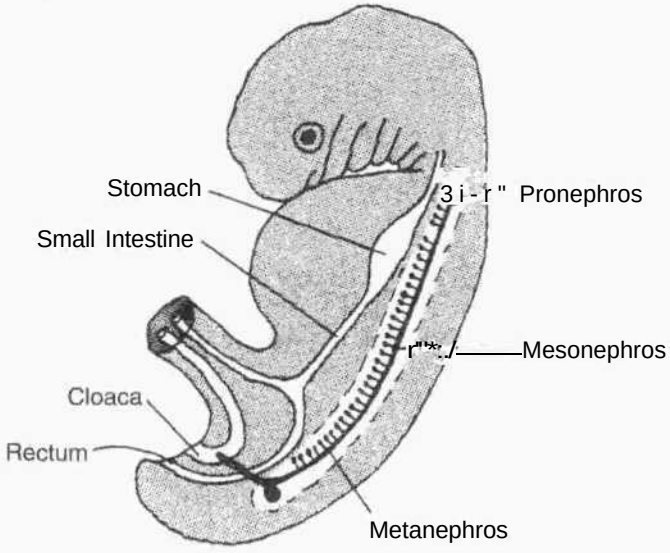


Figure 111-3-18. Pronephros, Mesonephros, and Metanephros

Development of the Urinary System

The ureteric bud penetrates the metanephric mass, which condenses around the diverticulum to form the metanephrogenic cap (Fig III-3-19). The bud dilates to form the renal pelvis, which subsequently splits into the cranial and caudal major calyces. Each major calyx buds into the metanephric tissue to form the minor calyces. One to 3 million collecting tubules develop from the minor calyces, thus forming the renal pyramids.

Penetration of collecting tubules into the metanephric mass induces cells of the tissue cap to form nephrons, or excretory units.

- The proximal nephron forms Bowman's capsule, whereas the distal nephron connects to a collecting tubule.
- Lengthening of the excretory tubule gives rise to the proximal convoluted tubule, the loop of Henle, and the distal convoluted tubule.

The kidneys develop in the pelvis but appear to ascend into the abdomen as a result of fetal growth of the lumbar and sacral regions. With their ascent, the ureters elongate, and the kidneys become vascularized by lateral splanchnic arteries, which arise from the abdominal aorta.

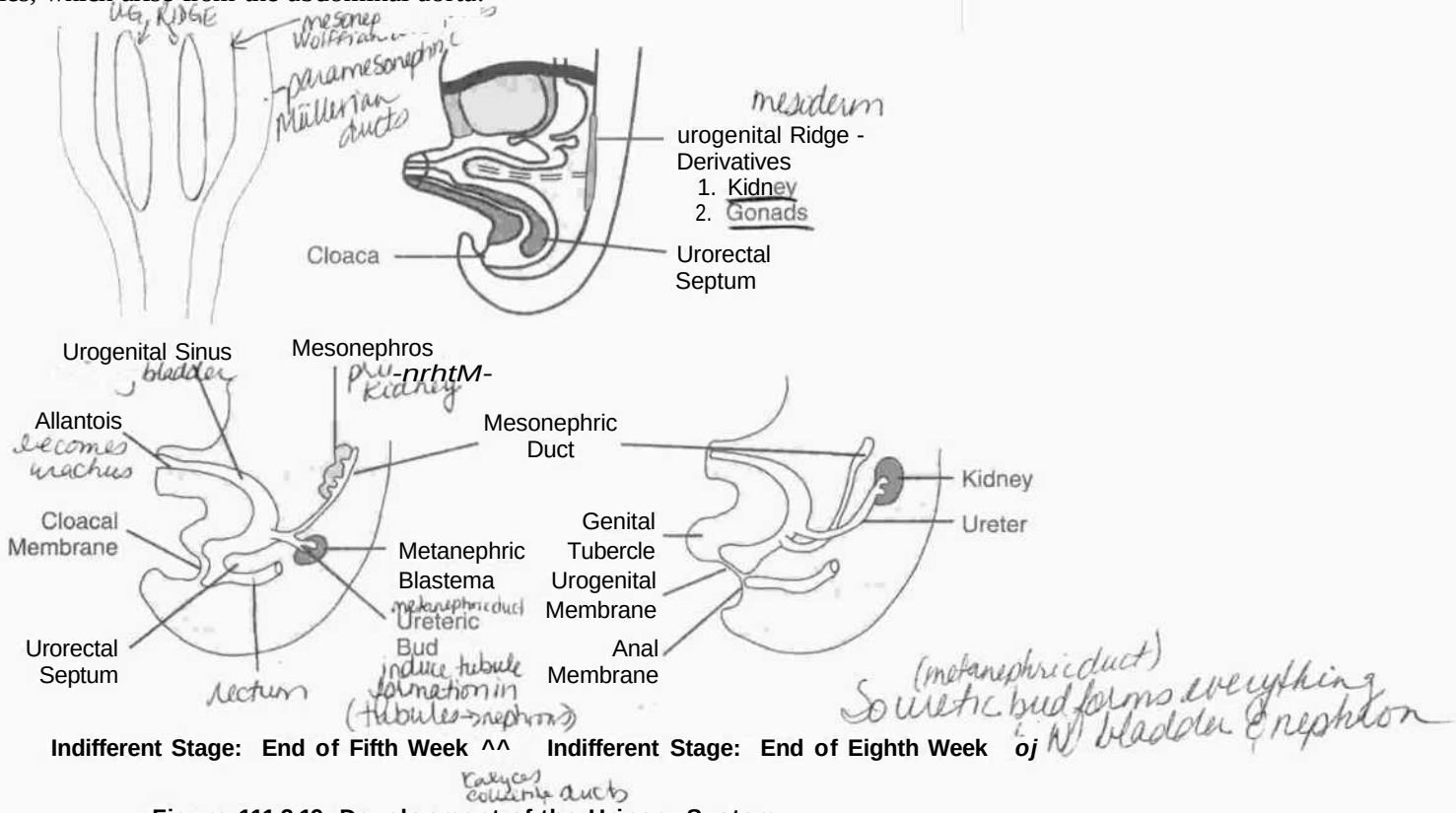


Figure 111-3-19. Development of the Urinary System

EMBRYOLOGY OF BLADDER AND URETHRA

The urorectal septum divides the cloaca into the anorectal canal and the urogenital sinus by week 7.

- The upper and largest part of the urogenital sinus becomes the urinary bladder, which is initially continuous with the allantois. As the lumen of the **allantois** becomes obliterated, a fibrous cord, the **urachus,** connects the apex of the bladder to the umbilicus. In the adult, this structure

becomes the **median umbilical ligament.**

- The mucosa of the trigone of the bladder is formed by the incorporation of the caudal mesonephric ducts into the dorsal bladder wall. This mesodermal tissue is eventually replaced by endodermal epithelium so that the entire lining of the bladder is of endodermal origin.
- The smooth muscle of the bladder is derived from splanchnic mesoderm.

The male urethra is anatomically divided into three portions: prostatic, membranous, and spongy (penile).

- The prostatic urethra, membranous urethra, and proximal penile urethra develop from the narrow portion of the urogenital sinus below the urinary bladder.
- The distal spongy urethra is derived from the ectodermal cells of the glans penis.

The female urethra is derived from two sources. The upper two thirds develops from the mesonephric ducts, and the lower portion is derived from the urogenital sinus.

Congenital Abnormalities

Renal Agenesis

Failure of one or both kidneys to develop because of early degeneration of the ureteric bud. Agenesis is fairly common in the unilateral form but leads to death shortly after birth in the bilateral form.

Renal Cysts

The formation of thin-walled, fluid-filled cysts from blind tubules, perhaps arising from improper linkage between the collecting ducts and distal convoluted tubules.

Pelvic and Horseshoe Kidney

Pelvic kidney is caused by a failure of one kidney to ascend. Horseshoe kidney is a fusion of both kidneys at their ends and failure of the fused kidney to ascend.

Double Ureter

Caused by the early splitting of the ureteric bud or the development of two separate buds.

Patent Urachus

Failure of the allantois to be obliterated. It causes urachal fistulas or sinuses. Remnants of the allantoic stalk may give rise to urachal cysts. In male children

with congenital valvular obstruction of the prostatic urethra or in older men with enlarged prostates, a patent urachus may cause drainage of urine through the umbilicus.

KIDNEYS AND URETER

Kidney's Relation to the Posterior Abdominal Wall

Both kidneys are in contact with the diaphragm, psoas major, and quadratus lumborum (Figs III-3-20 and III-3-21).

- Right kidney—contacts the above structures and the 12th rib
- Left kidney—contacts the above structures and the 11th and 12th ribs

Ureter's Relation to the Posterior Abdominal Wall

The ureter lies on the anterior surface of the psoas major.

Figure 111-3-20. Muscles of the Posterior Abdominal Wall

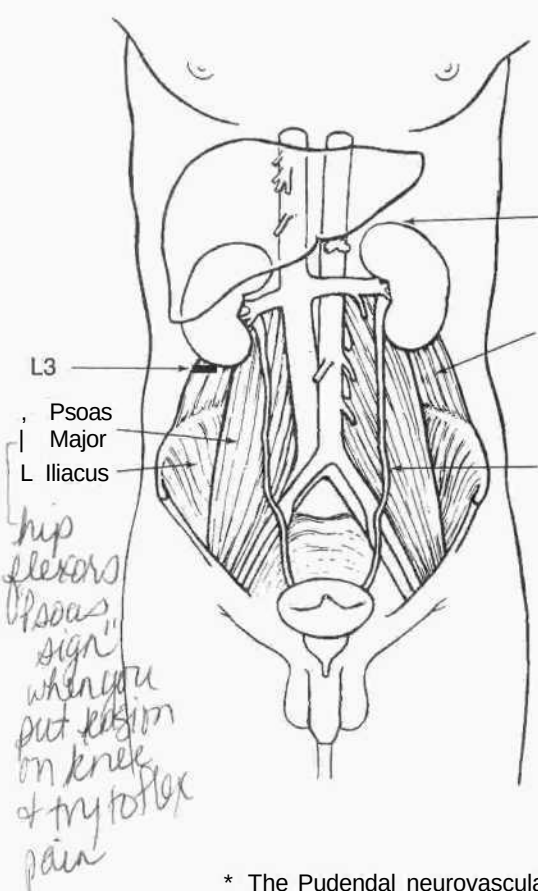
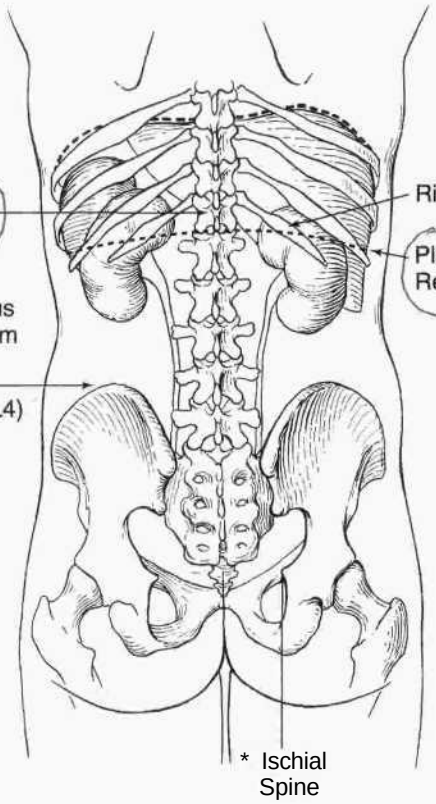


Figure 111-3-21. Bony Landmarks of the Posterior Abdominal Wall



* The Pudendal neurovascular bundle crosses the ischial spine, which marks the anesthetic injection site for pudendal block.

Kidneys

The kidneys are a pair of bean-shaped organs approximately 12 cm long. They extend from vertebral level T12 to L3 when the body is in the erect position. The right kidney is positioned slightly lower than the left because of the mass of the liver.

InternalStructure

Within the dense, connective tissue of the renal capsule, the kidney substance is divided into an outer cortex and an inner medulla (Fig III-3-22):

- **Cortex**—contains glomeruli, Bowman's capsules, and proximal and distal convoluted tubules. It forms renal columns, which extend between medullary pyramids.
- **Medulla**—consists of 10 to 18 striated pyramids and contains collecting ducts and loops of Henle. The apex of each pyramid ends as a papilla where collecting ducts open.
- **Calyces**—the minor calyces receive one or more papillae and unite to form major calyces, of which there are two to three per kidney.
- **Renal pelvis**—the dilated upper portion of the ureter that receives the major calyces.

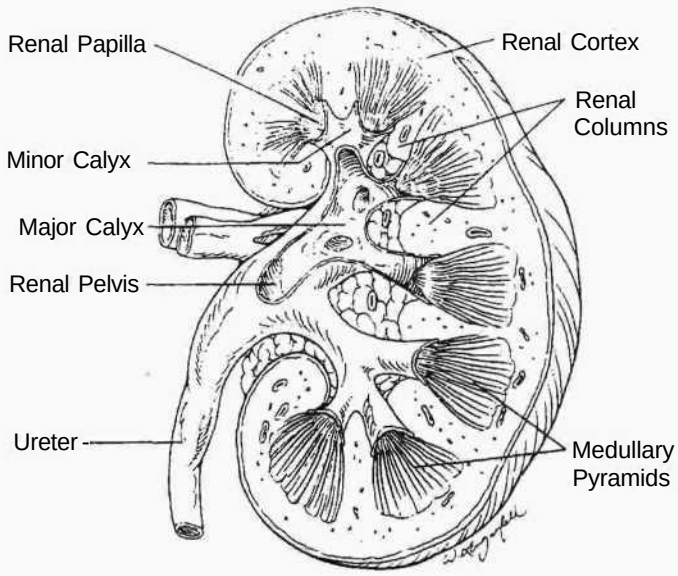


Figure III-3-22. Internal Structure of the Kidney

ArterialSupply

The paired renal arteries are branches of the abdominal aorta.

- Interlobar arteries travel in renal columns in the cortical areas between pyramids.

- Arcuate arteries run parallel to bases of pyramids.
- Interlobular arteries are branches of arcuate arteries.
- Afferent arterioles lead to capillary tufts of glomeruli.

VenousDrainage

Follows the same pattern as the arteries.

- The right renal vein enters the inferior vena cava.
- The left renal vein receives the kftjgonadaWein, the left suprarenal vein, and the left inferior phrenic vein, and may receive a root of the hemiazygos vein before crossing anterior to the aorta to join the inferior vena cava.

LymphaticDrainage

The kidneys drain to the lumbar nodes.

Innervation

Primarily sympathetic with postganglionic cell bodies located in the renal plexus.

- Preganglionic sympathetic fibers are from splanchnic nerves.
- Pain afferents from the renal pelvis travel in splanchnic nerves.

Ureters

Ureters are fibromuscular tubes that connect the kidneys to the urinary bladder in the pelvis. They run posterior to the ductus deferens in males and posterior to the uterine artery in females.

They begin as continuations of the renal pelves and run retroperitoneally, crossing the external iliac arteries as they pass over the pelvic brim.

Urinary Bladder

Structure

The urinary bladder is covered superiorly by peritoneum.

The body is a hollow muscular cavity.

The neck is continuous with the urethra.

The trigone is a smooth triangular area of mucosa located internally at the base of the bladder. The base of the triangle is superior and bounded by the two openings of the ureters. The apex of the trigone points inferiorly and is the opening for the urethra.

Clinical Correlate

Testicular Varlcocele

A left renal tumor with infiltration into the renal vein would result in back pressure in the left gonadal vein, resulting in a varicocele of the left testis.

Note

The renal arteries are "end arteries," i.e., there is insufficient collateral flow to maintain perfusion in the case of occlusion.

Blood Supply

The bladder is supplied by vesicular branches of the internal iliac arteries.

The vesicular venous plexus drains to internal iliac veins.

Lymphatics

Drain to the external and internal iliac nodes.

Innervation

Parasympathetic innervation is from sacral segments S2, S3, and S4. The preganglionic parasympathetic fibers travel in pelvic splanchnic nerves to reach the detrusor muscle.

Sympathetic innervation is through preganglionic fibers, which are derived from T11 through L2.

Urethra

The male urethra is a muscular tube approximately 20 cm in length. The urethra in men extends from the neck of the bladder through the prostate gland (prostatic urethra) to the urogenital diaphragm of the perineum (membranous urethra), and then to the external opening of the glans (penile or spongy urethra) (Fig III-3-23).

The female urethra is approximately 4 cm in length and extends from the neck of the bladder to the external urethral orifice of the vulva (Fig III-3-24).

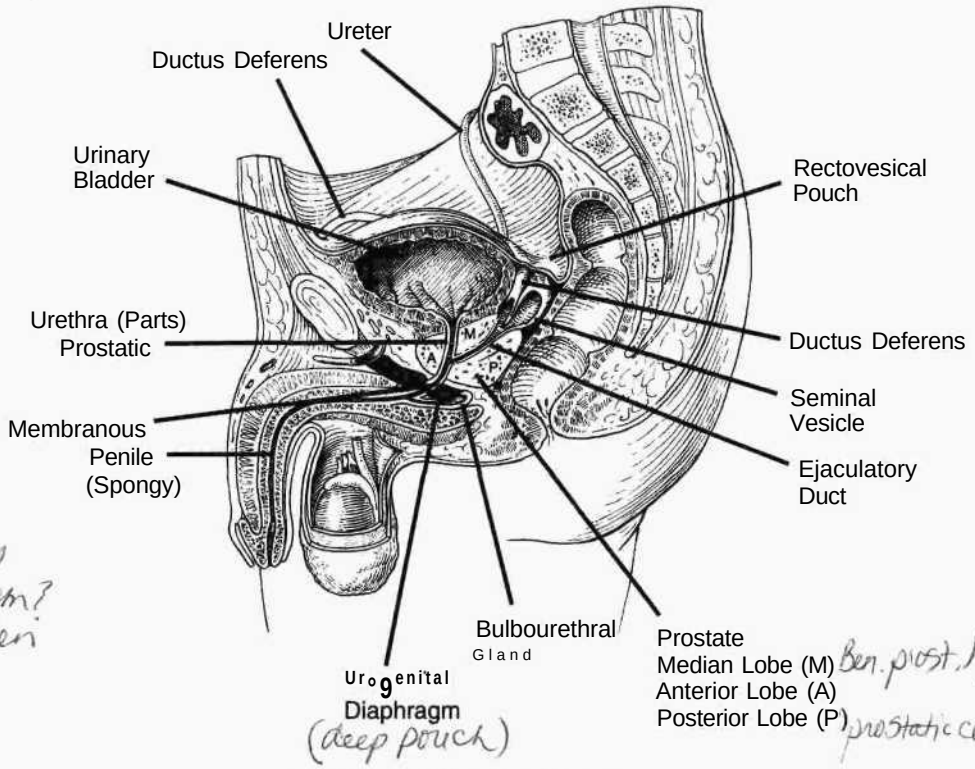


Figure III-3-23. Male Pelvis

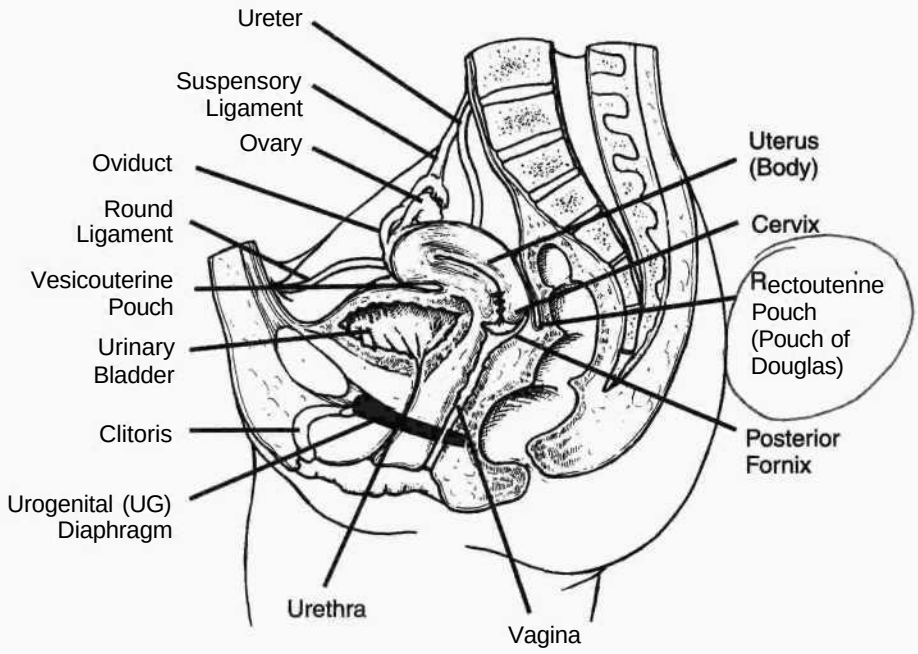


Figure Hl-3-24. Female Pelvis

Clinical Correlate

Blockage by Renal Calculi

The most common sites of ureteral constriction susceptible to blockage by renal calculi are:

- Where the renal pelvis joins the ureter
- Where the ureter crosses the pelvic inlet
- Where the ureter enters the wall of the urinary bladder

PELVIC DIAPHRAGM

Pelvic and urogenital (UG) diaphragms are illustrated in Figures III-3-25 and III-3-26.

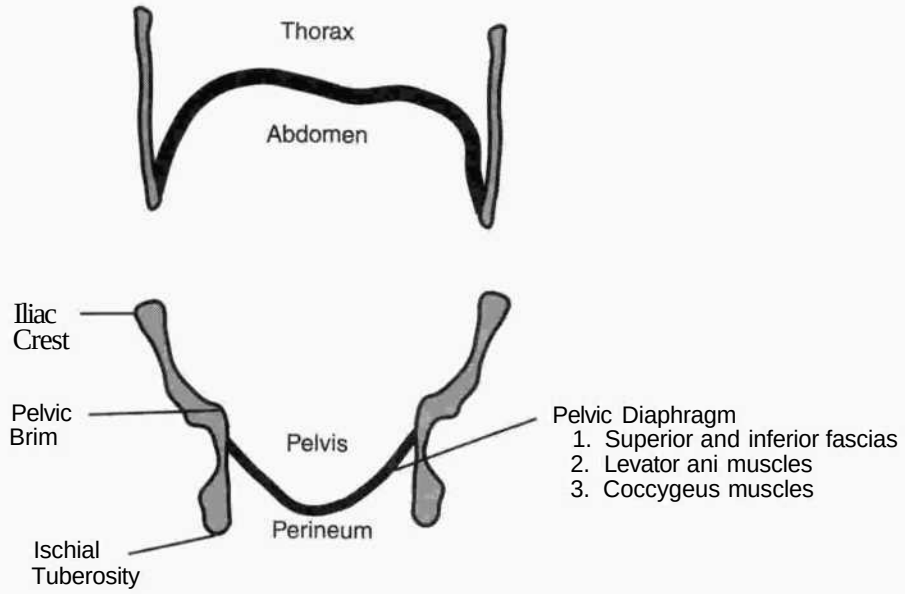


Figure III-3-25. Pelvic Diaphragm

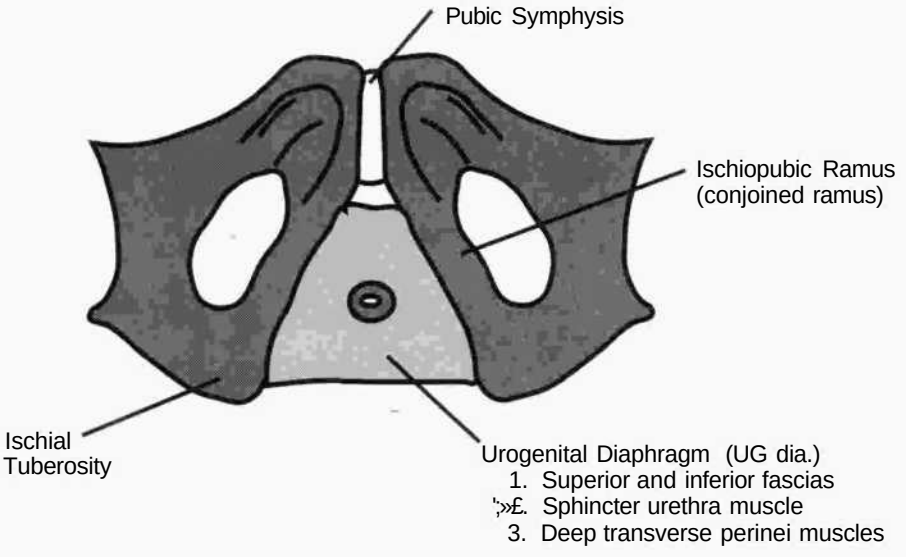


Figure III-3-26. Urogenital Diaphragm

PERINEUM

Contents of Pouches

Boundaries of the Superficial Perineal Pouch (Space)

- Superficial perineal fascia (Colles' fascia)
- Inferior fascia of the UG diaphragm (perineal membrane)
- Conjoined (ischiopubic) rami

Contents of the Superficial Perineal Pouch

- Crura of penis or clitoris
- Bulb of penis or bulbs of vestibule
- Ischiocavernosus muscles
- Bulbospongiosus muscle
- Greater vestibular (Bartholin's) gland (female)

Boundaries of the Deep Perineal Pouch (Space)

- Superior and inferior fascia of the urogenital diaphragm

Contents of the Deep Perineal Pouch

- Sphincter urethrae muscle
- Deep transverse perineal muscle
- Bulbourethral (Cowper's) gland (male)

LOWER ABDOMEN:
skin
Camper's fascia
SCARPA'S fascia

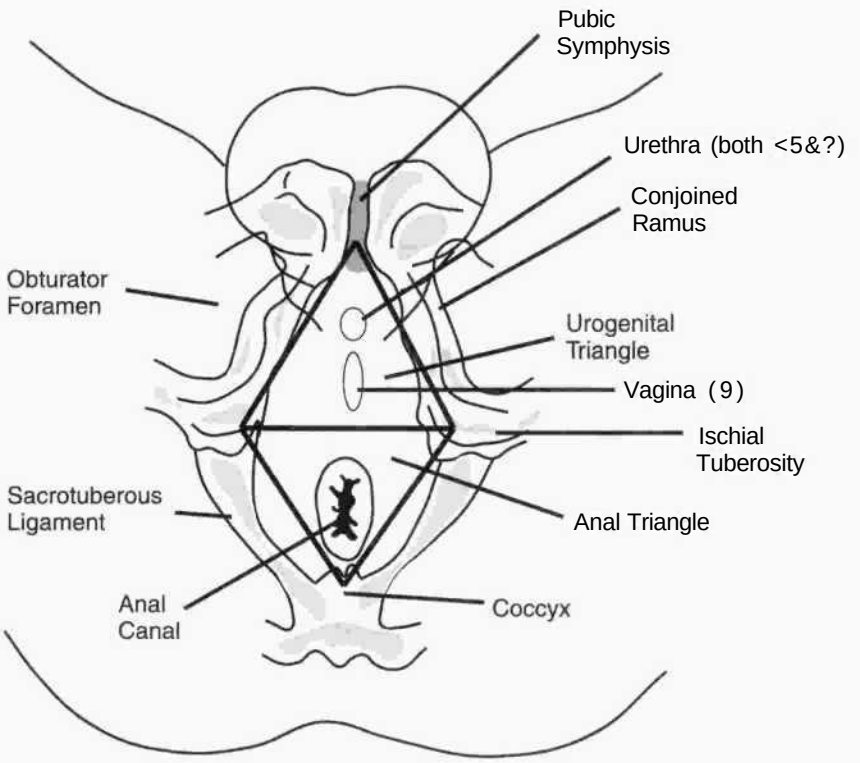


Figure III-3-27. Perineum

EMBRYOLOGY OF THE REPRODUCTIVE SYSTEM

Table III-3-2. Adult Female and Male Reproductive Structures Derived From Each Precursor of the Indifferent Embryo

Adult Female	Indifferent Embryo	Adult Male
Ovary, follicles, rete ovarii	Gonads	Testes, seminiferous tubules, rete testes
Uterine tubes, uterus, cervix and upper part of vagina	Paramesonephric ducts	Appendix of testes
Duct of Gartner	Mesonephric ducts	Epididymis, ductus deferens, seminal vesicle, ejaculatory duct
Clitoris	Phallus	Glans and body of penis
Labia minora	Urogenital folds	Ventral aspect of penis
Labia majora	Labioscrotal swellings	Scrotum

Female Pseudo-Intersexuality

Characterized by having ovarian (but no testicular) tissue histologically and masculinization of the female external genitalia.

- Individuals have a 46,XX genotype.
- Most common cause is **congenital adrenal hyperplasia,** a condition in which the fetus produces excess androgens.

Male Pseudo-Intersexuality

Characterized by having testicular (but no ovarian) tissue histologically and various stages of stunted development of the male external genitalia.

- Individuals have a 46.XY genotype.
- Most common cause is inadequate production of testosterone and Müllerian inhibiting factor (MIF) by the fetal testes. This is due to a 5a-reductase deficiency

5a-Reductase 2 Deficiency

Caused by a mutation in the 5oc-reductase 2 **gene** that renders 5cc-reductase 2 enzyme underactive. Normally, 5cx-reductase catalyzes the conversion of testosterone to dihydrotestosterone.

testosterone (T) —» dihydrotestosterone (DHT)

The deficiency produces the following clinical findings:

- Underdevelopment of the penis and scrotum (microphallus, hypospadias, and bifid scrotum) and prostate gland.
- The epididymis, ductus deferens, seminal vesicle, and ejaculatory duct are normal.

These clinical findings have led to the inference that DHT is essential in the development of the penis and scrotum (external genitalia) and prostate gland in genotypic XY fetus.

At puberty, these individuals demonstrate a striking virilization owing to an increased **T:DHT ratio.** This increase is diagnostic (normal, 5; 5a-reductase 2 deficiency, 20-60).

Complete Androgen Insensitivity (CAIS; or testicular feminization syndrome)

Occurs when a fetus with a 46.XY genotype develops testes and female external genitalia with a rudimentary vagina; the uterus and uterine tubes are generally absent.

- Testes may be found in the labia majora and are surgically removed to circumvent malignant tumor formation.
- These individuals present as normal-appearing females, and their psychosocial orientation is female despite their genotype.
- Most common cause is a mutation in the androgen receptor (AR) gene that renders the AR inactive.

Hypospadias

Occurs when the urethral folds fail to fuse completely, resulting in the external urethral orifice opening onto the ventral surface of the penis.

- It is generally associated with a poorly developed penis that curves ventrally, known as chordee.

Epispadias

Occurs when the external urethral orifice opens onto the **dorsal** surface of the penis.

- It is generally associated with exstrophy of the bladder.

Undescended Testes (cryptorchidism)

Occurs when the testes fail to descend into the scrotum. This normally occurs within 3 months after birth.

- Bilateral cryptorchidism results in sterility.
- The undescended testes may be found in the abdominal cavity or in the inguinal canal.

Hydrocele of the Testes

Occurs when a small patency of the processus vaginalis remains so that peritoneal fluid can flow into the processus vaginalis.

- Results in a fluid-filled cyst near the testes.

MALE PELVIC VISCERA

Sagittal Section

The position of organs and peritoneum in the male pelvis is illustrated in Figure III-3-23.

FEMALE PELVIC VISCERA

Sagittal Section

The position of organs and peritoneum in the female pelvis is illustrated in Figure III-3-24.

Clinical Correlate

Culdoscopy

The procedure of entering the pelvic cavity via the posterior fornix for observation or surgery.

The sampling of intraperitoneal fluid provides important diagnostic information on several gynecologic conditions such as pelvic inflammatory disease (PID) and ectopic pregnancy. This is usually accomplished by performing a procedure known as culdocentesis, during which a needle is passed through the posterior vaginal fornix into the rectouterine pouch to obtain a sample of the fluid for analysis.

During an improperly performed abortion a speculum might not be used to widen the vagina to view the cervical opening. In such a case an instrument could penetrate the posterior wall of the vagina and damage blood vessels and introduce an infection. You are most likely to see a victim of this procedure in the emergency department after the woman has suddenly collapsed and has severe vaginal bleeding.

Woman coming in and has abdominal pain
if PID can spread to pelvis you get fluid will accumulate in pouch of Douglas.

woman has hysterectomy
common mistake is surgeon UW^J ureter

Clinical Correlate

Hypertrophic **Prostate Gland**

An enlarged prostate gland will compress the urethra. The patient will complain of the urge to urinate often and has difficulty with starting urination.

Because the prostate gland is enclosed in a dense connective tissue capsule, hypertrophy will compress the prostatic portion of the urethra.

Laceration of Membranous or Penile Urethra

Accumulation of fluid in the scrotum, around the penis, and in the anterolateral abdominal wall is indicative of a laceration of either the membranous or penile urethra. This can be caused by trauma to the perineal region (saddle injury) or laceration of the urethra during catheterization.

Uterus and Broad Ligament

Figure III-3-28 illustrates a posterior view of the female reproductive tract.

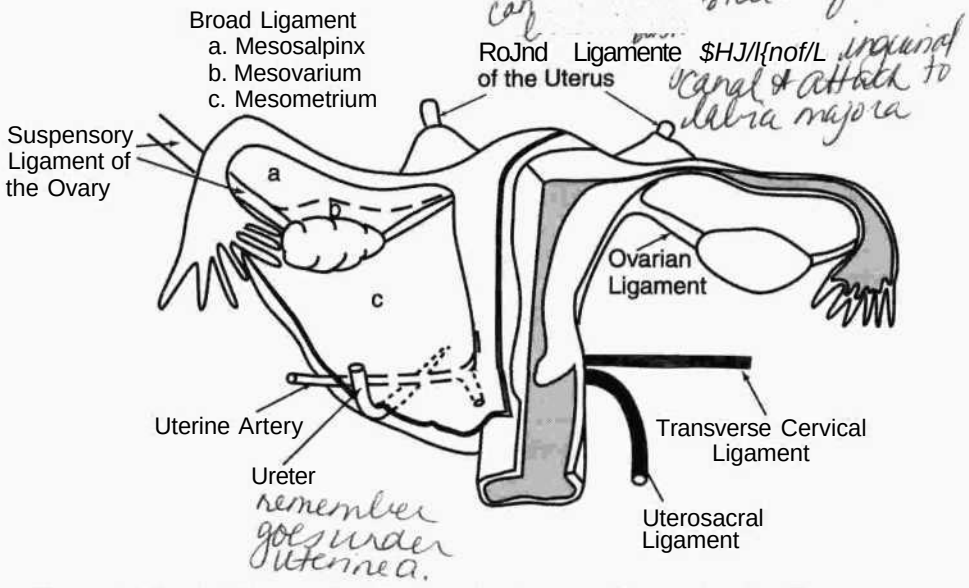


Figure II1-3-28. **A Posterior View of the Female Reproductive Tract**

ABDOMINAL VASCULATURE

Arterial Supply

Abdominal Aorta

Figures III-3-29 and III-3-30 illustrate the major anatomic features of the abdominal vasculature.

- The most common site for an abdominal aneurysm is in the area between the renal arteries and the bifurcation of the abdominal aorta. Signs include decreased circulation to the lower limbs and pain radiating down the back of the lower limbs.
- The most common site of atherosclerotic plaques is at the bifurcation of the abdominal aorta.

• Blockage of ext. iliac art. can cause cramps in lower limb of same side

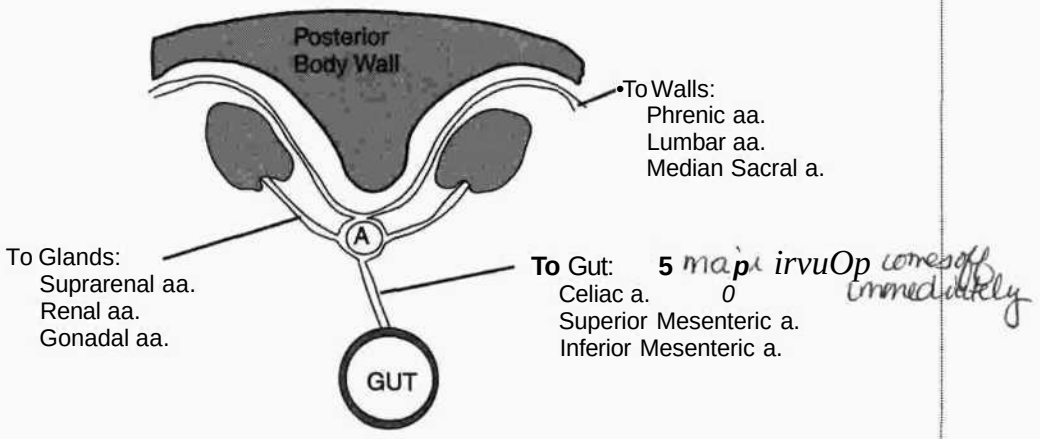
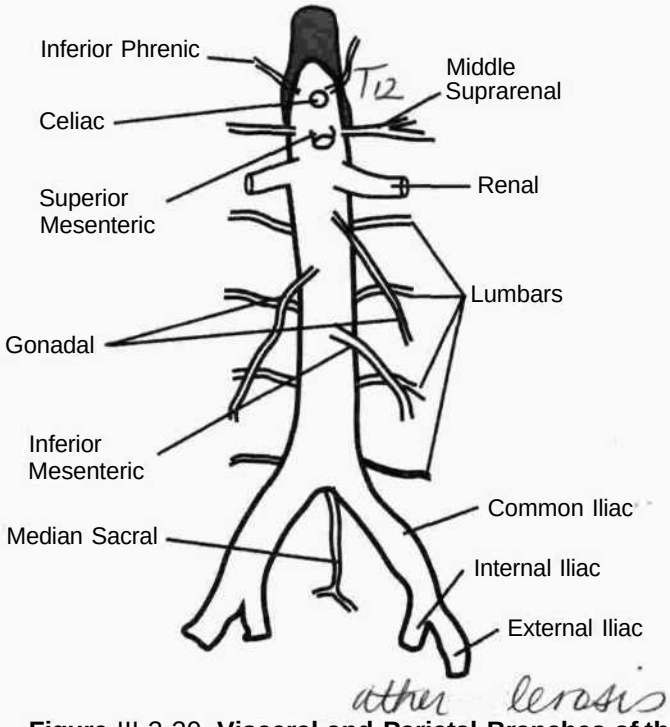


Figure III-3-29. **Abdominal Aorta: General Plan**



Abdominal Aorta

1. Visceral branches
   - Unpaired
     - Celiac
     - Superior Mesentric
     - Inferior Mesentric
   - Paired
     - Middle Suprarenals
     - Renals
     - Gonadals

2. Parietal Branches
   - Unpaired
     - Median Sacral
   - Paired
     - Inferior Phrenics
     - Lumbars
     - Common Iliac

Figure III-3-30. **Visceral and Parietal Branches of the Abdominal Aorta**

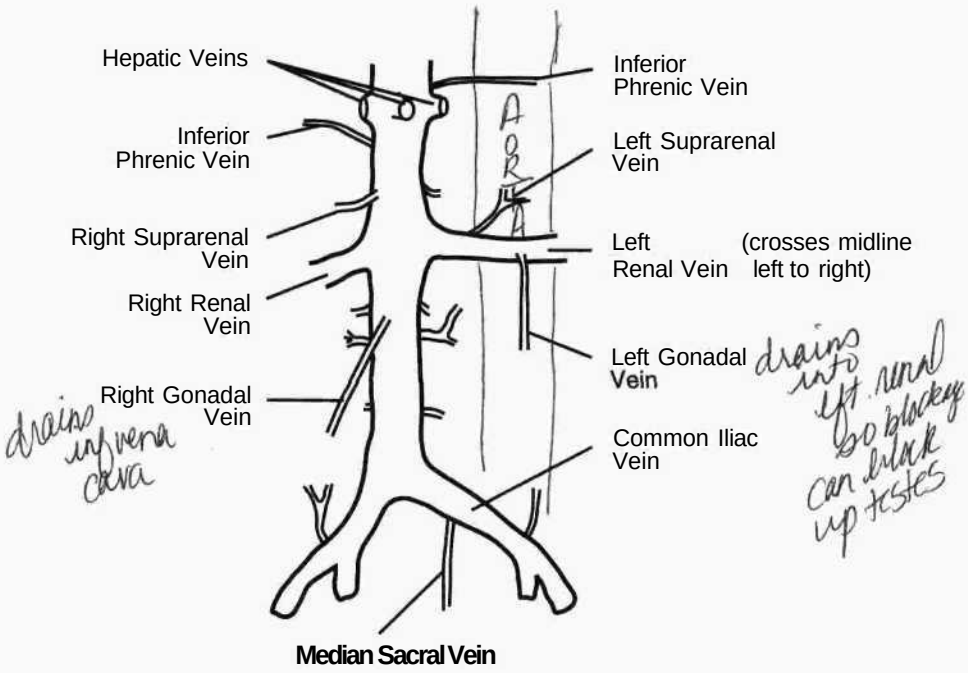


Figure 111-3-31. Inferior Vena Cava (IVC) and Tributaries

Venous Drainage

The drainage of the inferior vena cava and its tributaries is shown in Figure III-3-31.

Hepatic Portal System

what happens if you block portal system? depends where you block

GI tract veins to liver sinusoids to hepatic veins (Fig III-3-32).

- The hepatic portal vein is formed by the union of the superior mesenteric and splenic veins (posterior to the head of the pancreas).
- The inferior mesenteric vein enters near the area of the junction of the superior mesenteric and splenic veins.
- The hepatic portal vein also receives gastric veins from the stomach.

The portal vein drains into the liver sinusoids, which drain to the hepatic vein, which then goes into the inferior vena cava and ultimately into the right atrium (Fig III-3-33).

Portosystemic Anastomoses

If there is an obstruction to flow through the portal system (portal hypertension), blood can flow in a retrograde direction (because of the absence of valves in the portal system) and pass through anastomoses to reach the caval system. Sites for these anastomoses include the esophageal veins, rectal veins, thoracoepigastric

veins, and retroperitoneal veins. Enlargement of these veins may result in esophageal varices, hemorrhoids, and a caput medusae.

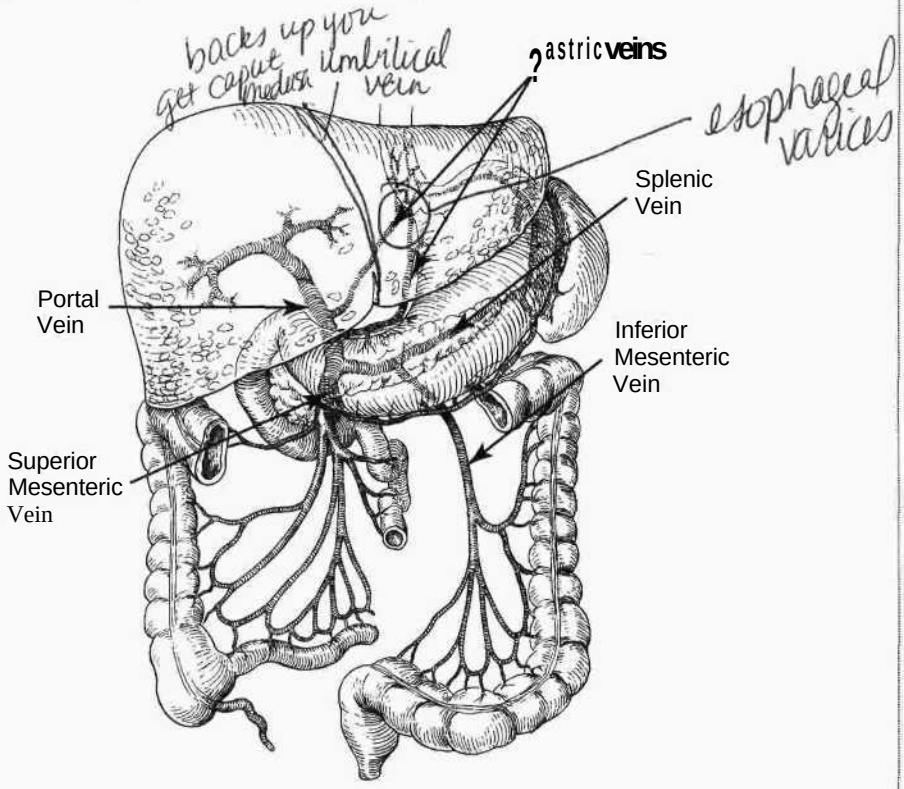


Figure 111-3-32. **Hepatic Portal System**

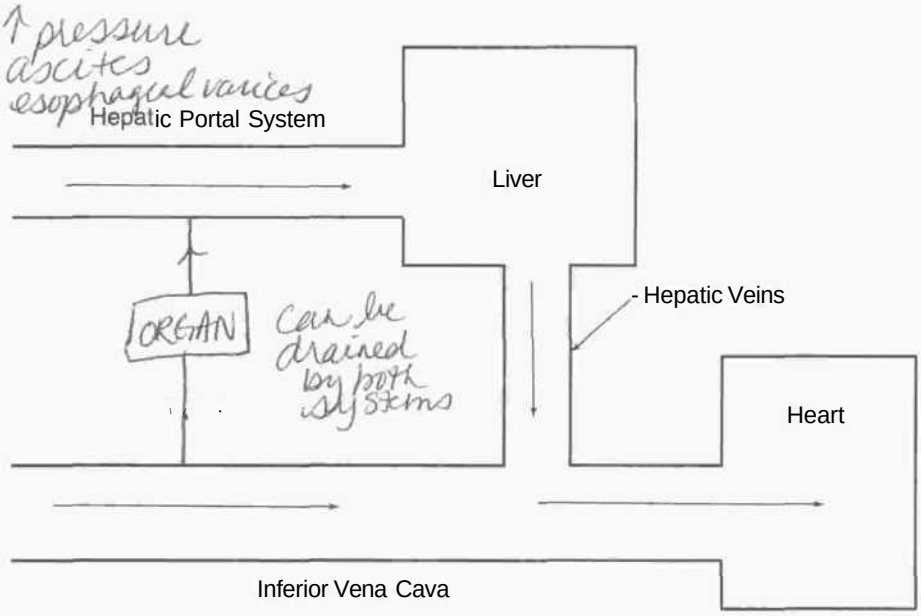


Figure III-3-33. Comparison of Normal Caval and Portal Blood Flow

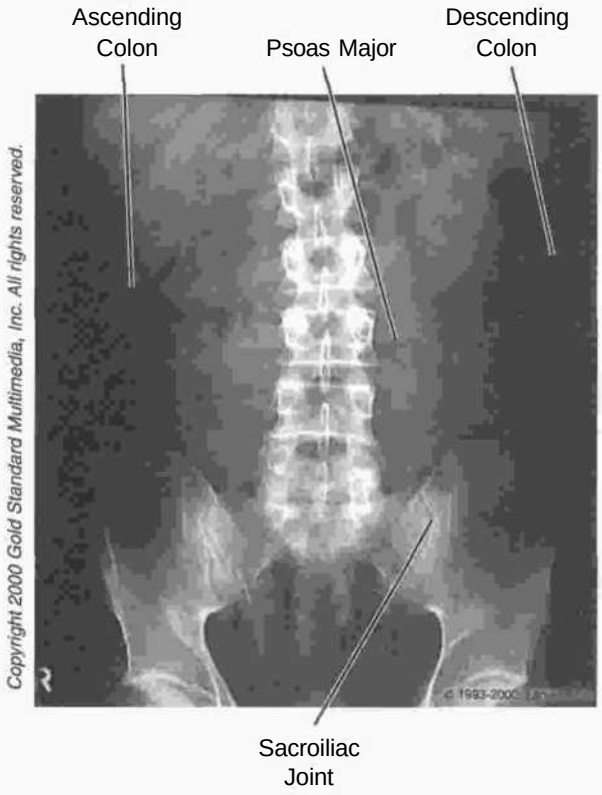


Figure IH-3-34. Anteroposterior View of Abdomen

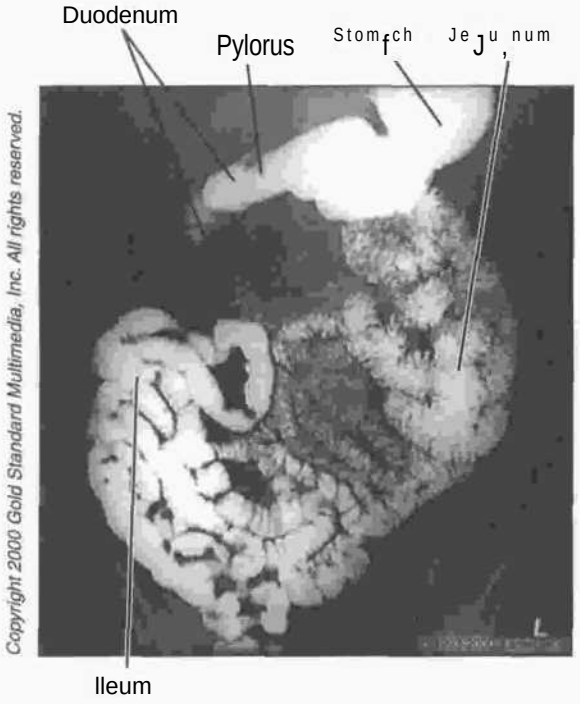


Figure 111-3-35. Abdomen: Upper GI, Small Bowel

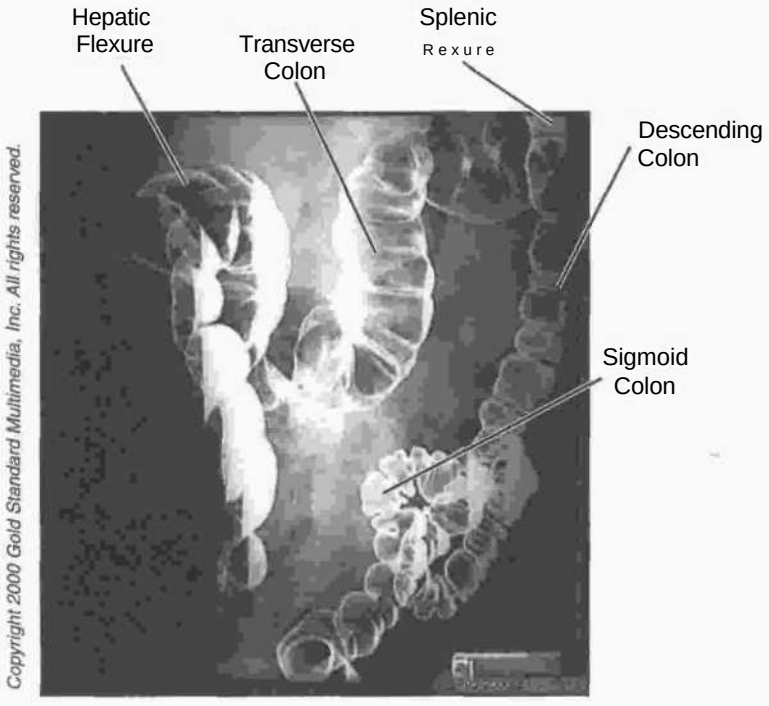


Figure lil-3-36. Abdomen: Barium Enema

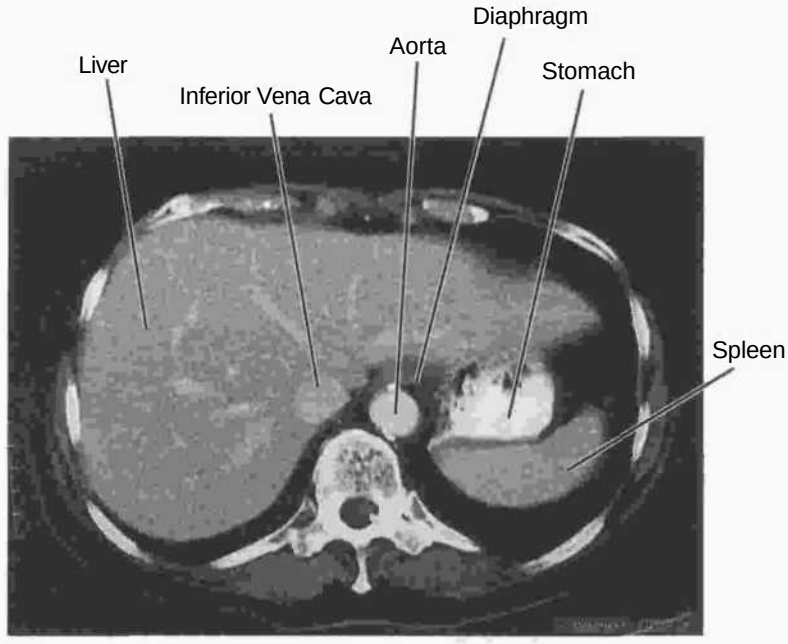


Figure HI-3-37. Abdomen: CT, T^

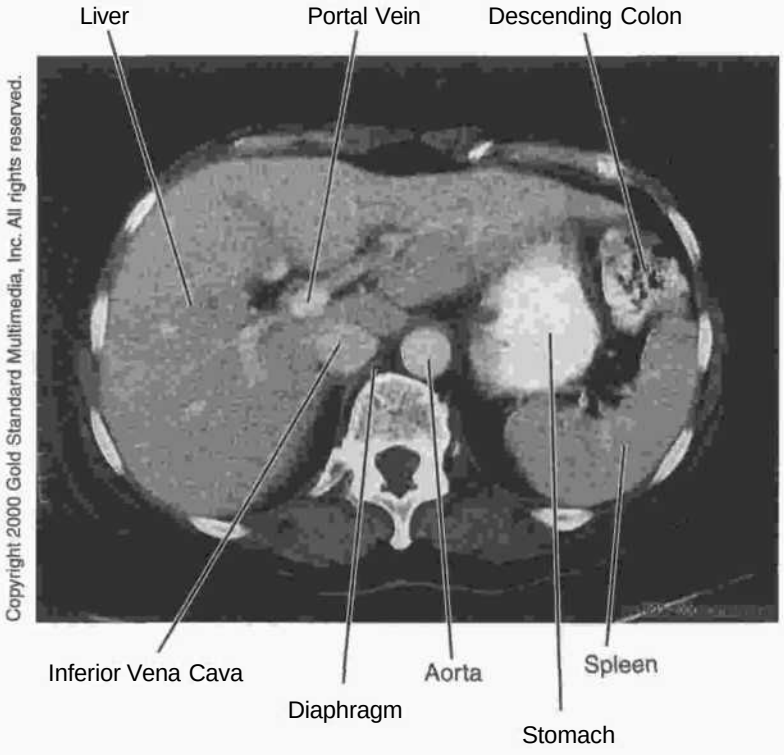


Figure III-3-38. Abdomen: CT, T_{12}

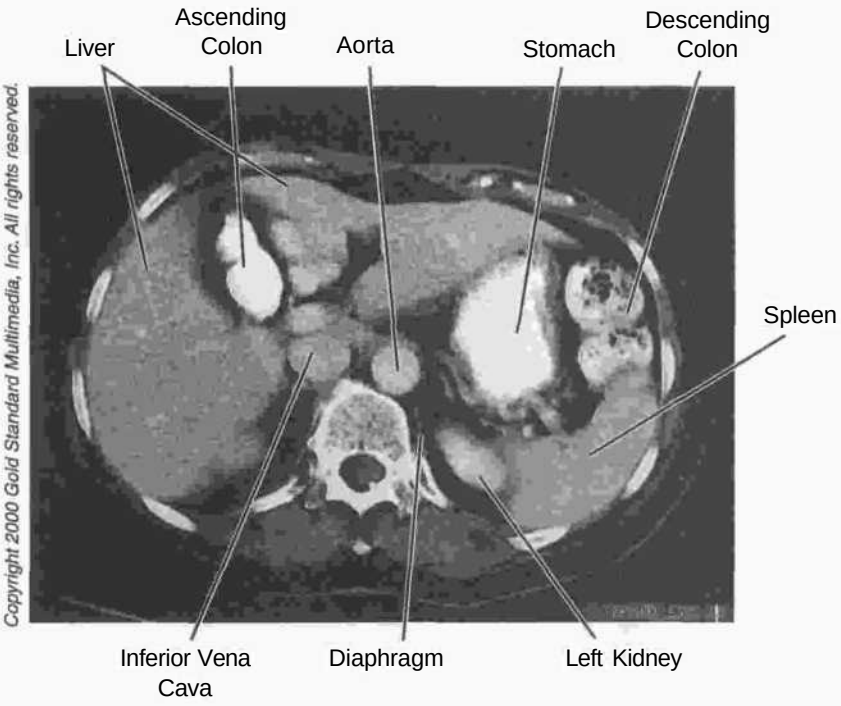


Figure III-3-39. Abdomen: CT, T_{12}

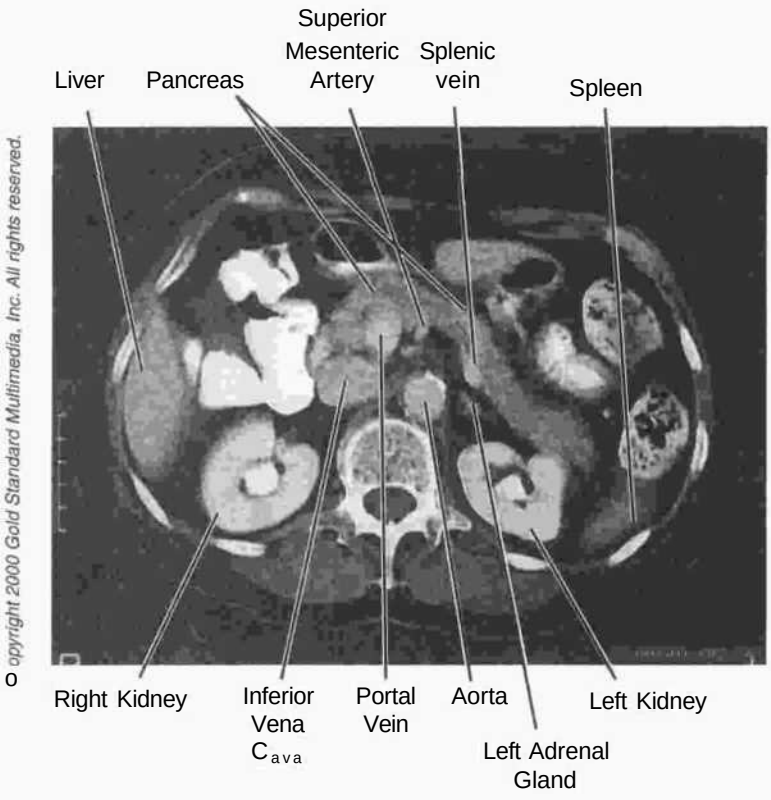


Figure IH-3-40. Abdomen: CT, Li

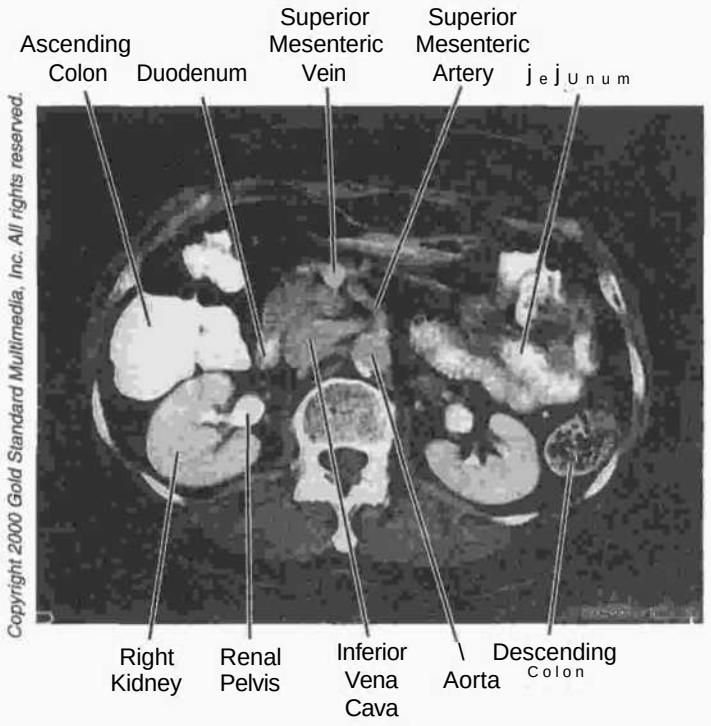


Figure 111-3-41. Abdomen: CT, L_2

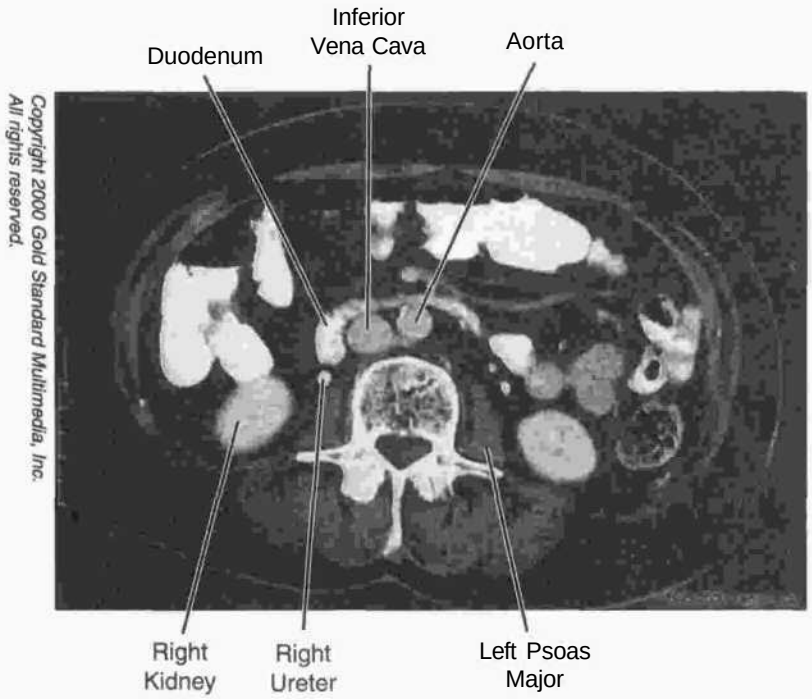


Figure III-3-42. **Abdomen: CT, L_3**

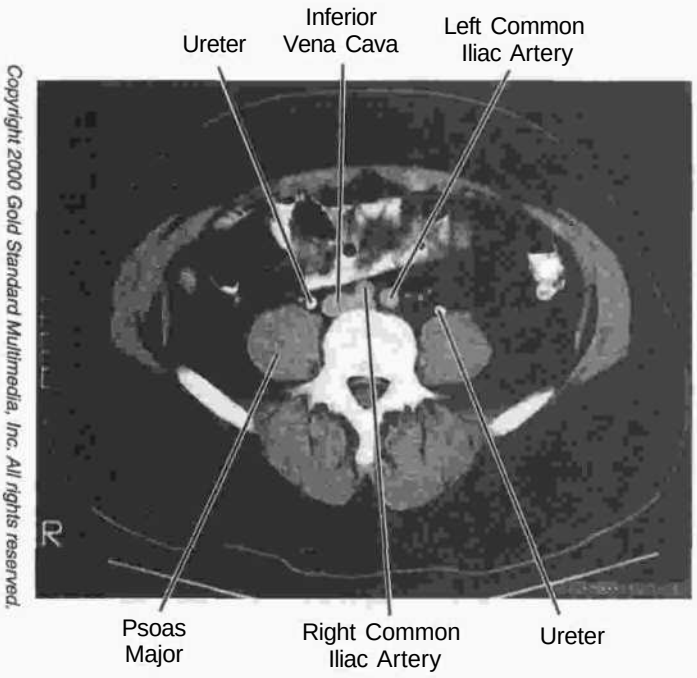


Figure IH-3-43. Abdomen: CT, L_4

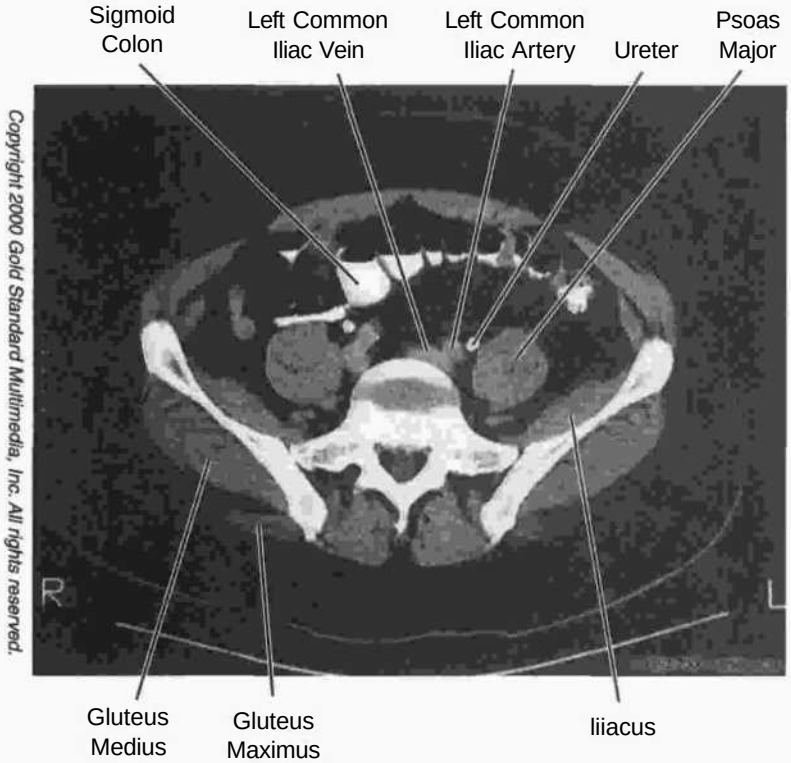


Figure IH-3-44. Abdomen: CT, Si

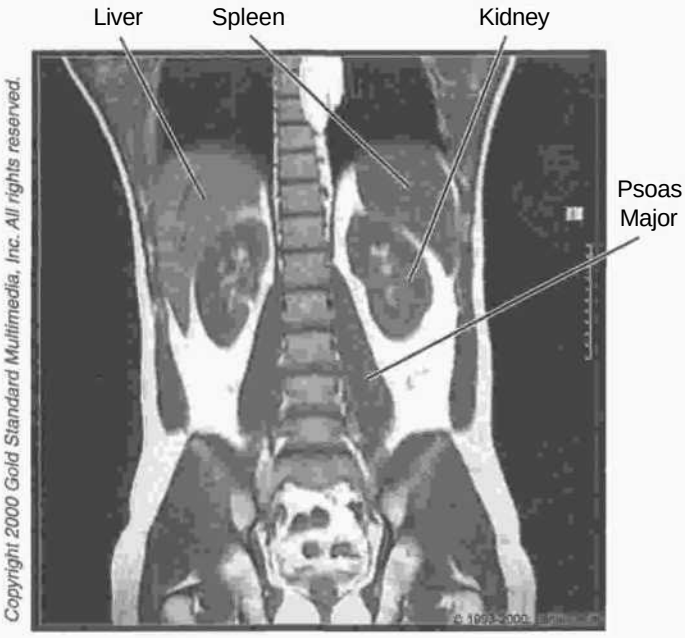


Figure 111-3-45. Abdomen: MRI, Coronal

Upper Limb

4

BRACHIAL PLEXUS

Lesions of the Brachial Plexus

Upper Trunk (C5, C6)

Erb's paralysis affects axillary, suprascapular, and musculocutaneous nerves (Fig III-4-1). Loss of intrinsic muscles of the shoulder. Loss of muscles of the anterior arm. Arm is medially rotated and adducted. The forearm is extended and pronated. Sign is "waiter's tip."

Lower Trunk (C8, T1)

Thoracic outlet syndrome. Loss of all the muscles of the forearm and hand. Sign is combination of "claw hand" and "ape hand." May include a Horner's syndrome.

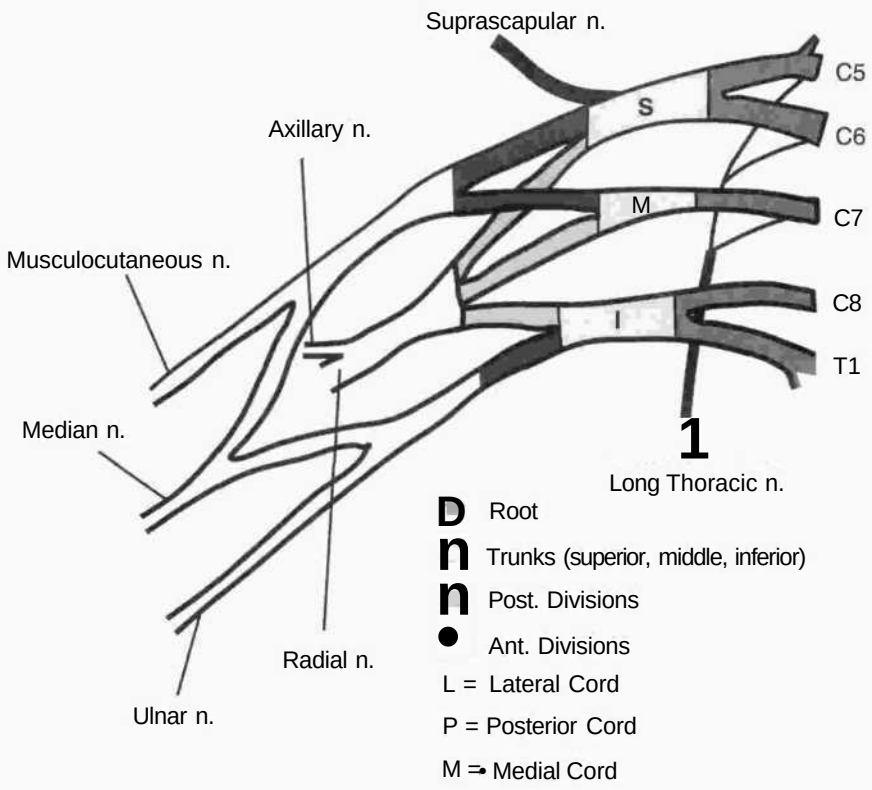


Figure III-4-1 .The Brachial Plexus

MUSCLE INNERVATION

Terminal Nerves of Upper Limbs

The motor innervation by the five terminal nerves of the arm muscles is summarized in Table III-4-1.

Table HI-4-1. The Motor Innervation by the Five Terminal Nerves

Terminal Nerve	Muscles Innervated
Musculocutaneous nerve	All the muscles of the anterior compartment of the arm
Median nerve	All the muscles of the anterior compartment of the forearm except 1 [1/2] muscles (flexor carpi ulnaris and the ulnar [1/2] of the flexor digitorum profundus) The 3 thenar compartment muscles and the 1st and 2nd lumbricals
Ulnar nerve	The 1 [1/2] muscles of the forearm not innervated by the median nerve All the muscles of the hand except those innervated by the median nerve *0ll>^ki7f%A* ,
Axillary nerve	Deltoid and teres minor
Radial nerve	The posterior muscles of the arm and forearm *(ML M-4<n9cr<,*

ACTION
assist shoulder flexion, elbow flexion, and supinator (brio)
wrist flexion (1/2)
digit flexion
pronation
(lumbricals 1, 2)
opposition of thumb
wrist flexion 1/2
abduction of fingers
adduction of fingers
abduction of arm
extension of shoulder, elbow, wrist, metacarpalangeal joints

Note

All the muscles that form the walls of the axilla are innervated by collateral nerves: the three posterior wall muscles are innervated by the three subscapular nerves; the two anterior wall muscles are innervated by the two pectoral nerves; and the medial wall muscle is innervated by the long thoracic nerve.

Collateral Nerves

In addition to the five terminal nerves, there are several collateral nerves that arise from the brachial plexus proximal to the terminal nerves (i.e., from the rami, trunks, or cords). These nerves innervate proximal limb muscles (shoulder girdle muscles). Table III-4-2 summarizes the collateral nerves.

Table III-4-2. The Collateral Nerves of the Brachial Plexus

Collateral Nerve	Muscles or Skin Innervated
Dorsal scapular nerve	Rhomboids
-Hong thoracic nerve	Serratus anterior ^ ^ p t $C*fuA^
Suprascapular nerve	Supraspinatus and infraspinatus Jyfc/. fpittfffIT
Lateral pectoral nerve	Pectoralis major
Medial pectoral nerve	Pectoralis major and minor
Upper subscapular nerve	Subscapularis
^Middle subscapular (thoracodorsal) nerve	Latissimus dorsi ^JL^rkJlOLd ^Jmi£l^i^
Lower subscapular nerve	Subscapularis and teres major
Medial brachial cutaneous nerve	Skin of medial arm
Medial antebrachial cutaneous nerve	Skin of medial forearm

Segmental Innervation to Muscles of Upper Limbs

The **segmental innervation** to the muscles of the upper limbs has a **proximal-distal gradient,** i.e., the more proximal muscles are innervated by the higher segments (C5 and C6) and the more distal muscles are innervated by the lower segments (C8 and T1). Therefore, the intrinsic shoulder muscles are innervated by C5 and C6, the intrinsic hand muscles are innervated by C8 and T1, the distal arm and proximal forearm muscles are innervated by C6 and C7, and the more distal forearm muscles are innervated by C7 and C8.

SENSORY INNERVATION

The sensory innervation of the hand is summarized in Figure III-4-2.

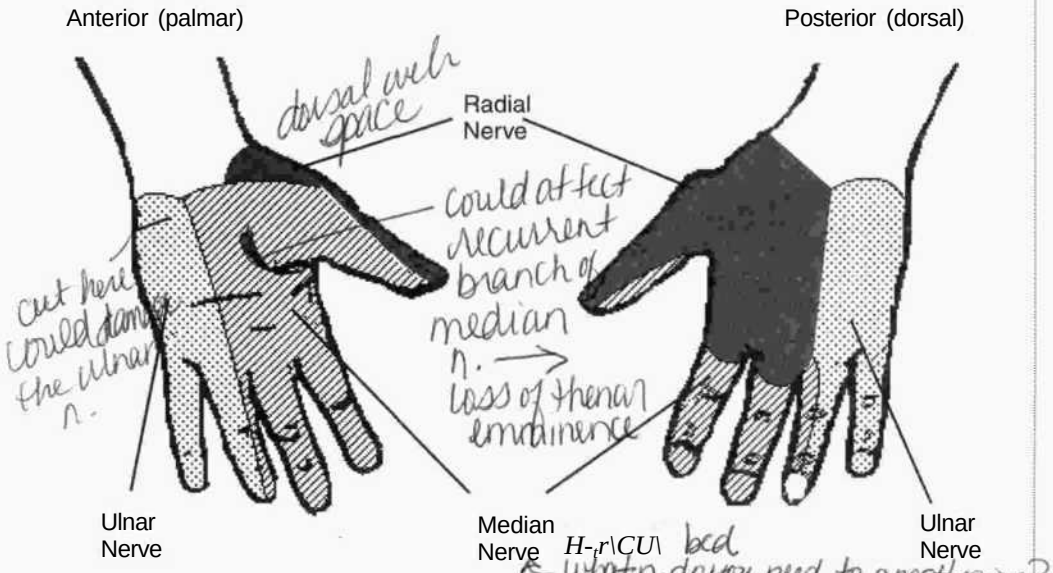


Figure 111-4-2. **Sensory Innervation of** trie **Hand**

NERVE INJURIES

Remember: Follow clues in the questions as to the location of the injury. An injury will manifest in symptoms distal to the site of injury.

Example: Radial nerve cut at the wrist. Sensory loss on the dorsum of the hand. No muscular loss as these are already innervated above the site of the lesion.

Thoughts on Muscle-Nerve Lesions

- Without specifically naming all the muscles, assign a function to the various compartments of the limbs. Example: posterior brachium = extension of the forearm and shoulder.
- List the nerve(s) that innervate those muscles or that area. Example: posterior brachium == radial nerve.
- You have an area of the limb, a function of the muscles within that area, and a nerve responsible for that function.

Now you can damage a nerve and note what function(s) is lost or weakened.

RadialNerve

At the Axilla

Loss of extensors at the elbow, wrist, and digits; weakened extension at the shoulder; weakenjd-Siipination. Sensory loss on posterior arm, forearm, and hand. Sign isv^wrist drop."

At the Elbow

Loss of extensors at the wrist and digits. Sensory loss on the posterior forearm and hand. Sign is "wrist drop." Fracture of the shaft of the humerus could lacerate the radial nerve, and the deficits would be the same as if the nerve were damaged at the level of the elbow.

At the Wrist

Sensory loss on the posterior hand (first dorsal web space).

Median Nerve

At the Elbow

Loss of flexion of the digits, thenar muscles, and lumbricals 1 and 2; weakened wrist flexion; ulnar deviation upon flexion of the wrist; loss of pronation. Sensory loss on lateral palm and digits 1, 2, and 3, and one half of 4. Sign is "ape or simian hand" and "flattening of the thenar eminence."

At the Wrist (in the carpal tunnel)

Loss of function of the thenar muscles and lumbricals 1 and 2; "clawing" of digits 2 and 3. Sensory loss on palmar surface of digits 1,2, and 3, and one-half of 4. Note: There is no sensory loss for the palm of the hand. Sign is "ape or simian hand" and "flattening of thenar eminence."

Ulna; Nerve

At the Elbow (medial epicondyle)

Weakened wrist flexion; radial deviation upon flexion of the wrist; loss of abduction and adduction of the digits; loss of hypothenar muscles and lumbricals 3 and 4. Weakened flexion of digits 4 and 5. Sensory loss on digits 5 and one half of 4. Sign is "claw hand."

At the Wrist
Loss of abduction and adduction of the digits; loss of the hypothenar muscles and lumbricals 3 and 4. Sensory loss on digits 5 and one half of 4. Sign is "claw hand."

Musculocutaneous Nerve

At the Axilla
Greatly weakened shoulder flexion; severely weakened flexion at the elbow; greatly weakened supination. Sensory loss on lateral forearm.

Axillary Nerve

Loss of abduction of the arm to the horizontal plane. The axillary nerve could be damaged with a fracture of the surgical neck of the humerus.

ARTERIAL SUPPLY AND MAJOR ANASTOMOSES

Arterial Supply to the Upper Limb

Subclavian Artery

Branch of brachiocephalic trunk on the right and aortic arch on the left (Fig III-4-3).

Axillary Artery

From the first rib to the posterior edge of the teres major muscle.

- Superior thoracic artery
- Thoracoacromial artery
- Lateral thoracic artery—supplies mammary gland
- Subscapular artery—collateral to shoulder
- Posterior humeral circumflex artery—at surgical neck with axillary nerve
- Anterior humeral circumflex artery

BrachialArtery

Profunda brachii artery with radial nerve.

Radial Artery

Deep palmar arch.

Ulnar Artery

Common interosseus artery.

Superficial palmar arch.

A. Subclavian Artery

B. Axillary Artery - from the first rib to the posterior edge of the teres major muscle

1. Superior thoracic artery
2. Thoracoacromial artery
3. Lateral thoracic artery - supplies mammary gland
4. Subscapular artery - collateral to shoulder
5. Posterior humeral circumflex artery - at surgical neck with axillary nerve
6. Anterior humeral circumflex artery

C. Brachial Artery

7. Profunda brachii artery with radial nerve

D. Radial Artery

8. Deep palmar arch

E. Ulnar Artery

9. Common interosseus artery
10. Superficial palmar arch

Collateral Circulation

Shoulder
Subscapular (axillary) and Suprascapular (subclavian)
Hand
Palmar arches (8 and 10)

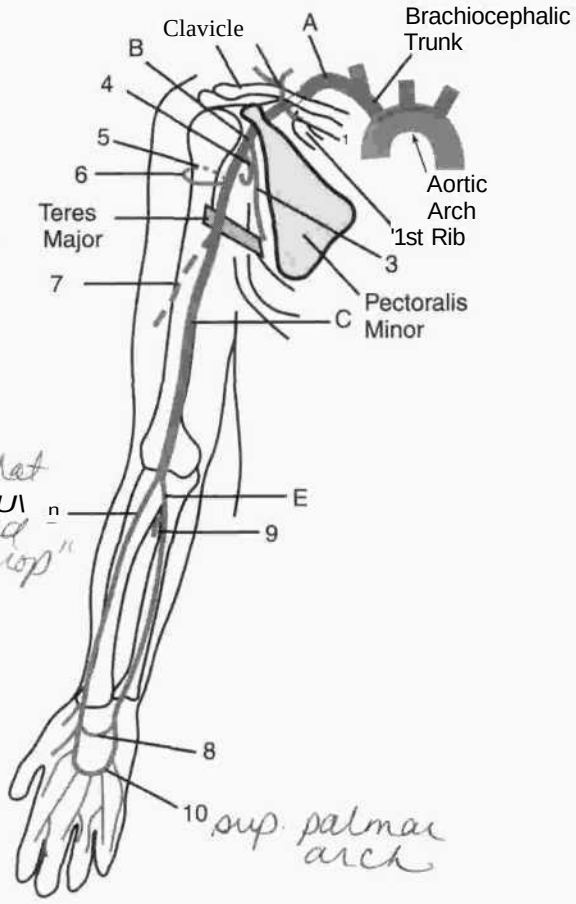


Figure III-4-3. Arterial Supply to the Upper Limb

Collateral Circulation

Shoulder

Subscapular (axillary) and suprascapular (subclavian).

Hand

Palmar arches.

Mammaries

The lateral thoracic artery is the principle blood supply to the mammaries. It would be ligated in the event of a radical mastectomy.

Break the clavicle in middle and the distal piece will be down the proximal part will be up

SHOULDER

The shoulder girdle (pectoral girdle) is composed of the clavicle and scapula.

The scapula articulates with the humerus at the **glenohumeral joint.**

The **sternodavicular joint** is the only bony connection between the upper limb and the axial skeleton.

The humeral head is stabilized in the glenoid fossa by the rotator cuff muscles (musculotendinous cuff) composed of the **supraspinatus, infraspinatus, teres minor,** and **subscapularis** muscles (SITS musc^s)-Ai^n^)iy*Jyu

med. rotator upper + lower subscapular

abductor

ELBOW

The elbow is a compound joint composed of the humeroradial joint, humeroulnar joint, and proximal radioulnar joint.

The humeroradial and humeroulnar joints permit flexion and extension.

The radioulnar joint permits supination and pronation.

WRIST AND HAND

The wrist joints are composed of the **radiocarpal joint** between the radius and the proximal row of carpal bones (primarily the **scaphoid** and **lunate),** the **ulnocarpal joint** (there is a small fibrous disk between the ulna and the triquetrum), the **midcarpal joint** between the proximal and distal rows of carpal bones, and the **carpometacarpal joints** between the distal row of carpal bones and the metacarpal bones.

The **carpal tunnel** is the space bounded by the **flexor retinaculum** anteriorly and the carpal bones posteriorly. Passing through the carpal tunnel are nine tendons (four tendons of the **flexor digitorum superficialis,** four tendons of the **flexor digitorum profundus,** and the tendon of the **flexor pollicis longus)** and the median **nerve.**

Clinical Correlate

Humeral Neck Fracture

The axillary nerve accompanies the posterior humeral circumflex artery as it passes around the surgical neck of the humerus.

A fracture in this area could lacerate both the artery and nerve.

Mid-Shaft Humeral Fracture

The radial nerve accompanies the profunda brachii artery.

Both could be damaged as a result of a mid-shaft humeral fracture.

What deficits would result from laceration of the radial nerve?

Clinical Correlate

Humeral Head Dislocation

Dislocation of the humeral head from the glenohumeral joint typically occurs through the inferior portion of the joint capsule where the capsule is the slackest and is not reinforced by a rotator cuff tendon. After dislocation, the humeral head is pulled superiorly and comes to lie anterior to the glenohumeral joint.

Clinical Correlate

Elbow Dislocation

Dislocation of the elbow typically involves posterior displacement of the ulna and anterior displacement of the humerus. This dislocation may damage the **ulnar nerve** as it passes behind the medial epicondyle, the **median nerve** as it passes anterior to the elbow, and the brachlai **artery** as it passes anterior to the elbow.

Volkmann's **Contracture**

Compression of the brachial artery may result in ischemic contracture (Volkmann's contracture) in the hand.

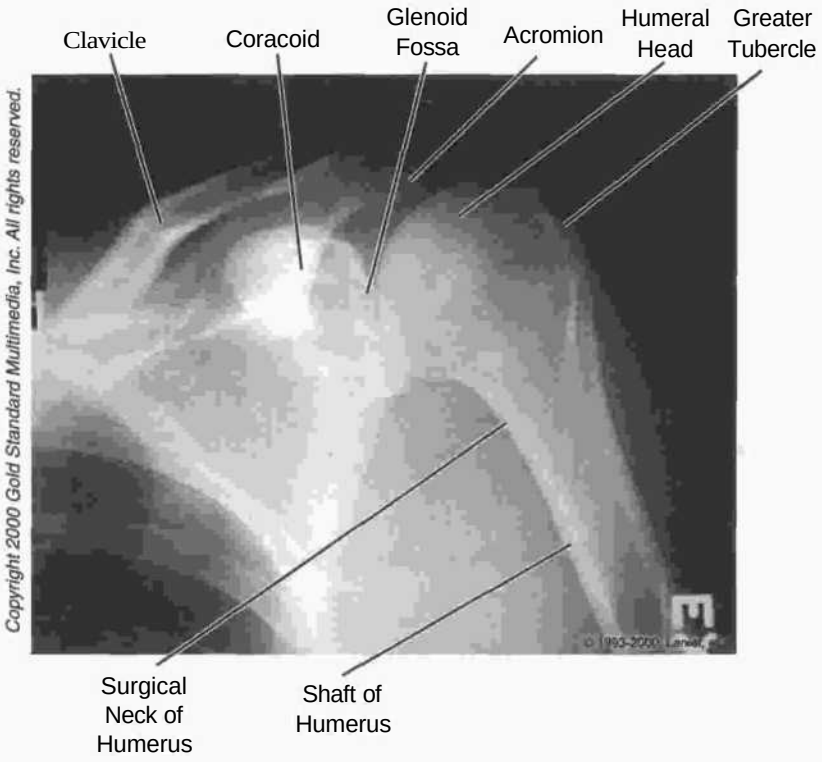


Figure III-4-4. Upper Extremities: Anteroposterior View of Shoulder (External Rotation)

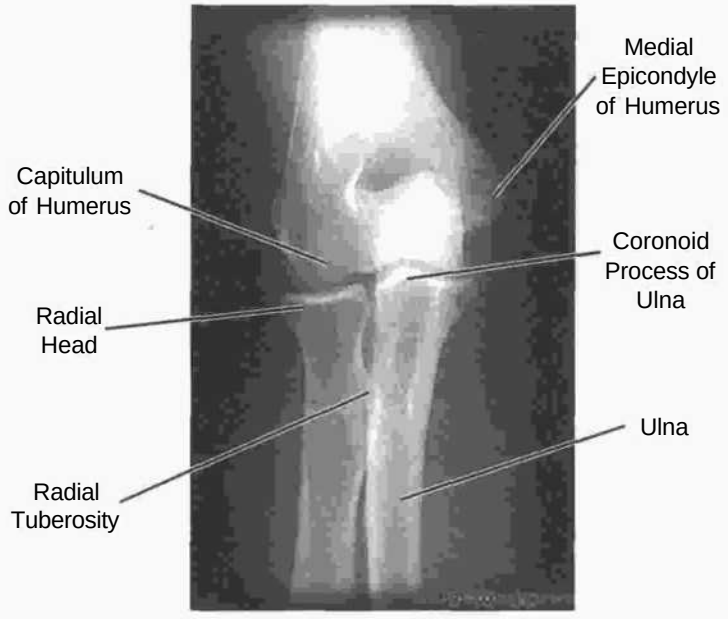


Figure III-4-5. Upper Extremities: Anteroposterior View of Elbow

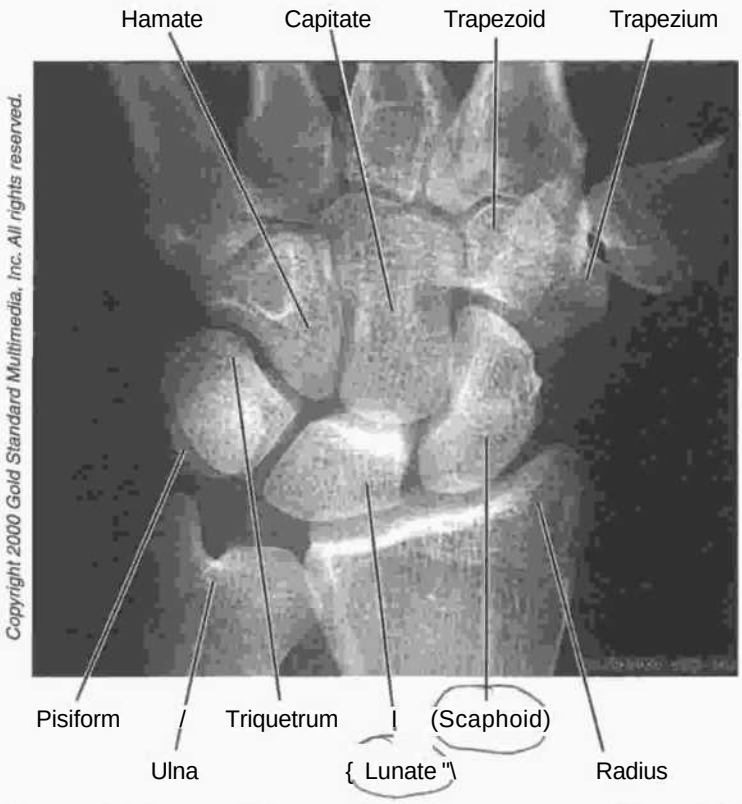


Figure **111-4-6.** Upper Extremities: Posteroanterior View of Wrist

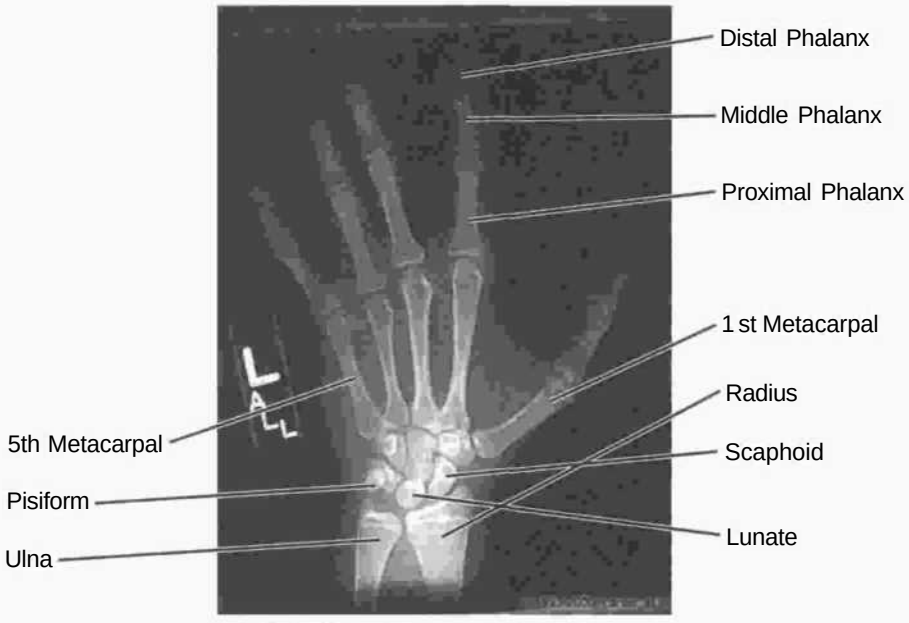


Figure **111-4-7.** Upper Extremities: Posteroanterior View of Wrist and Hand

Clinical Correlate

The **scaphoid** is the most frequently fractured of the carpal bones. This fracture may separate the proximal head of the scaphoid from its blood supply (which enters the bone at the distal head) and may result in **avascular necrosis** of the proximal head.

The lunate is the most commonly dislocated carpal bone (it dislocates anteriorly into the carpal tunnel and may compress the median nerve).

Clinical Correlate

Carpal Tunnel Syndrome

Results from compression of the median nerve within the tunnel.

Fracture of the Hook of the Hamate

A fall on the outstretched hand may fracture the hook of the hamate, which may damage the ulnar nerve as it passes into the hand.

carpal tunnel
9 tendons
1 nerve
median n. below
flexor retinaculum

Lower Limb

5

LUMBOSACRAL PLEXUS

The lumbosacral plexus is formed by the anterior rami of spinal nerves T12 through S4 (Fig III-5-1). The innervation of the lower limb arises from segments L2 through S3. The major nerves of the lower limb are the:

- **Femoral nerve**—posterior divisions of L2 through L4
- **Obturator nerve**—anterior divisions of L2 through **L4**
- **Tibial nerve**—anterior divisions of L4 through S3
- **Common peroneal nerve**—posterior divisions of L4 through S2

The tibial nerve and common peroneal nerve travel together through the gluteal region and thigh in a common connective tissue sheath and together are called the **sciatic nerve.**

The common peroneal nerve divides in the proximal leg into the **superficial and deep peroneal nerves.**

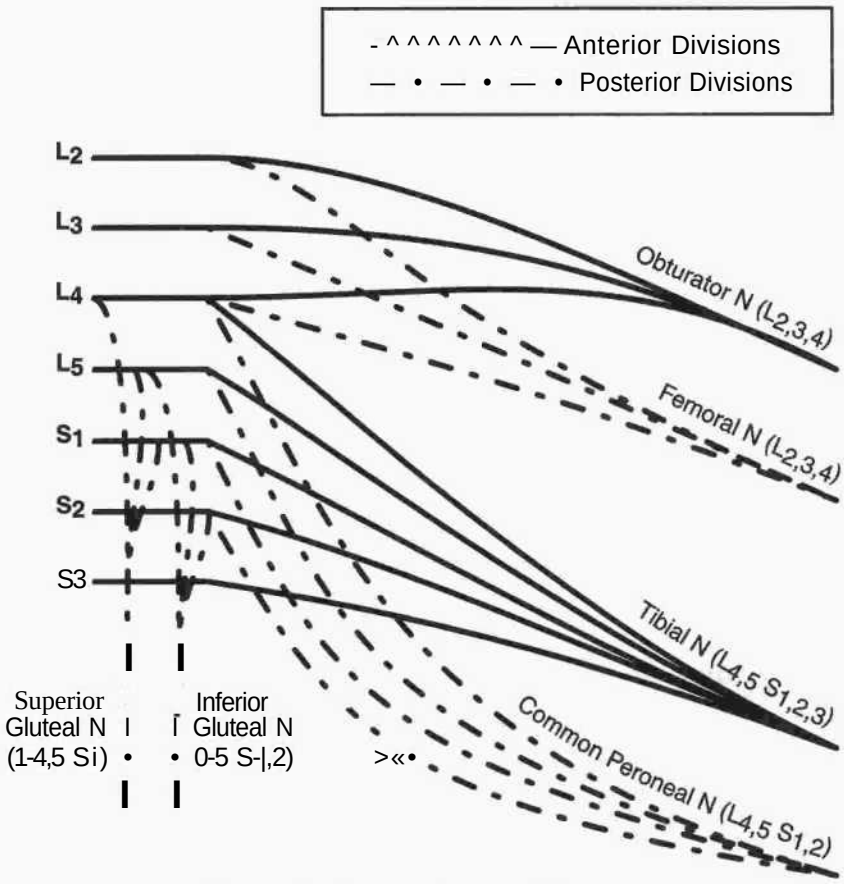


Figure 111-5-1. **Lumbosacral Plexus**

tibial i Cmmcn) mrw£ = Sciati C II.

Terminal Nerves of Lumbosacral Plexus

The terminal nerves of the lumbosacral plexus are described in Table III-5-1.

Table III-5-1. Terminal Nerves of Lumbosacral Plexus

Terminal Nerve	Origin	Muscles Innervated
Femoral nerve	L2 through L4 posterior divisions *hj paklU-.AxJjlwc*	Anterior compartment of thigh (quadriceps femoris, sartorius, pectineus)
Obturator nerve	L2 through L4 anterior divisions	Medial compartment of thigh (gracilis, adductor longus, adductor brevis, anterior portion of adductor magnus)
Tibial nerve	L4 through S3 anterior divisions	Posterior compartment of thigh (semimembranosus, semitendinosus, long head of biceps femoris, posterior portion of adductor magnus) Posterior compartment of leg (gastrocnemius, soleus, flexor digitorum longus, flexor hallucis longus, tibialis posterior) Plantar muscles of foot
Common peroneal nerve	L4 through S2 posterior divisions	Short head of biceps femoris
Superficial peroneal nerve		Lateral compartment of leg (peroneus longus, peroneus brevis)
Deep peroneal nerve		Anterior compartment of leg (tibialis anterior, extensor hallucis, extensor digitorum, peroneus tertius)

Collateral Nerves of Lumbosacral Plexus

The collateral nerves of the lumbosacral plexus (to the lower limb) are summarized in Table III-5-2.

Table III-5-2. Collateral Nerves of Lumbosacral Plexus

Collateral Nerve	Origin	Muscles or Skin Innervated
Superior gluteal nerve	L4 through Si posterior divisions	Gluteus medius, gluteus minimus, tensor fasciae latae
Inferior gluteal nerve	L5 through S2 posterior divisions	Gluteus maximus
Nerve to superior gemellus and obturator internus	L5 through S2 posterior divisions	Superior gemellus, obturator internus
Nerve to inferior gemellus and quadratus femoris	L4 through Si posterior divisions	Inferior gemellus, quadratus femoris
Lateral femoral cutaneous nerve	L2 through L3 posterior divisions	Skin of anterolateral thigh
Posterior femoral cutaneous nerve	SI through S2 posterior divisions and S2 through S3 anterior divisions	Skin of posterior thigh

Segmental Innervation to Muscles of Lower Limb

The **segmental innervation** to the muscles of the lower limb has a **proximal-distal gradient,** i.e., the more proximal muscles are innervated by the higher segments and the more distal muscles" are innervated by the lower segments.

- The muscles that cross the **anterior side of the hip** are innervated by **L2andL3.**
- The muscles that cross the **anterior side of the knee** are innervated by **L3and**
- The muscles that cross the **anterior side of the ankle** are innervated by **L4andO)**

- The muscles that cross the **posterior side of the hip** are innervated by **L4andL5.**
- The muscles that cross the **posterior side of the knee** are innervated by L5 **and** SI.
- The muscles that cross the **posterior side of the ankle** are innervated by **and S2.**

NERVE INJURIES AND ABNORMALITIES OF GAIT

Superior Gluteal Nerve

Causes loss of abduction of the limb; impairment of gait; patient cannot keep pelvis level when standing on one leg. Sign is "Trendelenburg gait."

Inferior Gluteal Nerve

Produces a weakened hip extension; patient has difficulty rising from a sitting position or climbing stairs.

Femoral Nerve

Induces weakened hip flexion; loss of extension of the knee. Sensory loss occurs on the anterior thigh, mefiTaTleg, and foot.

Obturator Nerve

Causes a loss of adduction of the thigh as well as sensory loss on medial thigh.

Sciatic Nerve

Brings about a weakened extension of the thigh; loss of flexion of the knee; and loss of function below the knee. Sensory loss on the posterior thigh, leg (except medial side), and foot is also observed.

Tibial Nerve Only

Causes a loss of flexion of the knee and digits; loss of plantar flexion; weakened inversion and sensory loss on the leg (except medial) and plantar foot.

Common Peroneal Nerve

Produces a combination of deficits of lesion of the deep and superficial peroneal nerves. Sign is "foot-drop."

- Deep peroneal nerve—weakened inversion; loss of extension of the digits; loss of dorsiflexion "foot drop." Sensory loss on anterolateral leg and dorsum of the foot.
- Superficial peroneal nerve—loss of eversion of the foot. Sensory loss on dorsum of foot except the first web space.

Sensory Innervation of the Lower Leg and Foot

The salient features of the sensory innervation of the lower leg and foot are shown in Figure III-5-2.

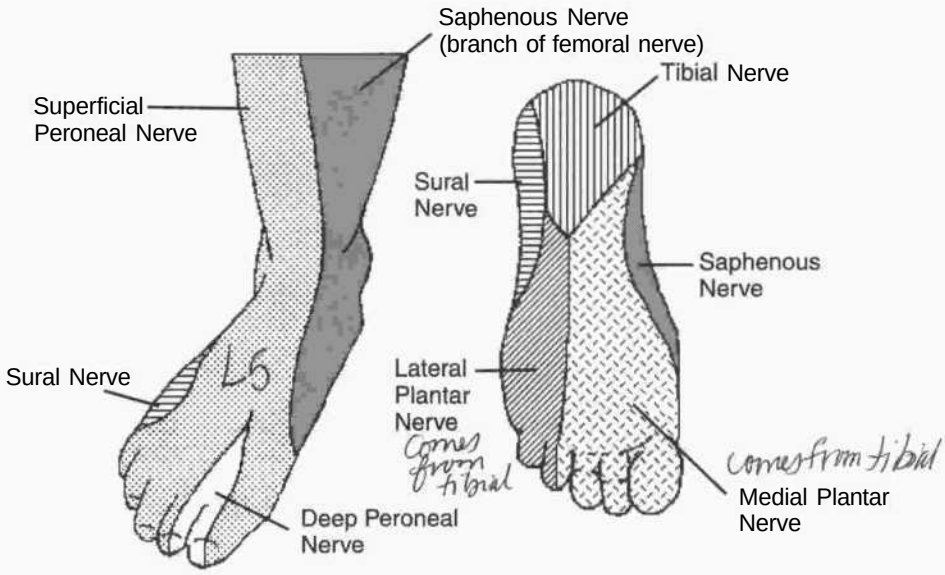


Figure III-5-2. Sensory Innervation of the Lower Leg and Foot

ARTERIAL SUPPLY AND MAJOR ANASTOMOSES

Figure III-5-3 illustrates the arterial supply to the legs.

External iliac artery
Femoral artery
    Profunda femoris artery
    Medial circumflex femoral artery
    Lateral circumflex femoral artery
Popliteal artery
Anterior tibial artery
    Dorsalis pedis artery
Posterior tibial artery

Peroneal artery
Lateral plantar
Plantar arterial arch
Medial plantar artery
Obturator artery

What does femoral a. pass through to become the popliteal a?
Adductor hiatus

A. External iliac artery

B. Femoral artery
1. Profunda femoris artery
2. Medial circumflex femoral artery
3. Lateral circumflex femoral artery

C. Popliteal artery very deep in fossa

D. Anterior tibial artery
4. Dorsalis pedis artery

E. Posterior tibial artery
5. Peroneal artery
6. Lateral plantar
7. Plantar arterial arch
8. Medial plantar artery

F. Obturator artery

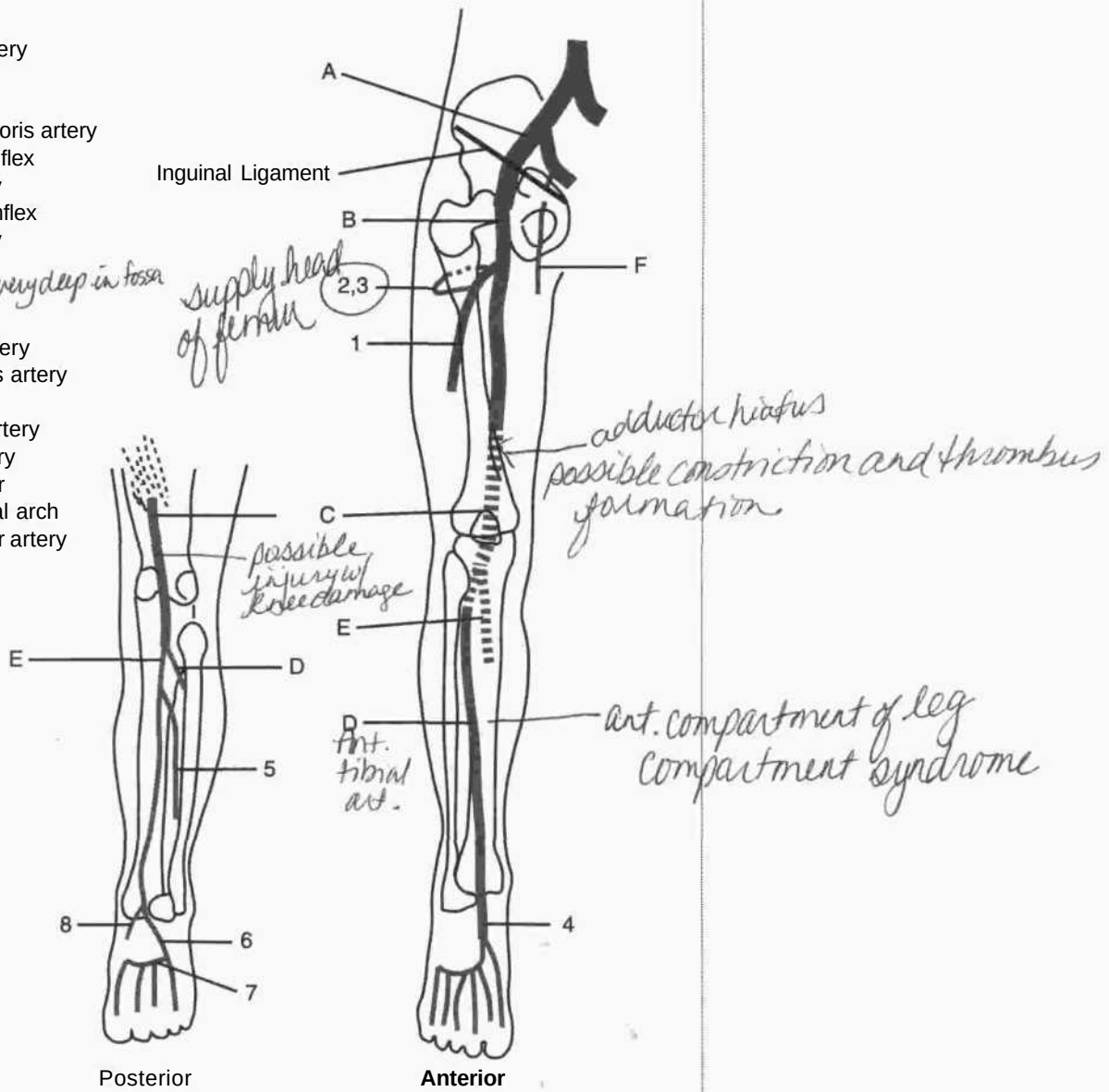
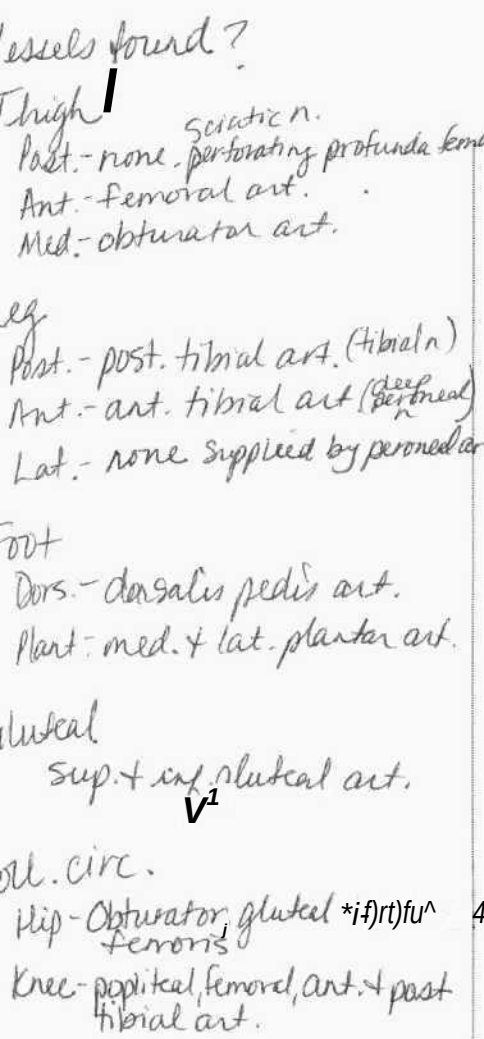


Figure III-5-3. Arterial Supply to the Lower Limb



HIP

The hip joint is formed by the **head of the femur** and the **acetabulum.**

The fibrous capsule of the hip joint is reinforced by three ligamentous thickenings: iliofemoral **ligament, ischiofemoral ligament,** and **pubofemoral ligament.**

Most of the blood supply to the head of the femur (arising mostly from the medial femoral circumflex artery) ascends along the neck of the femur. Fracture of the femoral neck can compromise this blood supply and lead to **avascular necrosis of the head of the femur.**

FEMORAL TRIANGLE

The femoral triangle is bounded by the inguinal ligament and the sartorius and adductor longus muscles.

Within the triangle are the femoral sheath (containing the femoral artery and vein) and the femoral nerve (which is outside of the femoral sheath).

Passing under the inguinal ligament (from lateral to medial) are the: femoral nerve, femoral artery, femoral vein, an empty space within the femoral sheath called the femoral canal, and an inguinal lymph node within the femoral canal (NAVEL). The femoral canal is the site of femoral hernias.

POPLITEAL FOSSA

The popliteal fossa is a diamond-shaped region bounded by the **biceps femoris** superolaterally, the **semimembranosus** and **semitendinosus** superomedially, and the two heads of the **gastrocnemius** inferolaterally and inferomedially.

The floor of the fossa is formed by (from superior to inferior) the **popliteal surface of the femur,** the **knee joint capsule,** and the **popliteus muscle.**

Within the fossa (from posterior to anterior) are the **tibial nerve, popliteal vein,** and **popliteal artery.** Note that the artery is the deepest structure and closest to the femur. It may be endangered by a fracture of the supracondylar region of the femur.

The **common peroneal nerve** is in the lateral part of the fossa and lies against the tendon of the biceps femoris. As the tendon of the biceps femoris inserts on the head of the fibula, the common peroneal nerve wraps around the lateral surface of the fibular neck. In this location, the nerve may be damaged by trauma to the fibular head or neck.

KNEE JOINT

The knee joint is formed by the articulations of the medial and lateral femoral condyles, the medial and lateral tibial condyles (plateaus), and the patella.

Medially and laterally, the knee joint capsule is strengthened by the medial and lateral collateral ligaments. These ligaments resist abduction and adduction, respectively.

There are two major intracapsular ligaments: the anterior and posterior cruciate ligaments. These are named according the site of inferior attachment of the ligament on the tibia, i.e., the anterior cruciate ligament attaches to the tibia anterior to the posterior cruciate ligament. These ligaments prevent anterior and posterior displacement of the tibia on the femur, respectively. The tests for the integrity of these ligaments are the anterior and posterior drawer signs (anterior drawer sign indicates damage to the anterior cruciate ligament).

The medial and lateral menisci are wedge-shaped fibrous and fibrocartilaginous structures between the femoral condyles and the tibial plateaus. The medial meniscus is C-shaped, more firmly anchored to the tibia, and attached to the medial collateral ligament. The lateral meniscus is O-shaped, less firmly anchored to the tibia, and not attached to the lateral collateral ligament. Therefore, the medial meniscus is more commonly injured than the lateral meniscus. The "triad" knee injury is composed of tears of the medial collateral ligament, medial meniscus, and anterior cruciate ligament.

med. coll. lig. injured more commonly than lat coll. lig.
ACL injured more often than PCL
ACL prevents hyperextension

ANKLE JOINT

There are three anklebone joints: the **talocrural joint,** the **subtalar joint,** and the **transverse tarsaljoint.**

The **talocrural joint** is formed by the distal ends of the **tibia and fibula** and the **talus.** The movements at this joint are dorsiflexion **and plantar flexion.** The **medial collateral (deltoid) ligament** and the **lateral collateral ligament** prevent abduction and adduction, respectively. These are the ligaments commonly sprained in eversion and inversion ankle injuries, respectively. Ankle injuries occur mostly when the ankle is plantar flexed.

ant. talofibular most commonly injured

The **subtalar joint** is a compound joint formed by the **talocalcaneal joint** and the talocalcaneal part of the **talocalcaneonavicular joint.** Inversion and eversion are permitted at this joint.

The **transverse tarsaljoint** is a compound joint formed by the **talocalcaneonavicular joint** and the **calcaneocuboid joint.** Inversion and eversion are also permitted at this joint.

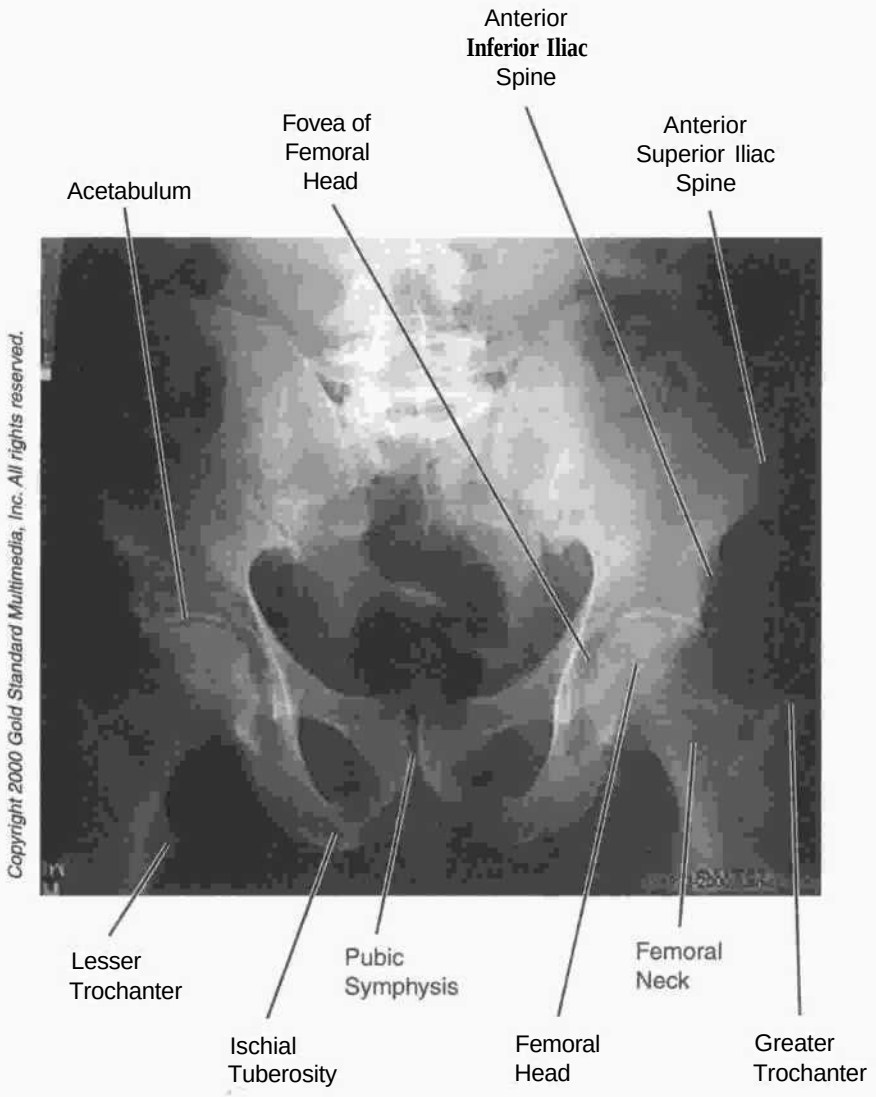


Figure III-5-4. Lower Extremities: Anteroposterior View of Pelvis (Hip)

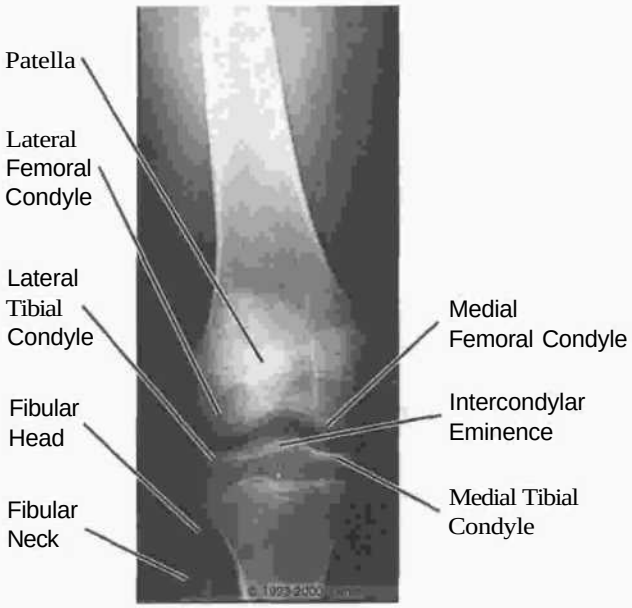


Figure III-S-5. Lower Extremities: Anteroposterior View of Knee

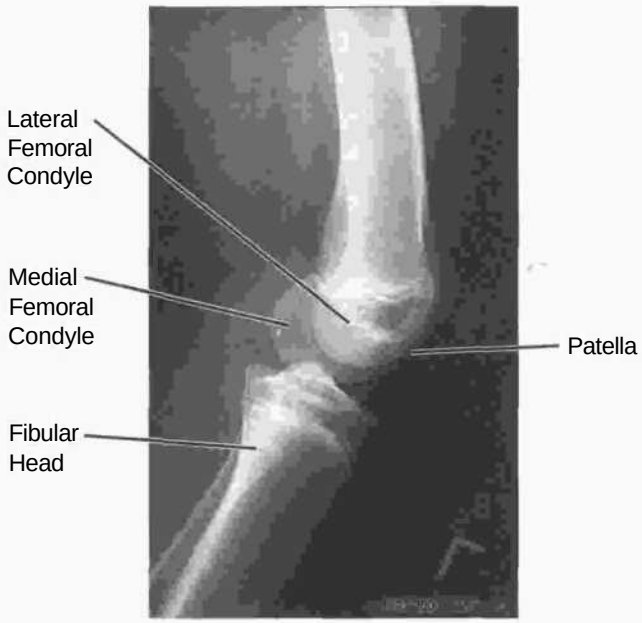


Figure 111-56. Lower Extremities: Lateral Knee

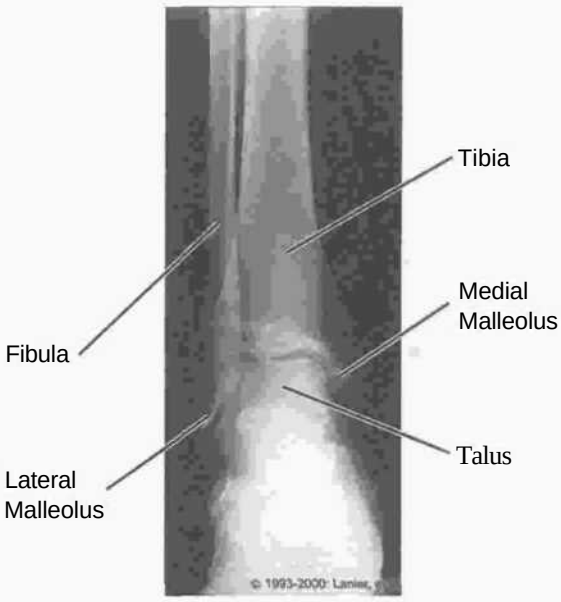


Figure III-5-7. Lower Extremities: Anteroposterior View of Ankle

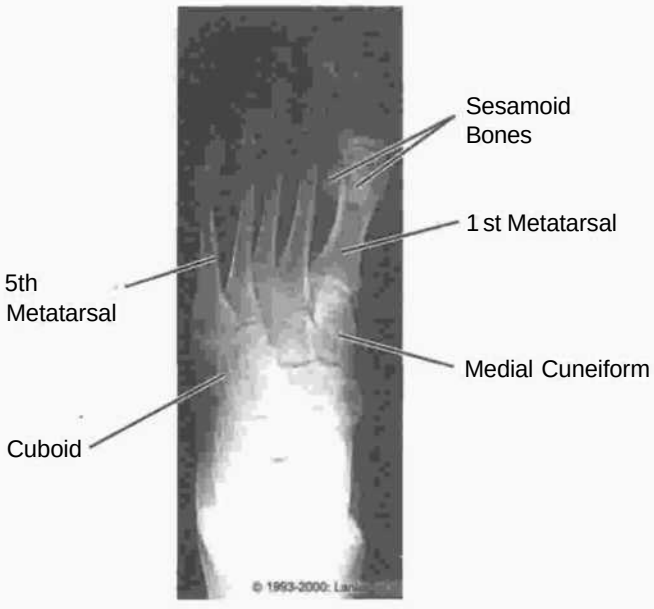


Figure III-5-8. **Lower Extremities: Anteroposterior View of Foot**

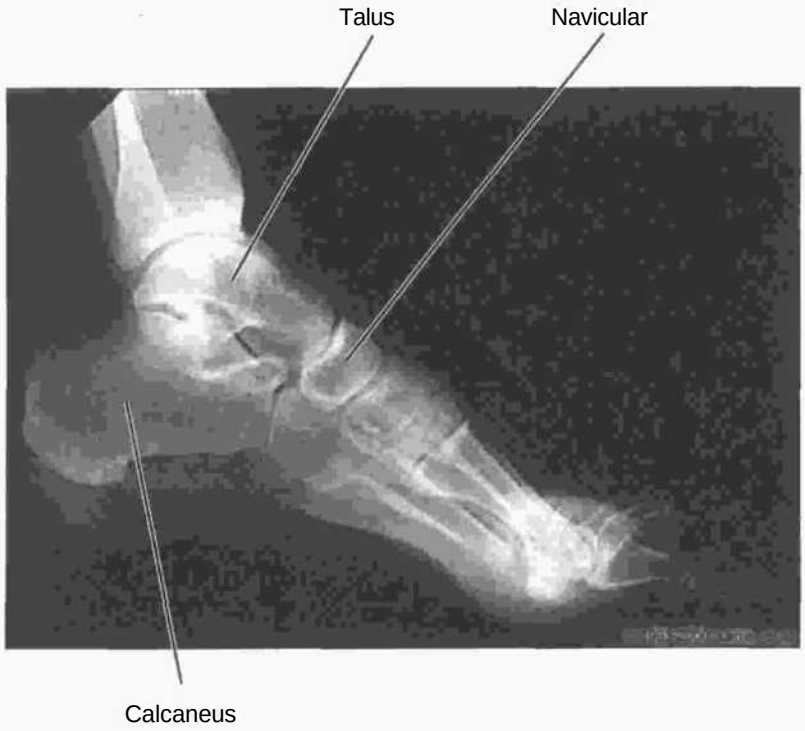


Figure 111-5-9. **Lower Extremities: Lateral Foot**

Head and Neck

6

NECK

General Features

The neck can be divided into two compartments: an anterior or visceral part containing the hyoid bone, pharynx, esophagus, larynx, and associated cartilages, and a posterior or vertebral compartment consisting mostly of muscles associated with cervical vertebrae and the ventral rami of the cervical plexus and brachial plexus. Both compartments are partially covered by two superficial muscles, the trapezius and the sternocleidomastoid, which serve to divide each side of the neck into anterior and posterior triangles (Fig III-6-1).

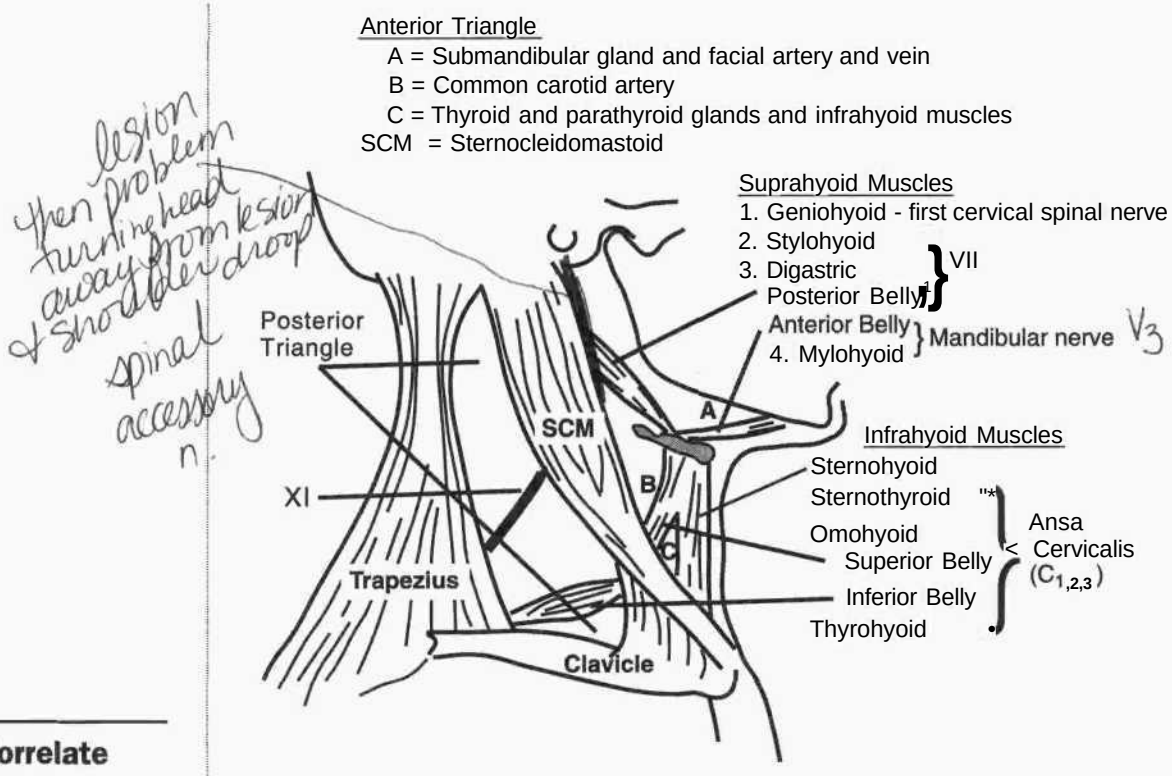


Figure 111-6-1. Triangles of the Neck

Clinical Correlate

Accessory Nerve In the Posterior Triangle

Lesions of the accessory nerve in the posterior triangle result in paralysis and wasting of the trapezius and weakness in elevating the shoulder. If the nerve is injured as it leaves the skull through the jugular foramen, the sternocleidomastoid will also be affected, resulting in a weakness in the ability to turn the head to the opposite side.

Posterior Triangle

The posterior triangle is bounded by the trapezius muscle, the sternocleidomastoid muscle, and the clavicle.

In the floor of the triangle are the anterior scalene, middle scalene, posterior scalene, levator scapulae, and splenius capitis muscles.

- The three trunks of the brachial plexus and the subclavian artery pass through the narrow scalene interval in the floor of the posterior triangle, which lies between the anterior and middle scalene muscles, then under the clavicle, before they enter the axilla (Fig III-6-2).

The accessory nerve (cranial nerve XI) innervates the sternocleidomastoid muscle, then crosses the middle of the posterior triangle to pass under the trapezius muscle, which it also innervates.

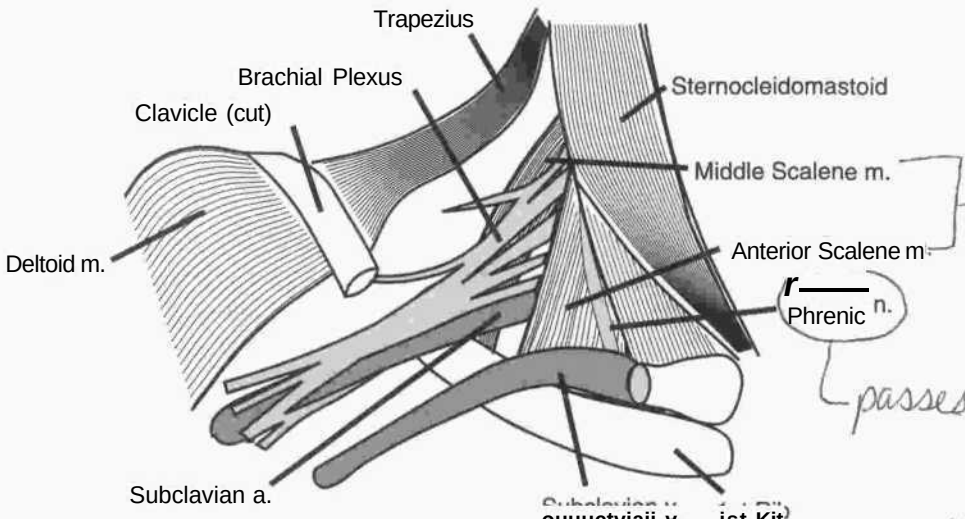


Figure 111-6-2. Anterior Inferior Angle of the Neck

Also in the posterior triangle are the phrenic nerve (formed from the ventral rami of cervical spinal segments C3, C4, and C5), which lies on the anterior surface of the anterior scalene muscle.

In the posterior triangle cutaneous branches of the cervical plexus (great auricular, lesser occipital, transverse cervical, and supraclavicular nerves) emerge at the midpoint of the sternocleidomastoid muscle. These nerves supply the skin of the neck and posterior scalp.

In the superior part of the scalene interval, the upper trunk of the brachial plexus may be compressed, causing weakness of shoulder and arm muscles. In the inferior part of the interval, the lower trunk of the plexus may be compressed by a cervical rib or an apical luna (Pancoast) tumor, causing sensory deficits and weakness of muscles in the hand

Anterior Triangle

The anterior triangle is bounded by the anterior border of the sternocleidomastoid muscle, the anterior midline, and the body of the mandible (Fig III-6-1). Subdivisions of the anterior triangle contain the strap muscles, the submandibular gland, the common carotid, internal carotid and external carotid arteries, and parts of cranial nerves X and XII. The strap muscles consist of a series of five pairs of muscles which have attachments to bony or cartilaginous structures adjacent to the midline beginning at the sternum and extending to the underside of the mandible. Strap muscles act on the mandible, hyoid bone, and thyroid cartilage.

CervicalPlexus

There are two major muscular branches of the cervical plexus, the ansa cervicalis and the phrenic nerve. The cervical plexus is formed by the ventral rami of spinal nerves from Clthrongh C4 and is situated behind the sternocleidomastoid muscle and in front of the scalenus medius and levator scapulae muscles.

Ansa Cervicalis

The ansa cervicalis is a loop formed by fibers from Cl (the superior root), which courses inferiorly by hitchhiking with fibers of the hypoglossal nerve to join fibers from C2 and C3 (the inferior root). The fibers of the ansa are distributed to three strap muscles (sternohyoidrEToth bellies of omohyoid, and sternothyroid). The thyrohyoid and geniohyoid are strap muscles innerYated by Cl fibers, which do not leave in the, superior tQQtJo form the ansa but continue further medially along the hyjgoglQssaLnerve to reach these two muscles. Three suprahyoid muscles (mylohyoid, stylohyoid, and both bellies of the digastric muscle) act on the hyoid bone or the mandible but are innervated by branches of cranial nerves (CN) V3 or VII. The posterior belly (innervated by CN VII) of the digastric elevates and steadies the hyoid bone, and the anterior belly (innervated by CN V3) opens the mouth by depressing the mandible. The stylohyoid muscle (innervated by CN VII) elevates and retracts the hyoid bone. The phrenic nerve (C3, C4, and C5) descends from the neck through the mediastinum to innervate the skeletal muscle of the diaphragm. The phrenic nerve also carries sensory fibers from the central part of the diaphragm.

CarotidTriangle

The carotid triangle is a subdivision of the anterior triangle. The carotid triangle contains the internal jugular vein, the vagus nerve (CN X), and the common or internal and external carotid arteries. All of these structures are found in the carotid sheath.

The **common carotid artery** bifurcates at the upper border of the thyroid cartilage into the internal and external carotid arteries. The external carotid artery has six proximal branches: the superior thyroid, ascending pharyngeal, lingual, facial, occipital, and posterior auricular arteries. These supply structures of the neck, face, and scalp (Fig III-6-3).

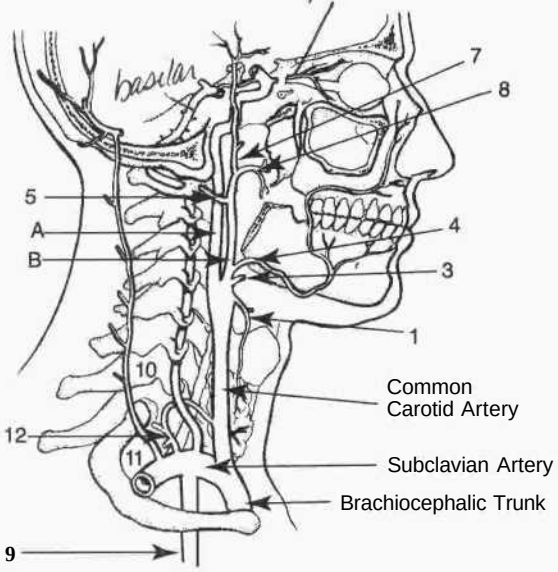
Posterior to the mandible, the **external carotid artery** ends by dividing into the maxillary artery and the superficial temporal artery. The maxillary artery supplies structures in the infratemporal fossa and the mandibular teeth and courses through the pterygopalatine fossa to supply the maxillary teeth, maxillary face, and the nasal cavity. The internal carotid artery has no branches in the neck and enters the skull to supply the brain and the orbit.

CAROTID
SHQyr 4

Clinical Correlate

The most significant artery of the external carotid system is the middle meningeal artery. It arises from the maxillary artery in the infratemporal fossa and enters the skull through the foramens spinosum to supply skull and dura. Lacerations of this vessel result in an epidural hematoma.

1st branch of int. car. art → ophthalmic art. → central a. of retina
Sudden drop in blood press. of int. car. a. → transient loss of vision



Common Carotid Artery

A. Internal carotid artery - ophthalmic artery and brain
B. External carotid artery
\yf. Superior thyroid
2. Ascending pharyngeal
, (not shown)
^. Lingual
K Facial
5. Occipital
6. Posterior auricular (not shown)
U7T" Superficial temporal
i-er"Maxillary - deep face; jneningeal artery

Subclavian Artery

9. Internal thoracic - Cardiac by-pass
10. Vertebral-Brain
H.Costocervical
12.Thyrocervical
A. Transverse cervical
B.Suprascapular- coilaterals to shoulder
C. Inferior thyroid

epicranial vessel

Figure 111-6-3. **Arteries to the Head and Neck**

HEAD

Embryology of Pharynx, Tongue, and Palate

Pharyngeal Apparatus

The pharyngeal apparatus consists of pharyngeal arches (1,2,3,4, and 6), pouches (1, 2,3, and 4), and grooves (1,2,3, and 4). The anatomic associations relating to these structures, in the fetus and adult, are summarized in Figures III-6-4 and III-6-5.

Table III-6-1 summarizes the relationships among the nerves, arteries, muscles, and skeletal elements derived from the pharyngeal arches, and Table III-6-2 shows which adult structures are derived from the various pouches.

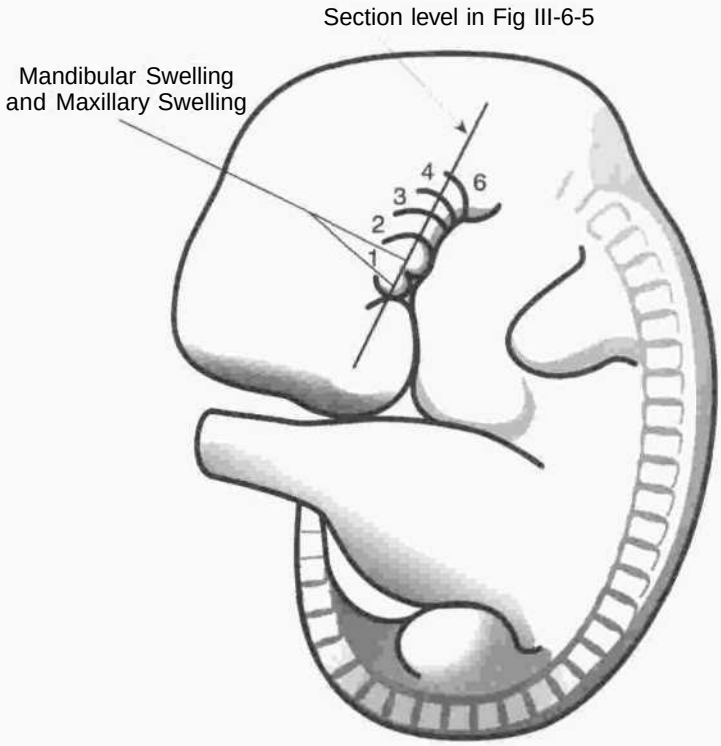


Figure III-6-4.The Fetal Pharyngeai Apparatus

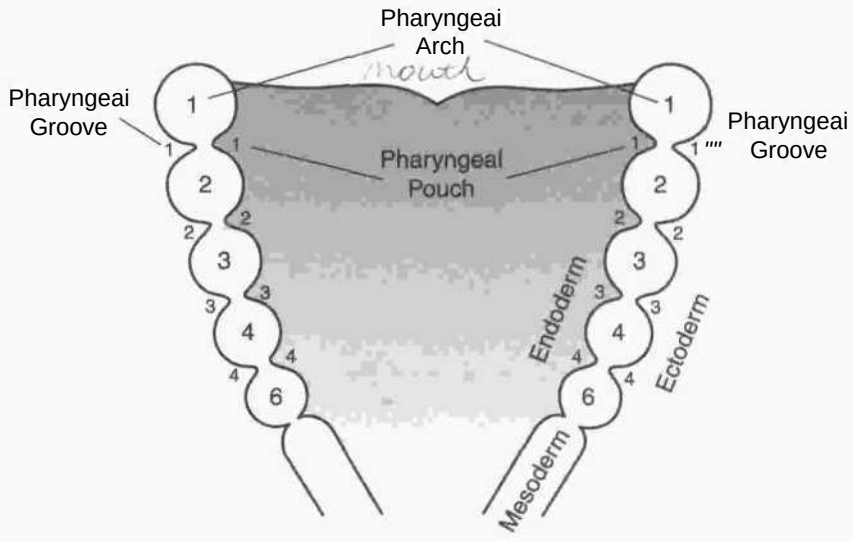


Figure III-6-5. Section Through the Developing Pharynx

Pharyngeal Arches Mesoderm

The components of the pharyngeal arches are summarized in Table III-6-1.

Table III-6-1. The Neural, Arterial, Muscular, and Skeletal Elements Derived From the Pharyngeal Arches

Arch	Nerve	Artery	Muscle	Skeletal
1	V3		Muscles of mastication	Maxilla Mandible
			Tensor tympani muscle	Incus Malleus
2	VII		Muscles of facial expression	Stapes
			Stapedius muscle	Lesser horn and upper body of hyoid bone
3	IX	Right and left common carotid arteries	Stylopharyngeus muscle	Greater horn and lower body of hyoid bone
		Right and left internal carotid arteries		
4	X Superior laryngeal nerve	Right subclavian artery	Cricothyroid muscle	Laryngeal cartilages
		Arch of aorta		
6	X			
	Recurrent laryngeal nerve	Right and left pulmonary arteries	Intrinsic muscles of larynx (except cricothyroid muscle)	Laryngeal cartilages
		Ductus arteriosus		

Note

The origins of pharyngeal and palatine muscles innervated by CN X is controversial.

Pharyngeal Pouches

The anatomic structures relating to the pharyngeal pouches are summarized in Figure III-6-6.

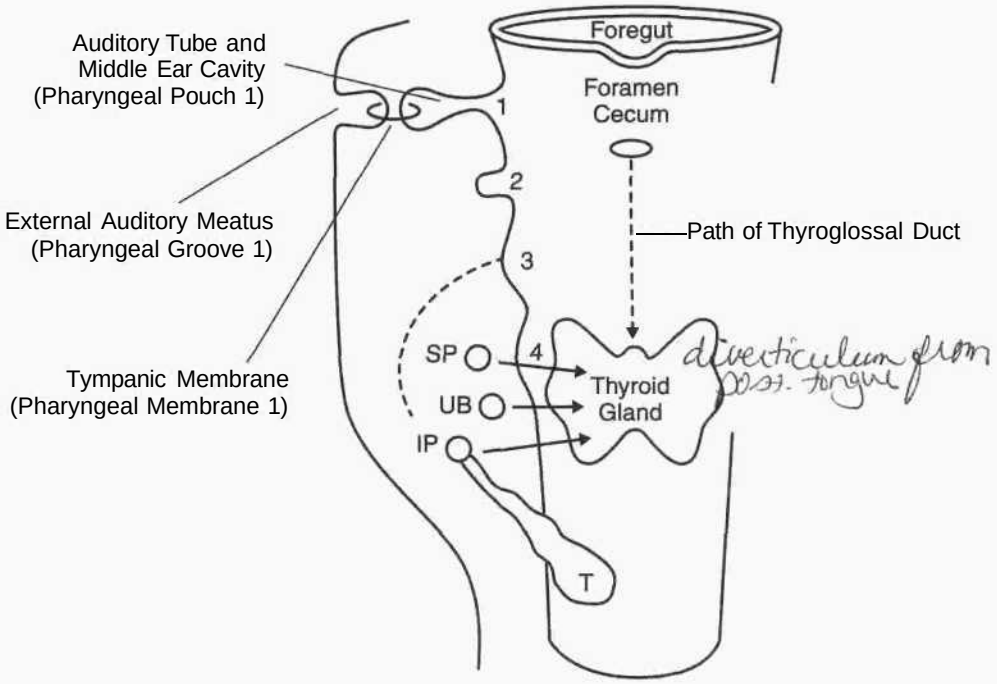


Figure III-6-6. Fetal Pharyngeal Pouches

The adult structures derived from the fetal pharyngeal pouches are summarized in Table III-6-2.

Table III-6-2. Adult Structures Derived From the Fetal Pharyngeal Pouches

pouch	Adult Derivatives
1	Epithelial lining of auditory tube and middle ear cavity
2	Epithelial lining of crypts of palatine tonsil
3	Inferior parathyroid gland (IP)
	Thymus (T)
	Superior parathyroid gland (SP)
	Ultimobranchial body (UB)

Neural crest cells migrate into the ultimobranchial body to form parafollicular (C) cells of the thyroid.

Pharyngeal Grooves

Pharyngeal groove 1 gives rise to the epithelial lining of **external auditory meatus.**

All other grooves are obliterated.

Thyroid Gland

The thyroid gland develops from the **thyroid diverticulum,** which forms in the midline, in the floor of the foregut. The thyroid diverticulum migrates caudally to its adult anatomic position but remains connected to the foregut via the **thyroglossal duct,** which is later obliterated. The former site of the thyroglossal duct is indicated in the adult by the **foramen cecum.**

Tongue and Palate

The gntprinr *turn* thirds nf the tnngiie is associated with pharyngeal arch 1. General sensation is carried by the lingual branch of CN V. Taste sensation is carried by **chorda tympani of CN VII** (Fig III-6-7).

The **posterior one third of the tongue** is associated with **pharyngeal arch** 3. General sensation and taste are carried by CN DC

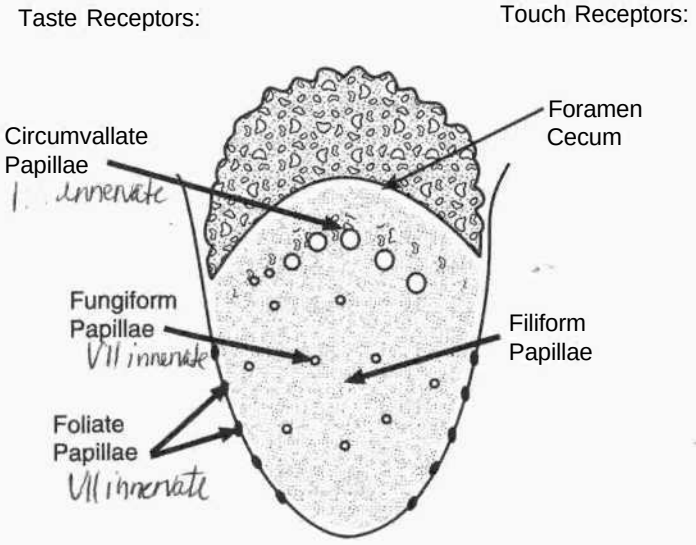


Figure 111-6-7. Tongue

Intrinsic and extrinsic muscles of the tongue are derived from myoblasts that migrate into the tongue region from **occipital somites.** Motor innervation is supplied by CN **XII** (Fig III-6-8).

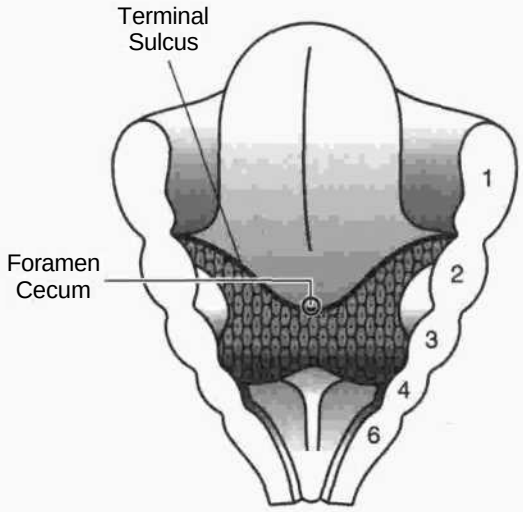


Figure III-6-8. The Tongue

Development of the Face and Palate

The face develops from the frontonasal prominence, a pair of maxillary prominences, and a pair of mandibular prominences.

Intermaxillary Segment and Primary Palate

The intermaxillary segment forms when the two medial nasal prominences fuse together at the midline and gives rise to the **philtrum of the lip, four incisor teeth,** and **primary palate** of the adult (Fig III-6-9). The primary palate forms anterior to the incisive foramen.

Secondary Palate

The secondary palate forms from outgrowths of the maxillary prominences called **palatine shelves,** which fuse in the midline, posterior to the incisive foramen.

The primary and secondary palate fuse at the **incisive foramen** to form the definitive palate.

Clinical Correlation

Cleft Up

Cleft lip occurs when the maxillary prominence fails to fuse with the medial nasal prominence.

Cleft Palate

Cleft palate occurs when the palatine shelves fail to fuse with each other or the primary palate.

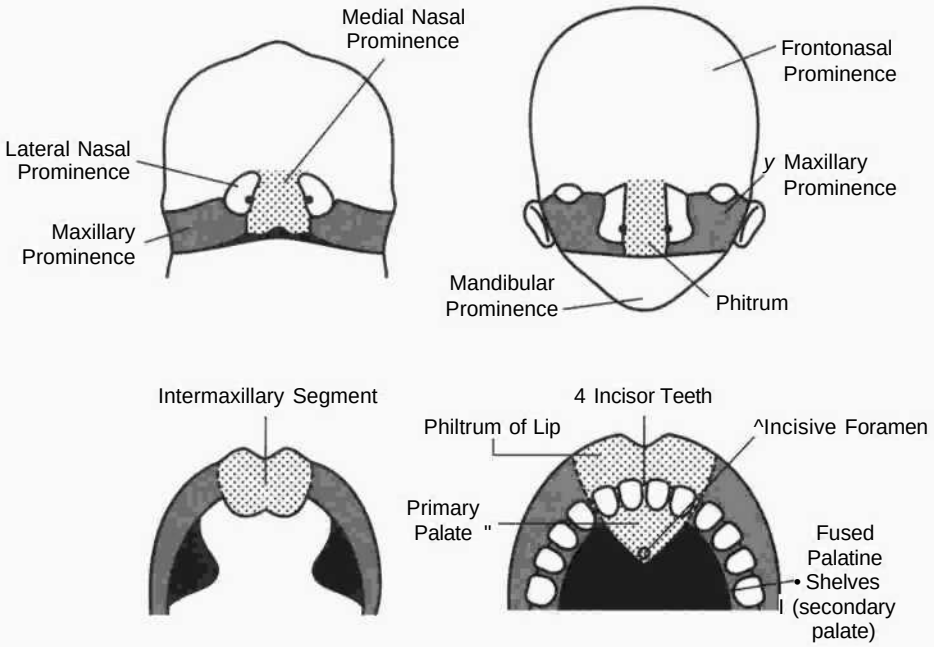


Figure III-6-9. Palate and Face Development

Clinical Considerations

First **Arch Syndrome**

First arch syndrome results from abnormal formation of pharyngeal arch 1 because of faulty migration of neural crest cells, causing facial anomalies. Two well-described syndromes are Treacher Collins syndrome and Pierre Robin sequence. Both defects involve neural crest cells.

Pharyngeal Fistula

Pharyngeal fistula occurs when pouch 2 and groove 2 persist, thereby forming a fistula generally found along the anterior border of the sternocleidomastoid muscje.

Pharyngeal Cyst

Pharyngeal cyst occurs when pharyngeal grooves that are normally obliterated persist, forming a cyst usually located at the angle of the mandible.

Ectoplc Thyroid, Parathyroid, or Thymus

Ectopic thyroid, parathyroid, or thymus results from abnormal migration of these glands from their embryonic position to their adult anatomic position. Ectopic thyroid tissue is found along the midline of the neck. Ectopic parathyroid or thymus tissue is generally found along the lateral aspect of the neck. May be an important issue during neck surgery.

Clinical Correlate

Robin sequence presents with a triad of poor mandibular growth, cleft palate, and a posteriorly placed tongue.

Treacher Collins syndrome also presents with mandibular hypoplasia, zygomatic hypoplasia, down-slanted palpebral fissures, colobomas, and malformed ears.

Clinical Correlate

The **DiGeorge sequence** presents with immunological problems, hypocalcemia, and may be combined with cardiovascular defects (persistent troncus arteriosis), abnormal ears, and micrognathia.

0

Clinical Considerations (continued)

Thyroglossal **Duct Cyst or** Fistula

Thyroglossal duct cyst or fistula occurs when parts of the thyroglossal duct persist, generally in the midline near the hyoid bone. The cyst may also be found at the base of the tongue (lingual cyst).

DiGeorge Sequence

DiGeorge sequence occurs when pharyngeal pouches 3 and 4 fail to differentiate into the parathyroid glands and thymus. Neural crest cells are involved.

CRANIUM

General Features

The cranium contains the brain, its meningeal coverings, and the points of entrance or exit of the cranial nerves.

The cranial cavity also contains CSF, venous sinuses of the dura mater, and internal carotid and vertebral arteries and their branches that supply the brain, plus meningeal arteries and meningeal nerves.

The internal surface of the skull conforms to the shape of the brain and contains foramina and fissures, which are passageways for the entry or exit of cranial nerves and blood vessels.

All of the openings for the entry or exit of cranial nerves are found in the floor of the cranium, which is divided into three shallow compartments, the anterior, middle, and posterior cranial fossae (Figs III-6-10 and III-6-11).

1. Cribriform plate
   I
2. Optic canal
   II and ophthalmic artery
3. Foramen rotundum
   Maxillary nerve (V2)
4. Foramen ovale
   *Mandibular nerve (V^*
5. Foramen spinosum
   Middle meningeal artery
6. Foramen lacerum
   Nothing
7. Internal auditory meatus
   VII and VIII
8. Jugular foramen
   IX, X, and XI: Sigmoid sinus
9. Hypoglossal canal
   XII
10. Foramen magnum
    XI, spinal-cord-brainstem junction, vertebral arteries

Figure 111-6-10. Foramina: Cranial Fossa

1. Stylomastoid foramen
   VII
2. **Carotid canal**
   Internal carotid artery
3. Jugular foramen
   IX, X, and XI; sigmoid sinus
4. Foramen ovale
   *Mandibular nerve (V^*
5. Foramen spinosum
   Middle meningeal artery
6. Foramen lacerum
   Nothing
7. Foramen magnum
   XI, spinal-cord-brainstem junction, vertebral arteries

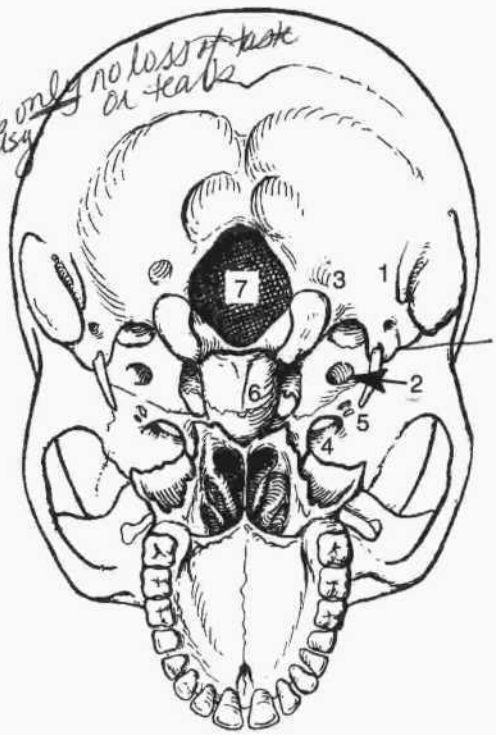


Figure 111-6-11. Foramina: Base of Skull

Clinical Correlate

Cribriform plate fractures may result in dysosmia and rhinorrhea (CSF).

Anterior Cranial Fossa

One cranial nerve, the olfactory (CN I), enters the cranial cavity in the anterior cranial fossa through the cribriform plate.

The cribriform plates form the roof of the nasal cavity. Fifteen to 20 olfactory nerve fibers, which arise from the nasal mucosa, pass through the small foramina in the cribriform plate to terminate in the olfactory bulb, which sits on the cranial side of the plate.

Middle Cranial Fossa

The middle cranial fossa is deeper than the anterior fossa and contains openings for the entry or exit of five cranial nerves (CN II-VI), the optic, oculomotor, trochlear, the three divisions of the trigeminal, and the abducens. In the midline of the middle cranial fossa is the sella turcica, which contains the pituitary gland and is covered by a shelf of dura, the diaphragma sellae. Anterior to the sella is the optic groove, which leads to the pair of optic canals. The optic nerves enter the cranial cavity from the orbit through the optic canals. Anteriorly, the middle cranial fossa communicates with the orbit through the superior orbital fissure. Cranial nerves III, IV, VI, and VI pass through the superior orbital fissure on their way to or from the orbit. In the floor of the middle cranial fossa the maxillary division of CN V passes through the foramen rotundum, and the mandibular division and motor root of CN V pass through the foramen ovale. The middle meningeal artery (a branch of the maxillary artery) enters the cranial fossa through the foramen spinosum. The cavernous sinus, a dural venous sinus at the juncture of the ophthalmic veins and petrosal sinuses, lies on either side of the sella turcica in the middle cranial fossa. Cranial nerves III, IV, VI, and the ophthalmic and maxillary divisions of CN V as well as the internal carotid artery and its periarterial plexus of postganglionic sympathetic fibers traverse the cavernous sinus before leaving the middle cranial fossa. The middle cranial fossa also contains the foramen lacerum, which is crossed by the internal carotid artery and its periarterial plexus of postganglionic sympathetic fibers.

Posterior Cranial Fossa

The posterior cranial fossa contains three small foramina, the internal auditory meatus, jugular foramen, and hypoglossal canal, and the large foramen magnum. These openings transmit the last six cranial nerves (CN VII, VIII, IX, X, XI, and XII). The foramen magnum transmits the end of the brain stem, the vertebral arteries, and the accessory nerve. Adjacent to the foramen magnum are the hypoglossal canals, through which pass the hypoglossal (CN XII) nerves. The

glossopharyngeal (DC), vagus (X), and accessory (CN XI) nerves pass through the jugular foramen. Extending from the jugular foramen along the walls of the posterior fossa are large grooves formed by the sigmoid and transverse dural venous sinuses. The sigmoid sinus joins the inferior petrosal sinus to form the internal jugular vein just below the jugular foramen. Cranial nerves VII and VIII pass through the internal auditory meatus.

Clinical Correlate

Jugular foramen syndrome may be caused by a tumor pressing on CN IX, X, and X. Patients present with hoarseness, dysphagia (CN X), loss of sensation over the oropharynx and posterior one third of the tongue (CN IX), trapezius and stemocleidomastiod weakness (CN XII). The nearby CN XII may be involved producing tongue deviation to the lesioned side.

Venous Drainage of the Brain and the Dural Venous Sinuses

*Venous**Drainage***

Two sets of cerebral veins drain into dural venous sinuses, which drain into the internal jugular vein. Venous sinuses form where the meningeal and periosteal layers of the dura mater separate (Fig III-6-12).

Table III-6-3. Cranial Nerves: Functional **Features**

CN	Name	Type	Function
I	Olfactory	Sensory	Smells
II	Optic	Sensory	Sees (optic nerve is really a tract of CNS with meninges)
VIII	Vestibulocochlear	Sensory	Hears Linear acceleration (gravity) Angular acceleration (head turning)
III	Oculomotor	Motor	Moves eyeball in all directions Adduction (medial rectus) most important action Constricts pupil (sphincter pupillae) Accommodates (ciliary muscle) Raises eyelid (levator palpebrae superioris)
IV	Trochlear	Motor	Superior oblique—depresses and abducts eyeball (makes eyeball look down and out) Intorts
VI	Abducens	Motor	Lateral rectus—abducts eyeball
XI	Accessory	Motor	Turns head to opposite side (sternocleidomastoid) Elevates and rotates scapula (trapezius)
XII	Hypoglossal	Motor	Moves tongue (styloglossus, hyoglossus, genioglossus, and intrinsics—palatoglossus is by X)
V	Trigeminal Ophthalmic (VI)	Mixed	General sensation (touch, pain, temperature) of forehead/scalp/ cornea
	Maxillary (V2)		General sensation of palate, nasal cavity, maxillary face, maxillary teeth
	Mandibulax (V3)		General sensation of anterior two thirds of tongue, mandibular face, mandibular teeth Motor to muscles of mastication (temporalis, masseter, medial and lateral pterygoids) and anterior belly of digastric, mylohyoid, tensor tympani, tensor palati

VII Facial

Lesions Result in	Exits/Enters Cranium:	Region Innervated
Anosmia	Cribriform plate	Nasal cavity
Visual field deficits (anopsia) Loss of light reflex with III Only nerve to be affected by MS (swinging flashlight test)	Optic canal	Orbit
Sensorineural hearing loss Loss of balance, nystagmus	Internal auditory meatus	Inner ear
Diplopia—external strabismus Loss of parallel gaze Dilated pupil, loss of light reflex with II Loss of near response Ptosis	Superior orbital fissure	Orbit
Weakness looking down and in Trouble going down stairs Head tilts away from lesioned side	Superior orbital fissure	Orbit
Diplopia—internal strabismus Loss of parallel gaze, "pseudoptosis"	Superior orbital fissure	Orbit
Weakness turning head to opposite side Shoulder droop	Jugular foramen	Neck
Tongue pointing toward same (affected) side on protrusion	Hypoglossal canal	Tongue
VI—loss of general sensation in skin of forehead/scalp Loss of blink reflex with VII	VI—superior orbital fissure (ophthalmic division)	Orbit and scalp
V2—loss of general sensation in skin over maxilla, maxillary teeth	V2—foramen rotundum (maxillary division)	Pterygopalau'ne fossa (leave by openings to face, oral and nasal cavity)
V3—loss of general sensation in skin over mandible, mandibular teeth, tongue, weakness in chewing Jaw deviation toward weak side Trigeminal neuralgia—intractable pain in V2 or V3 territory	V3—foramen ovale (mandibular division)	Infratemporal Fossa

Loss of facial n.
loss of saliva
loss of taste (ant. 2/3)
corneal reflex absent b/c eff. limb of corneal response
hyperacusis

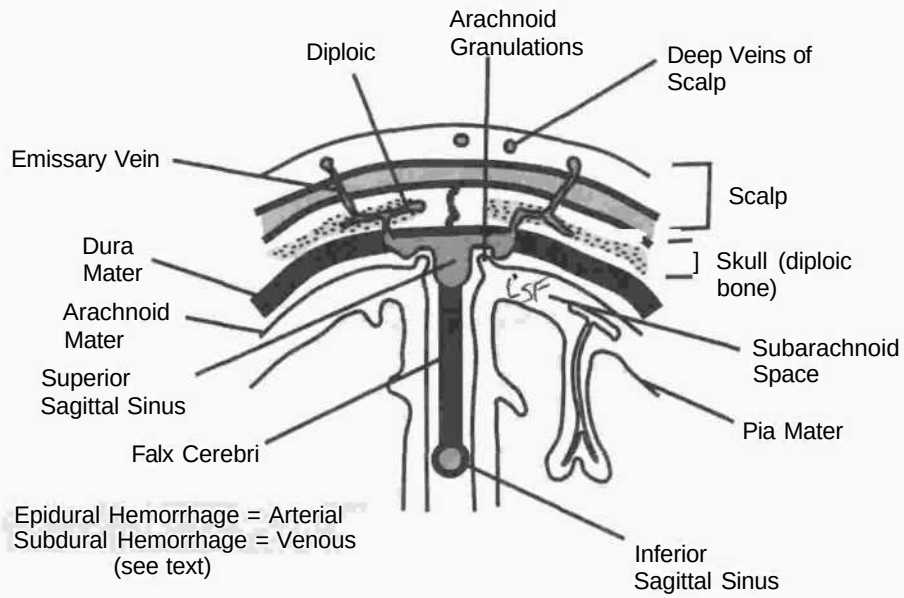


Figure HI-6-12. Coronal Section of the Dural Sinuses

Superficial (external) cerebral veins drain the cortex and the more superficial white matter. They mainly follow the sulci, lying between the gyri, and drain into the superior sagittal, transverse, and cavernous sinuses.

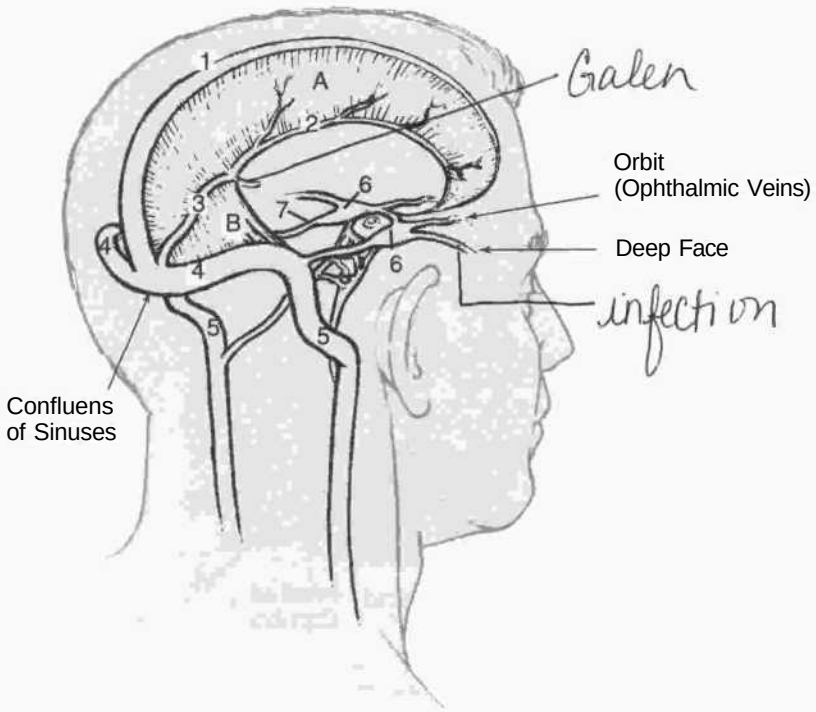
Two deep cerebral veins unite to form the great cerebral vein (of Galen), which drains into the straight sinus.

Emissary veins form anastomoses through bones of the skull between the venous sinuses and the veins external to the skull.

Diploic veins run between the inner and outer tables of the skull and communicate with the venous sinuses and extracranial veins via the emissary veins.

Dural Venous Sinuses

The dural venous sinuses receive cerebral veins from the brain and drain the venous blood mainly into the internal jugular vein (Fig III-6-13). The **superior sagittal sinus** is located in the midsagittal plane along the superior aspect of the falx cerebri. It drains into the confluence of the sinuses. Arachnoid granulations protrude through the walls of the superior sagittal sinus. The arachnoid granulations transmit CSF from the subarachnoid space into the venous circulation. The superior sagittal sinus drains into the confluens of the sinuses.



Names of the Dural Sinuses
1. Superior sagittal*
2. Inferior sagittal
3. Straight*
4. Transverse* (2)
5. Sigmoid (2)
6. Cavernous (2)
7. Superior petrosal (2)
8. Occipital* (not shown)

** Drain into the confluens of sinuses located at the inion*

Folds (Duplications) of Dura Mater
A. Falx cerebri
B. Tentorium cerebelli

Figure 111-6-13. Dural Venous Sinuses

The **inferior sagittal sinus** is located in the midsagittal plane, near the inferior margin of the falx cerebri. It terminates by joining with the great cerebral vein to form the straight sinus at the junction of the falx cerebri and tentorium cerebelli.

The **straight sinus** is formed by the union of the inferior sagittal sinus and the great cerebral vein. It usually terminates by draining into the confluens of sinuses (or into the transverse sinus).

The **occipital sinus** is found in the attached border of the tentorium cerebelli. It drains into the confluens of sinuses.

The **confluens of sinuses** is formed by the union of the superior sagittal, straight, and occipital sinuses. It drains into the two transverse sinuses.

The **transverse sinuses** drain venous blood from the confluence of sinuses into the sigmoid sinuses. Each sigmoid sinus joins with an inferior petrosal sinus to drain into the internal jugular vein below the jugular foramen.

Cavernous Sinuses

The cavernous sinuses are the most clinically significant dural sinuses (Fig III-6-14).

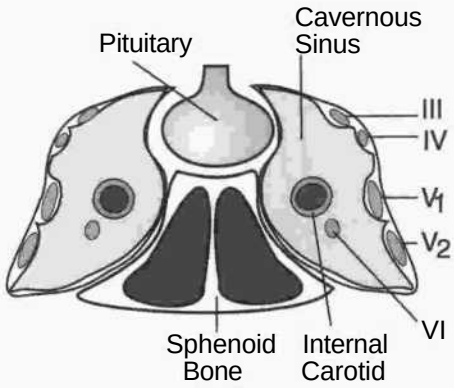


Figure 111-6-14. Coronal Section Through Pituitary Gland and Cavernous Sinuses

The cavernous sinuses are located on either side of the body of the sphenoid bone.

Each sinus receives blood from some of the cerebral veins, ophthalmic veins, and the sphenoparietal sinus.

Each cavernous sinus drains into a transverse sinus via the superior petrosal sinus, into the internal jugular vein via the inferior petrosal sinus, and by emissary veins through the foramen ovale into the pterygoid venous plexus.

Clinical Correlate

Cavernous Sinus Thrombosis

Infection can spread from veins of the face into the cavernous sinuses, producing infection and thrombosis. Such infection may involve the cranial nerves, which course through the cavernous sinus. Cranial nerves III, IV, and VI and the ophthalmic and maxillary divisions of CN V, as well as the internal carotid artery and its periarterial plexus of postganglionic sympathetic fibers traverse the cavernous sinus. All of these cranial nerves course in the lateral wall of the sinus except for CN VI, which courses through the middle of the sinus. As a result, CN VI is typically affected first in a cavernous sinus thrombosis or by an aneurysm of the internal carotid artery, with the other nerves being affected later.

Subarachnoid Hematoma

A subarachnoid hemorrhage results from a rupture of a berry aneurysm in the circle of Willis. The most common site is in the anterior part of the circle of Willis. A common site for an aneurysm is at the branch point of the anterior cerebral and anterior communicating arteries. Other common sites are in the proximal part of the middle cerebral artery, or at the junction of the internal carotid and posterior communicating arteries. A typical presentation associated with a subarachnoid hemorrhage is the onset of a severe headache.

Subdural Hematoma

A subdural hematoma results from head trauma that tears superficial ("bridging") cerebral veins at the point where they enter the superior sagittal sinus. A venous hemorrhage results between the dura and the arachnoid. If acute, large hematomas result in signs of elevated intracranial pressure such as headache and nausea. Small or chronic hematomas are often seen in elderly or chronic alcoholic patients. Over time, herniation of the temporal lobe, coma, and death may result if the venous blood is not evacuated.

CT scan
rough borders

Epldural Hematoma

An epidural hematoma results from trauma to the lateral aspect of the skull, which lacerates the middle meni"gg«i artqry. Arterial hemorrhage rapidly occurs in the space between the dura and the skull. The head trauma is associated with a momentary loss of consciousness followed by a lucid (asymptomatic) period of up to 48 hours. The patient then develops symptoms of elevated intracranial pressure such as headache, nausea, and vomiting, combined with neurologic signs such as hemiparesis. Herniation of the temporal lobe, coma, and death may result if the arterial blood is not evacuated.

in CT scan
smooth border

middle meatus gets drained by
① frontal
② maxillary
inf. meatus
① nasolacrimal duct

Nasal Cavity

The nasal cavity and associated paranasal sinuses are air-filled spaces lined by mucosa, which serve to warm, moisten, and filter inspired air. Each nasal cavity begins at the external nares and opens through the choanae into the nasopharynx. The cavities are separated medially by the nasal septum and bounded laterally by three shelflike bones, the conchae, on the lateral nasal wall. Four paranasal sinuses drain into each nasal cavity through one or more small openings and are named for the bones that contain them (frontal, ethmoid, maxillary, and sphenoid). The sinuses drain into meatuses, air-filled channels between the conchae and the lateral nasal wall. The olfactory nerve (CN I) and the ophthalmic (CN VI) and maxillary (CN V2) nerves of the trigeminal provide the sensory innervation of the nasal cavity. Glands in the mucosa of the nasal cavity and paranasal sinuses are supplied by the facial nerve (CN VII) and by postganglionic parasympathetic axons from the pterygopalatine ganglion.

Orbit

The orbit is a pyramidal shaped compartment that contains the eyeball, its associated muscles, and branches of five cranial nerves (CN II, III, IV, VI, and VI) (Fig III-6-15).

The medial walls of the orbit are parallel to one another and are separated by the nasal cavity.

The lateral walls diverge laterally from the apex of the orbit to the anterior orbital margins.

The posterior part of the orbit contains the optic canal, superior orbital fissure, and inferior orbital fissure.

1. Supraorbital foramen (notch)
   Supraorbital VAN (V-,)
2. Infraorbital foramen
   *Infraorbital VAN (V^*
3. Mental foramen
   Mental VAN (V3)
4. Superior orbital fissure
   III, IV, VI, and (V_{7I}); *ophthalmic veins*
5. Inferior orbital fissure
   Infraorbital VAN (V_2)
6. Optic canal
   (II) not shown

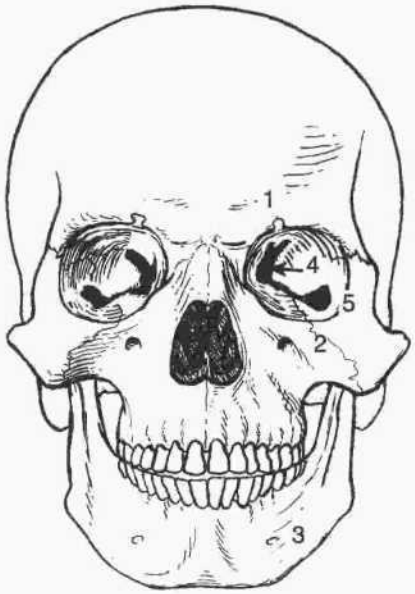


Figure 111-6-15, **Front of Skull**

- The optic canal transmits the optic nerve and ophthalmic artery.
- The superior orbital fissure contains the superior ophthalmic veins, which communicate with the cavernous sinus in the middle cranial fossa, and transmits branches of the oculomotor, trochlear, and abducens nerves and branches of the ophthalmic division of the trigeminal nerve (CN VI).
- The optic nerve innervates the retina; the oculomotor, trochlear, and abducens nerves innervate muscles that move the eyeball; and the oculomotor nerve innervates muscles involved in accommodation and a muscle that elevates the eyelid.
- Branches of the ophthalmic division of the trigeminal nerve carry general sensation from the eyeball and from the face adjacent to the orbit.

The **eyeball** is responsible for the collection and initial processing of light.

Light enters the eyeball through two transparent structures, the cornea and the lens, which refract or focus the light so that it impinges upon the retina.

The **cornea** is an avascular outer coating of the eyeball, which acts as the principal refractive medium.

The **lens** lies posterior to the cornea and is separated from it by an anterior and a posterior chamber. The chambers communicate through the pupil, the circular opening in the iris. The lens forms the posterior boundary of the posterior chamber and is held in place by the fibers of the suspensory ligament. Changes in the

see Neuro.

Clinical Correlate

An emmetropic cornea achieves refraction with no refractive error. A flat cornea has too little refractive power and focuses an object behind the retina, resulting in hyperopia or far-sightedness. Corneas that are too round have too much refractive power, focusing an object in front of the retina, resulting in myopia or near-sightedness. An irregularly shaped cornea forms distorted images known as astigmatism. Lenses correct for defects in corneal shape, allowing the cornea to become emmetropic. Corneal transplants are performed if opacities reduce the transparency of the cornea.

Clinical Correlate

Glaucoma

Glaucoma results from a blockage or restriction of aqueous drainage into the canals of Schlemm. This increases the intraocular pressure in the entire eyeball and results in a decrease in axoplasmic flow in the optic nerve.

Clinical Correlate

Over time, the lens becomes less elastic, reducing the ability to focus on near objects, a condition known as presbyopia.

The lens, like the cornea, can develop opacities known as cataracts. Lens replacements restore visual clarity but not accommodation.

V - sup. oblique
1 - ~~lateral~~ lat. rectus
1 - all rest
(Levator palp.)

tension of the suspensory ligament result in changes in the shape of the lens, altering its refractive power. The anterior and posterior chambers are fluid-filled. The fluid in both chambers is aqueous humor, which is produced in the ciliary body in the posterior chamber. It flows through the pupil and drains into specialized veins, the canals of Schlemm in the anterior chamber. Aqueous humor secreted into the posterior chamber can come in contact with the vitreous body behind the lens through the fibers of the suspensory ligament.

Orbital Muscles and Their Innervation

In the orbit, there are six extraocular muscles, which move the eyeball. A seventh muscle, the levator palpebrae superioris, elevates the upper eyelid. Four of the six extraocular muscles, the superior, inferior, and medial rectus, and the inferior oblique, plus the levator palpebrae superioris, are innervated by the oculomotor nerve (CN III). The superior oblique muscle is the only muscle innervated by the trochlear nerve (CN IV), and the lateral rectus is the only muscle innervated by the abducens nerve (CN VI). The levator palpebrae superioris is composed of skeletal muscle innervated by the oculomotor nerve (CN III) and smooth muscle (the superior tarsal muscle) innervated by sympathetic fibers. Sympathetic fibers reach the orbit from a plexus on the internal carotid artery of postganglionic axons that originate from cell bodies in the superior cervical ganglion.

In addition to the superior tarsal part of the levator palpebrae superioris, there are three other smooth muscles in the orbit, the dilator and constrictor pupillae and the ciliary muscle. The iris contains the dilator pupillae (radial) muscle and the sphincter pupillae (circular) constrictor muscle, which have antagonistic effects on the diameter of the pupil. The dilator pupillae muscle is innervated by preganglionic sympathetic fibers from the upper thoracic spinal cord and postganglionic sympathetics from the superior cervical ganglion. The constrictor pupillae muscle is innervated by preganglionic parasympathetic fibers from the nucleus of Edinger Westphal, which exit the midbrain in CN III, and by postganglionic parasympathetic fibers from the ciliary ganglion.

The ciliary muscle is a smooth muscle that, when contracted, relaxes the suspensory ligament of the lens, allowing the lens to "round up" for near vision. Contraction of the ciliary muscle is part of the accommodation reflex under control of parasympathetic fibers in the oculomotor (CN III) nerve.

The orbit also contains the **lacrimal gland;** parasympathetic innervation to the gland comes from the facial nerve by way of the pterygopalatine ganglion.

Actions of Orbital Muscles

The movements of each eyeball occur about three axes, which pass through the eyeball at right angles to one another. Each ocular muscle moves the cornea about one or more of the three axes, toward or away from a primary or resting position where the eyeball is situated, such that gaze is directed straight ahead.

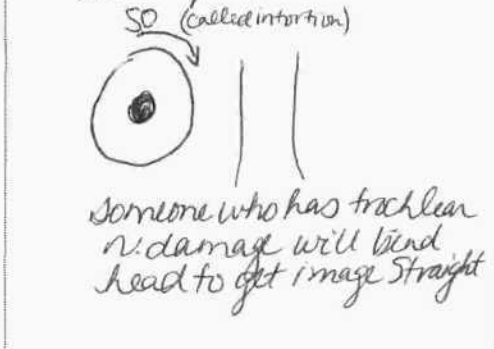
The **medial and lateral rectus muscles** each have a single action. They adduct andjabjiuct-th^-eyehall, respectively. Both are involved in horizontal conjugate gaze, or the side-to-side movements of both eyes together. The movements of the other two rectus muscles (superior and inferior) and the two oblique muscles (superior and inferior) are more complicated. The superior rectus elevates the eye and the inferior rectus depresses the eye. Both of these muscles also adduct the eyeball so that the net effect of the superior rectus is to make the eyeball look up and in and the inferior rectus to make the eyeball look down and in. The superior and inferior rectus muscles are tested for elevation and depression, respectively, when the eyeball is abducted (looking away from the nose).

The **superior oblique** depresses the eye, and the **inferior oblique** elevates the eye. Both of these muscles also abduct the eyeball so that the net effect of the superior oblique is to make the eyeball look down and out, and the inferior oblique, to look up and out. The oblique muscles work best and are tested when the eyeball is adducted (looking toward the nose). Elevation of the eye is achieved when both the superior rectus and inferior oblique muscles contract and their vectors for adduction and abduction cancel each other. Depression of the eye is achieved when both the inferior rectus and superior oblique muscles contract and their vectors for adduction and abduction cancel each other.

The superior oblique (and superior rectus) intort or medially rotate the eyeball, moving the right eyeball from the 12-o'clock position medially toward the 3-o'clock position as one looks at the patient. The inferior oblique (and inferior rectus) muscles extort or laterally rotate the eyeball, moving the right eyeball from the 12-o'clock position laterally toward the 9-o'clock position.

sup. & inf. rectus mm.
SR - up & in
IR - down & in

obliques: abduct eye
S.O. - down & out
I.O. - up & out



someone who has trochlear n. damage will bend head to get image straight

Clinical Features

Examination of the eyes can be used to evaluate the three cranial nerves that innervate muscles which move the eyeball (CN III, IV, and VI), sensory fibers of the trigeminal (CN V1) and motor fibers of the facial nerve (CN VII) through the blink reflex, the optic nerve (CN II) and parasympathetic fibers of CN III through the pupillary light reflex, and the sympathetic fibers to the head.

Lesions of the oculomotor nerve (CN III) present most dramatically in a weakness in the ability to adduct the eyeball. The eyeball will be deviated laterally, and it will be abducted and slightly depressed by the unopposed actions of the lateral rectus and superior oblique. Clinically, the lateral deviation of the eye is known as an external strabismus. CN HI lesions also cause a ptosis combined with a

dilated pupil (mydriasis), a loss of accommodation, and a loss of the motor limb ofthe pupillary light reflex, resulting in a loss of the ability to constrict the pupil on the affected side. Fibers in the oculomotor nerve are organized so that parasympathetic fibers lie external to those that supply the extraocular muscles. Therefore, compressive lesions (e.g., temporal lobe herniation, aneurysms) tend to involve the parasympathetic fibers first, producing mydriasis and loss of the pupillary light reflex before paralysis of the extraocular muscles. In contrast, vascular disease (e.g., diabetes mellitus) often affects the deeper fibers, causing ptosis and paralysis of the extraocular muscles while sparing the pupil. Common causes of peripheral CN III lesions include berry aneurysms (most often involving the posterior communicating artery) and compression secondary to a subdural or epidural hematoma caused by head trauma and herniation of the temporal lobe under the free edge of tentorium cerebelli.

Lesions of the trochlear nerve produce a diplopia when attempting to depress the adducted eye. The diplopia is most apparent when the patient looks dawn and away from the lesioned side. Patients complain of difficulty in reading or difficulty in going down stairs. A loss of intorsion may also be important diagnostically in CN IV lesions. Here, the patient tilts his or her head away from the side of the lesioned nerve to counteract tEe extorsion by the unopposed interior objigue and inferior rectus muscles. In children, the head tilt might be mistaken for torticollis caused by abnormal contractions of the sternocleidomastoid muscle.

Lesions ofthe abducens nerve result in a weakness in the ability to abduct the eyeball. CN VI lesions cause the eye to be deviated medially owing to the unopposed action of the medial rectus muscle and other adductors innervated by CN III. Clinically, a medially deviated eye in CN VI lesions is known as an internaLstrabismus. Patients with internal strabismus may also present with a "pseudoptosjs" in which the patient shuts the eye on the affected side in an attempt to eliminate the diplopia. The abducens nerve may be the first nerve affected in a cavernous sinus lesion. All three of the ocular nerves (CN III, IV, and VI) and the ophthalmic division of CN V traverse the cavernous sinus on their way either to or from the superior fissure. All but the abducens nerve course in the lateral wall of the sinus. The abducens nerve courses through the middle of the sinus adjacent to the internal carotid artery, and, as a result, an internal strabismus may precede a complete ophthalmoplegia on the affected side combined with altered sensation in the forehead, scalp, and over the bridge of the nose.

Pupillary Light and Accommodation Reflexes

The direct and consensual light reflex causes both pupils to constrict in response to light and uses the sensory fibers of the optic nerve and the parasympathetic fibers of the oculomotor nerve.

Shining a bright light into one eye causes the pupil of that eye to constrict (direct light reflex) and also causes constriction of the pupil in the other eye, which has not been directly stimulated by light (consensual light reflex). The light reflex

uses the sensory fibers in the optic nerve (CN II) and the parasympathetic component of the oculomotor nerve (CN III). The reflex has both direct and consensual components. Light stimulating one retina sends impulses into one optic nerve but into both optic tracts through the partial crossing at the optic chiasm. Both optic tracts send impulses to nuclei in the pretectal region of the midbrain, which in turn project back to both Edinger Westphal nuclei, causing both pupils to constrict. By separately testing the effects of light in each eye, localization of a lesion to either the optic or oculomotor nerve can be determined. The accommodation reflex or near response uses both skeletal motor and parasympathetic fibers in the oculomotor nerve. Movement of an object toward the patient results in a bilateral pupillary constriction, a rounding up of the lens (parasympathetic fibers), and convergence (skeletal motor fibers to both medial rectus muscles).

PupillaryDefects

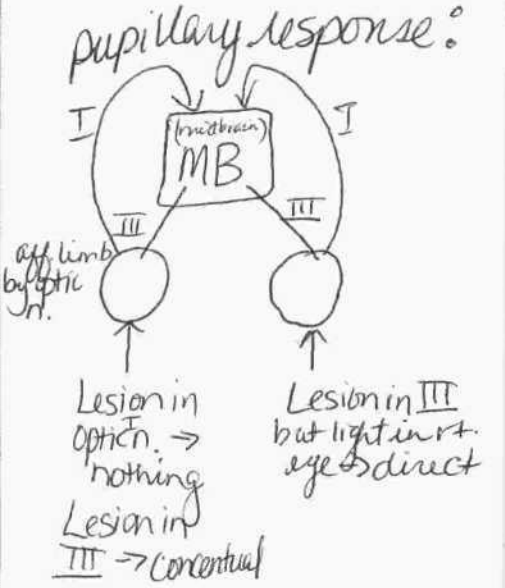
Defects in the response of both pupils to light can caused by lesions to either the afferent or efferent limbs of the light reflex. An afferent pupillary defect may result from lesions to the optic nerve and can be evaluatedujsLngthe swinging flashlight test. When light is presented to the normal eye, Hoflr pup\¥tivwul constrict, but when the flashlight is swung to the affected eye, both pupils will paradoxically dilate. Lesions to the oculomotor nerve will cause an efferent pupillary defect. Light presented to the normal eye will cause both pupils to constrict, but light presented to the affected eye will cause only the consensual pupil to constrict. Lesions to the ciliary ganglioffprooUces a "tonjcjlpupil. Here, the pupil on the affected side responds slowly to light but normally in accommodation because the postganglionic parasympathetic fibers innervating the ciliary muscle significantly outnumber those innervating the sphincter pupillae muscle. In Argyll Robertson pupils, there is a bilateral loss of pupillary constriction in response to light, but both pupils react normally in accommodation. The location of the lesion resulting in the Argyll Robertson pupils is thought to be inside the midbrain affecting neurons governing the pupillary response but sparing those controlling the near response. A n t *f\£(_ Q-ry\m^b4l<n }*

ORAL CAVITY

The oral cavity is bounded anteriorly and laterally by the teeth, superiorly by the hard and soft palate, and inferiorly by the mylohyoid muscle and the tongue in the floor of the mouth. The oral cavity continues posteriorly into the oropharynx. The palatoglossal arches, which contain the palatoglossus muscles, mark the boundary between the oral cavity and the oropharynx. The tongue is composed of skeletal muscles and is covered by a mucous membrane containing receptors for general sensations and taste. The dorsal surface of the tongue is divided into oral (anterior two thirds) and oropharyngeal (posterior one third) parts by the sulcus terminalis, a V-shaped groove, the apex of which points posteriorly. In the midline, at the apex of sulcus terminalis, is a small pit called the foramen cecum,

Clinical Correlate

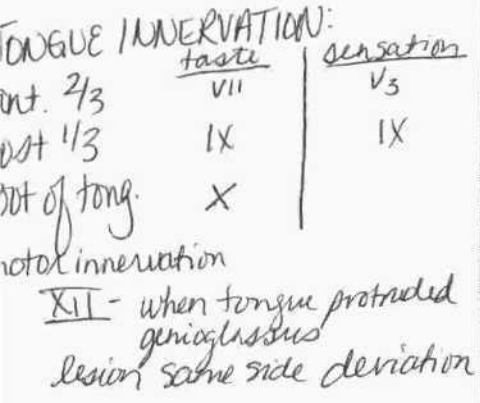
Argyll Robertson pupils may be seen in patients with tabes dorsalis caused by tertiary neurosyphilis. Tabetic patients present with pain, paresthesias, and polyuria.



Clinical Correlate

Lesions of the Hypogiossal Nerve

Lesions of the hypogiossal nerve result in deviation upon protrusion of the tongue toward the side of the injured nerve combined with fasciculations and atrophy.



which is a remnant of the opening of the embryonic thyroglossal duct. Four extrinsic muscles, the genioglossus, hyoglossus, styloglossus, and palatoglossus, insert into each half of the tongue. Unilateral contraction of a genioglossus muscle causes the tip of the tongue to deviate to the opposite side. The hyoglossus depresses the sides of the tongue. The styloglossus retracts the tongue and elevates its sides to create a trough for swallowing. The palatoglossus elevates and retracts the posterior part of tongue.

Innervation

The general sensory innervation of the oral cavity, including the teeth, is carried by the maxillary and mandibular divisions of the trigeminal nerve. Sensory branches of four cranial nerves (CN V3, VII, IX, and X) contribute to the sensory innervation of the tongue. The mucosa of the anterior two thirds of the tongue has a dual innervation. General sensation is carried by the lingual nerve of CN V3, and taste except for taste buds on the vallate papillae is carried by the chorda tympani of CN VII. In the posterior one third, the glossopharyngeal nerve carries fibers for both general sensation and taste including the vallate papillae. The mucosa at the base of the tongue (in front of the epiglottis) receives general sensory and taste innervation from the vagus nerve (CN X). Serous glands in the tongue (as well as the submandibular and sublingual glands) are supplied by postganglionic parasympathetic axons from the submandibular ganglion. Preganglionic parasympathetics to the submandibular ganglion are carried in the chorda tympani of CN VII.

All of the muscles of the tongue except the palatoglossus muscle are innervated by the hypogiossal nerve (CN XII). The palatoglossus muscle is innervated by nerve fibers from the vagus nerve (CN X) through the pharyngeal plexus.

INFRATEMPORAL FOSSA

The infratemporal fossa is situated medial to the ramus of the mandible and the zygomatic arch and contains the muscles of mastication, branches of the mandibular nerve of the trigeminal (CN V3), the otic ganglion and its preganglionic and postganglionic fibers, and the chorda tympani of CN VII. The foramen ovale, which lies in the roof of the fossa, transmits the mandibular division and motor root of the trigeminal nerve (CN V3) and preganglionic parasympathetic fibers to the otic ganglion in the lesser petrosal nerve (of CN IX). The foramen spinosum, also in the roof of the fossa, transmits the middle meningeal artery and the meningeal branch of CN V3. The mandibular fossa articulates with the condylar process of the mandible at the temporomandibular joint. Adjacent to the mandibular fossa is the petrotympanic fissure, which communicates with the middle ear cavity and transmits the chorda tympani of CN VII.

Muscles of Mastication

There are four major muscles of mastication: the masseter, temporalis, lateral pterygoid, and medial pterygoid. All but the masseter lie in the infratemporal fossa. The masseter, temporalis, and medial pterygoid muscles elevate the mandible. The lateral pterygoid depresses and protrudes the mandible. The medial and lateral pterygoids protrude the mandible when they contract together and deviate the mandible from side to side in a grinding motion. The anterior belly of the digastric and the mylohyoid are suprahyoid muscles, which also act as muscles of mastication by depressing the mandible. Muscles in the infratemporal fossa and, in general, muscles that move the mandible are innervated by the mandibular nerve of the trigeminal (CN V3). Skin over the mandible plus mucosa of the anterior two thirds of the tongue and adjacent oral cavity is innervated by sensory fibers of CN V3.

Clinical Correlate

Lesions of the Trigeminal **Nerve**

Lesions of the trigeminal nerve are usually associated with altered sensation and pain. Trigeminal neuralgia (tic douloureux) is characterized by episodes of sharp stabbing pain that radiate over the territory supplied by sensory branches of the maxillary or mandibular divisions of the trigeminal nerve. Branches of the ophthalmic division are rarely involved. The pain occurs most frequently in two areas. In most cases of neuralgia, pain radiates over the mandible, extending around the temporomandibular joint, then deep to the external ear, whereas in other cases, pain radiates up the nostril into and around the orbit. The pain is frequently triggered by moving the mandible, smiling, or yawning, or by cutaneous or mucosal stimulation, and it may be caused by pressure on or interruption of the blood supply to the trigeminal ganglion. Lesions to the motor fibers in the trigeminal nerve result in a weakness of muscles of mastication and a deviation of the jaw toward the side of the injured nerve.

PALATE

The palate separates the oral cavity from the nasal cavity and the nasopharynx from the oropharynx. The anterior two thirds of the palate contains a bony skeleton formed by the maxillary and palatine bones and is called the hard palate. The soft palate is the movable posterior third of the palate. It has no bony skeleton and ends posteriorly at a free border accentuated by a midline projection, the uvula. Within the mucosal lining of the hard and soft palates are glands and taste buds. Four pairs of skeletal muscles, the palatopharyngeus, palatoglossus, levator veli palatini, and tensor veli palatini, plus the uvular muscle, attach to the palatine aponeurosis. Both the palatopharyngeus and the palatoglossus muscles elevate the pharynx or position the tongue and soft palate to constrict the opening (the isthmus of the fauces) between the oral cavity and oropharynx during swallowing. The levator veli palatini elevates the soft palate in order to separate the

nasopharynx from the oropharynx to prevent regurgitation of liquids into the nasal cavity during swallowing. The tensor veli palatini muscle tenses the soft palate and pulls open the auditory tube.

Innervation

lesion of f)(→ uvula deviates away or opp. side

All thejnuscles of the soft palate excgrjjfrtr ttip tensor veli palatini receive their moto^innervatigjLfjpja-thg^vagus nerve (CN X). The tensor veli palatini muscle is innervated by the mandibuiar nerve~(CN V3). The inferior aspect of the hard and soft palates receives general sensory innervation from branches of the maxillary nerve (CN V2). Secretomotor (postganglionic parasympathetic) fibers reach mucous glands in the palate from postganglionic cell bodies in the pterygopalatine ganglion.

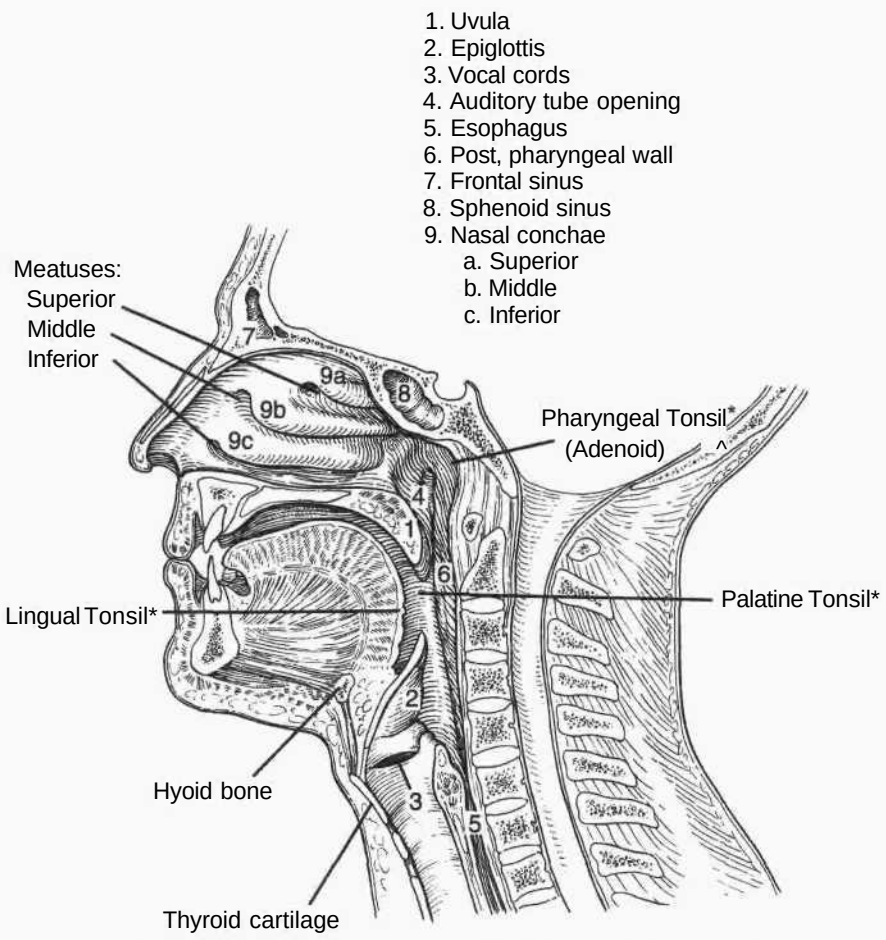
PHARYNX

The pharynx is a fibromuscular tube that extends from the base of the skull to the cricoid cartilage at the level of the sixth cervical vertebra (Fig III-6-16).

The pharynx is divided into three parts:

- The nasopharynx lies above the soft palate posterior to the nasal cavity.
- The oropharynx lies between the soft palate and the tip of the epiglottis posterior to the oral cavity.
- The laryngopharynx extends from the epiglottis behind the larynx to the level of the cricoid cartilage.

Inferior to the cricoid cartilage, the laryngopharynx becomes continuous with the esophagus.



'Approximate locations; Actual tonsilar tissue not demonstrated here.

Figure 111-6-16. Sagittal Section of the Head and Neck

Muscles

The pharynx is composed of skeletal muscles that form a circular layer and a longitudinal layer. Three muscles, the superior, middle, and inferior constrictor muscles, form the outer circular layer. These muscles overlap one another posteriorly. The inner longitudinal muscle layer of the pharynx is formed by three longitudinal muscles—the salpingopharyngeus, stylopharyngeus, and palatopharyngeus—which expand and insert into the pharyngeal wall. These three longitudinal muscles function by elevating the pharynx during swallowing.

lesion X -> dysphagia fc.

Innervation

The pharynx is innervated mainly by the glossopharyngeal nerve (CN IX) and the vagus nerve (CN X). All of the pharyngeal muscles are innervated by motor branches of the vagus nerve except for the stylopharyngeus, which is-UmervateH

by the glossopharyngeal nery Sensory innervation of the nasopharynx is provided by the maxillary division of the trigeminal nerve and by branches of the glossopharyngeal nerve. Sensory innervation of the oropharynx is provided by branches of the glossopharyngeal nerve. Sensory innervation of the laryngopharynx is provided by the vagus nerve.

Gag Reflex

IX - aff.
X - eff.

The gag reflex stimulates sensory fibers of the glossopharyngeal nerve (CN IX) in the oropharyngeal mucosa, followed by contraction of the pharyngeal musculature and elevation of the palate. The vagus (CN X) nerve is the motor limb of the gag reflex, inasmuch as muscles that elevate the palate and constrict the pharynx are innervated by its motor fibers. Testing the sensory fibers of CN IX in the wall of the oropharynx or in the posterior one third of the tongue is the most useful way of testing CN IX because evaluation of its skeletal or parasympathetic components is difficult.

Clinical Correlate

Lesions to the Glossopharyngeal Nerve

Lesions to the giossopharyngeal nerve usually occur in conjunction with the vagus (see below) and accessory nerves in jugular foramen syndrome and present reliably only with sensory deficits. The typical CN IX signs include **a** depressed sensory limb of the gag reflex as a result of a loss of all sensations on the affected side of the posterior one third of the tongue and in the wall of the oropharynx.

Middle ear infections may involve the preganglionic parasympathetic axons destined to innervate the otic ganglion and ultimately affect the secretory activity of the parotid gland. A reduction in parotid secretions into the oral cavity is difficult to evaluate, because the submandibular and sublingual salivatory glands, which are innervated by the facial nerve, are contributing to the content of saliva.

Deglutition

Deglutition, or swallowing, is a two-stage process. The first phase is under voluntary control, and the second phase is involuntary.

The first or voluntary stage of deglutition begins after food is taken into the oral cavity. In this stage, the lips and mouth are closed, mastication is completed, and the anterior part of tongue presses a bolus of food against the palate.

In the second or involuntary stage of swallowing, the bolus is pushed into the oropharynx by the posterior part of the tongue, and the muscles in the palatoglossal arches contract behind the bolus. The arrival of the bolus in the oropharynx is detected by sensory fibers of CN IX in the mucosa of the palatoglossal and palatopharyngeal arches and in the intervening tonsillar fossa, and in the posterior

one third of the tongue. Stimulation of visceral sensory fibers in the glossopharyngeal nerve sets in motion a series of muscle contractions in the palate, pharynx, and larynx. First, the soft palate is tensed and elevated against the posterior wall of the pharynx. These palatal movements prevent regurgitation of liquids into the nasal cavity. The pharynx and larynx are elevated, and the inlet of the larynx is reduced. The vocal folds are adducted by intrinsic muscles of the larynx to prevent food or liquid from falling into the trachea. Arrival of the bolus in the oropharynx causes the constrictor muscles to contract in sequence to push the bolus through the laryngopharynx into the esophagus. Laryngeal elevation pulls the larynx up against the epiglottic cartilage, allowing the bolus to pass over the epiglottis into the laryngopharynx and then into the esophagus. The presence of the bolus in the esophagus initiates peristalsis to propel the food through the inferior aspect of the neck, through the thorax, and into the abdomen to the stomach.

Cough Reflex

The cough reflex functions to expel substances from the vestibule of the larynx. The vagus nerve serves as both the afferent and efferent components of the cough reflex through sensory fibers in the internal branch of the superior laryngeal nerve of CN X and the motor fibers in the recurrent laryngeal nerve of CN X.

Cardiac Reflexes

Just distal to the origin of the internal carotid artery from the common carotid, there is a dilatation of the wall of the internal carotid artery, which contains the carotid sinus.

In the carotid sinus are baroreceptors for monitoring blood pressure. These receptors are innervated by visceral sensory branches of the glossopharyngeal and vagus nerves. Stimulation of these nerves causes a reflex firing of the parasympathetic fibers in the vagus nerve, resulting in a decrease in the rate and force of cardiac contraction as well as peripheral vasodilation and a decline in blood pressure. In some individuals, light pressure over the carotid sinus can cause fainting.

At the origin of the external and internal carotid arteries is the carotid body, which is a chemoreceptor for oxygen and carbon dioxide. It is also innervated by sensory branches from the glossopharyngeal and vagus nerves. In the carotid body reflex, changes are detected by chemoreceptors in the carotid body and cause alterations in respiratory rate.

LARYNX

The larynx protects the upper part of the respiratory system and serves as the organ of phonation (Fig III-6-17). The vestibule or superior chamber of the larynx begins at the inlet of the larynx behind the epiglottis and extends to the vestibular (false) folds. The ventricle is a small ellipse-shaped chamber between the vestibular folds and the vocal (true) folds. Below the vocal folds is the infraglottic space. Each vocal fold contains a vocal ligament, which is covered by the thyroarytenoid and vocalis muscles and an overlying mucosa. The rima glottidis is the opening between the vocal folds, and the glottis consists of the rima glottidis and the vocal folds. The larynx consists of three large single cartilages, the cricoid cartilage, thyroid cartilage, and epiglottis, and three pairs of small cartilages. The cricoid is ring-shaped and articulates above with the thyroid cartilage. Inferiorly, below the cricoid cartilage, the larynx is continuous with the trachea. The most important pair of small cartilages, the arytenoids, sit on the superior border of the cricoid cartilage and have muscular and vocal processes. The cricoid, thyroid, and arytenoid cartilages articulate with one another at synovial joints and are interconnected by several muscles that act on the vocal ligaments. The vocal ligaments extend anteriorly from the vocal processes of the arytenoids to attach to the back of the thyroid cartilage.

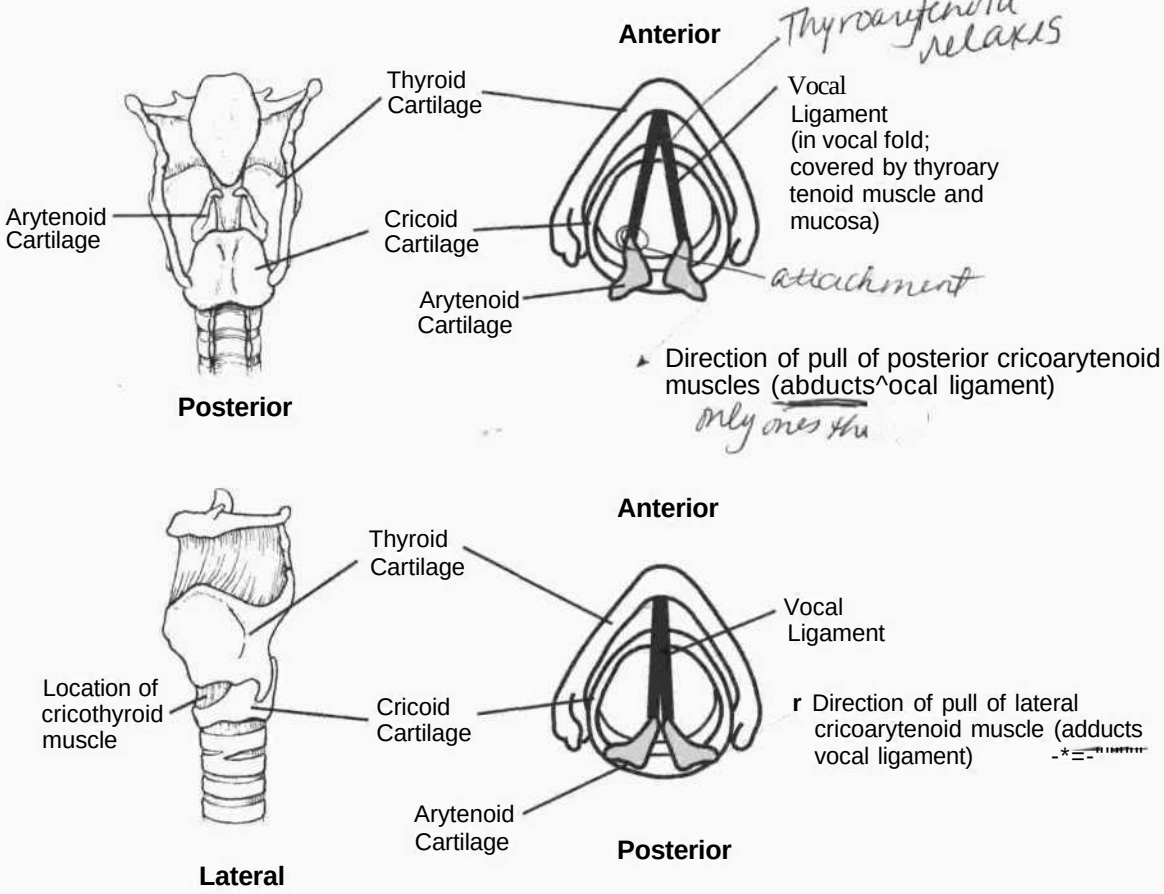


Figure 111-6-17. Larynx

Muscles

Two pairs of antagonistic skeletal muscles act on the vocal ligaments, resulting in changes in the position and tension of the vocal folds in the glottis.

The first pair, the lateral cricoarytenoid and posterior cricoarytenoid muscles, acts on the vocal ligament through attachments to the arytenoid cartilage.

These muscles rotate the arytenoid cartilages and cause the vocal ligaments to be abducted or adducted, resulting in the rima glottidis being opened or closed.

The lateral cricoarytenoid muscle adducts the vocal ligaments. Full adduction of the vocal ligaments causes the vocal folds to meet in the midline, closing off the air passage during swallowing. When the vocal ligaments are partially adducted, air passing between the vocal folds causes the folds to vibrate during phonation.

The posterior cricoarytenoid is the only muscle that abducts the ligaments by rotating the arytenoid cartilages in a direction opposite to that caused by the action of the lateral cricoarytenoid muscles.

The second pair of muscles, the thyroarytenoid and cricothyroid, relax and tense the vocal ligaments, respectively. Contraction of the thyroarytenoid muscles pulls the arytenoid cartilages closer to the thyroid and relaxes the vocal ligaments. The vocalis muscle, which is the medial part of the thyroarytenoid, adjusts the tension on small segments of the vocal ligament. The cricothyroid muscles, which lie on the anterior aspect of the larynx between the cricoid and thyroid, tense the vocal ligament by rocking the superior aspect of the thyroid anteriorly at its articulation with the cricoid, increasing the distance between these two cartilages.

Innervation

Two branches of the vagus nerve innervate all muscles of the larynx and carry sensory fibers from the laryngeal mucosa.

The recurrent laryngeal nerve innervates all muscles of the larynx except for the cricothyroid and provides sensory innervation of the laryngeal mucosa below the vocal folds (Fig III-6-18).

Sup. laryngeal

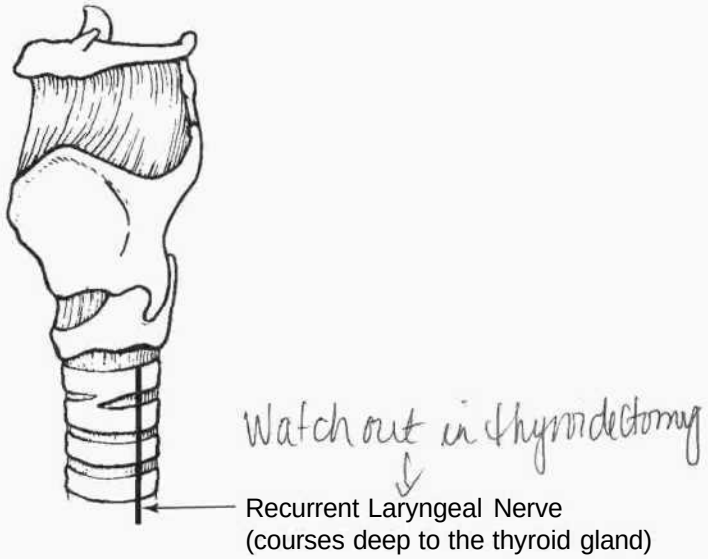


Figure 111-6-18. Laryngeal Innervation

The superior laryngeal nerve through its external and internal branches provides the remainder of motor and sensory innervation of the larynx.

- The external branch of the superior laryngeal nerve innervates the cricothyjoid muscle and fibers to supply the inferior constrictor muscle of the pharynx.
- The internal branch of the superior laryngeal nerve provides sensory innervation of laryngeal mucosa above the vocal folds.

Clinical Correlate

Vagus Nerve Lesions

Lesions of the vagus nerve result in a drooping of the palate ipsiiaterai to the injured nerve and a deviation of the uvula to the opposite side. Dysphagia, a difficulty in swallowing, and nasal speech may also be evident and may be accompanied by nasal regurgitation of liquids.

Vagus nerve lesions, which include laryngeal nerves, also result in a paralysis of the vocal cord musculature. The cord will assume a fixed position midway between abduction and adduction, resulting in speech that is hoarse and weak. Vagus nerve lesions may also result in a loss of the motor limb of the gag reflex and the cough reflex.

Lesions of the superior laryngeal nerve are largely asymptomatic, because its fibers are mainly sensory. If the motor fibers to the cricothyroid are affected in the external branch, there may some mild hoarseness and a slight decrease in vocal strength.

Both recurrent laryngeal nerves are susceptible to injury in surgical procedures involving the thyroid gland. Lesions of a recurrent laryngeal nerve result in a fixed vocal cord and transient hoarseness. Evaluation of the vagus nerve includes examination of palatal movements when the patient says "Aah," because the palate moves during vocalization. The left recurrent laryngeal nerve is injured more frequently than the right owing to its longer course through the superior mediastinum and the neck. The right recurrent laryngeal nerve is found only in the neck.

if paralysis or weakness of vocal cords → maybe problem or lesion in thorax

Muscles

Table III-6-4 summarizes the skeletal muscles innervated by cranial nerves.

Table III-6-4. Skeletal Muscles Innervated by Cranial Nerves

Muscles Derived From a Pharyngeal Arch	Cranial Nerve	Muscles	Skeletal Elements
1st arch—mandibular (V3 innervates muscles that move mandible plus two tensors)	**Trigeminal** **Mandibular Nerve (V3)**	Four muscles of mastication: Masseter Temporalis Lateral pterygoid Medial pterygoid, plus Digastric (anterior belly) Mylohyoid Tensor tympani Tensor veli palatini	Mandibular process Maxillary process (Meckels cartilage) Malleus Incus Sphenomandibular ligament

(continued)

Table III-6-4 *(continued)*

Muscles Derived From a Pharyngeal Arch	Cranial Nerve	Muscles	Skeletal Elements
2nd arch—hyoid (VII innervates muscles that change the shape of an opening on the face)	**Facial (VII)**	Orbicularis oculi Orbicularis oris Buccinator and others, plus Digastric (posterior belly) Stylohyoid Stapedius	Hyoid (superior part) Styloid process Stapes Stylohyoid ligament
3rd arch (IX innervates only one muscle, the stylopharyngeus)	**Glossopharyngeal (IX)**	Stylopharyngeus	Hyoid (inferior part)
4th arch	**Vagus (X) superior laryngeal (external branch)**	Cricothyroid Inferior Constrictor	Thyroid cartilage
Muscles of palate and pharynx (controversial origin) (pharyngeal branches of X innervate all muscles of palate except tensor veli palatini) (pharyngeal branches of X innervate all muscles of pharynx except stylopharyngeus and inferior constrictor)	**Vagus (X) pharyngeal branches to pharyngeal plexus**	Levator Veli Palatini Uvular Muscle Superior/ Middle Constrictors Salpingopharyngeus Palatoglossus Palatopharyngeus	
5th arch	**Lost**		
6th arch (recurrent laryngeal of X innervates all intrinsic muscles of larynx except cricothyroid)	**Vagus (X) recurrent laryngeal**	Lateral cricoarytenoid Posterior cricoarytenoid Transverse arytenoid Oblique arytenoid Thyroarytenoid (vocalis) Aryepiglottics Inferior constrictor	Cricoid, arytenoid, corniculate, cuneiform cartilages
Muscles of myotome origin (XI innervates two muscles that shrug shoulder or turn head)	**Accessory (XI)**	Trapezius Sternocleidomastoid	Scapula Skull
Occipital myotome muscles (XII innervates all tongue muscles (ending in -glossus except palatoglossus)	**Hypoglossal (XII)**	Genioglossus Hyoglossus Styloglossus	
Preoptic myotome muscles (III innervates all muscles that move the eyeball except superior oblique and lateral rectus)	**Oculomotor** (III)	Superior, inferior, and medial rectus; inferior oblique, levator palpebrae superioris	
	Trochlear (IV)	Superior oblique	
	Abducens (VI)	Lateral rectus	

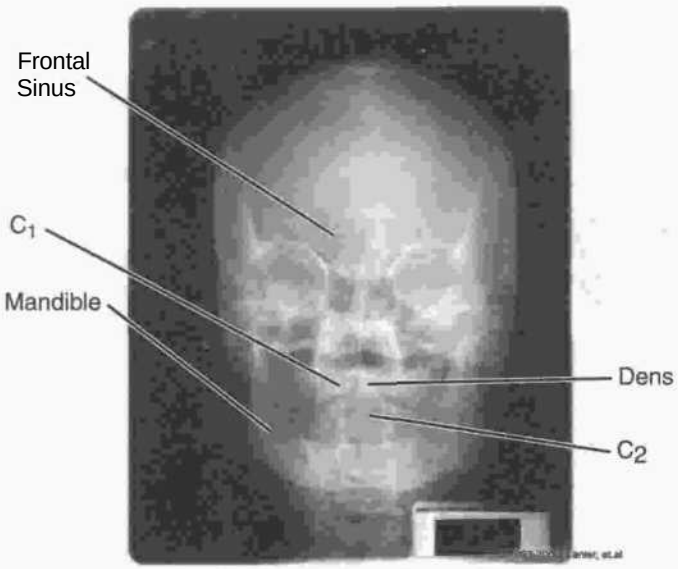


Figure 111-6-19. Head and Neck: Posteroanterior View of Skull

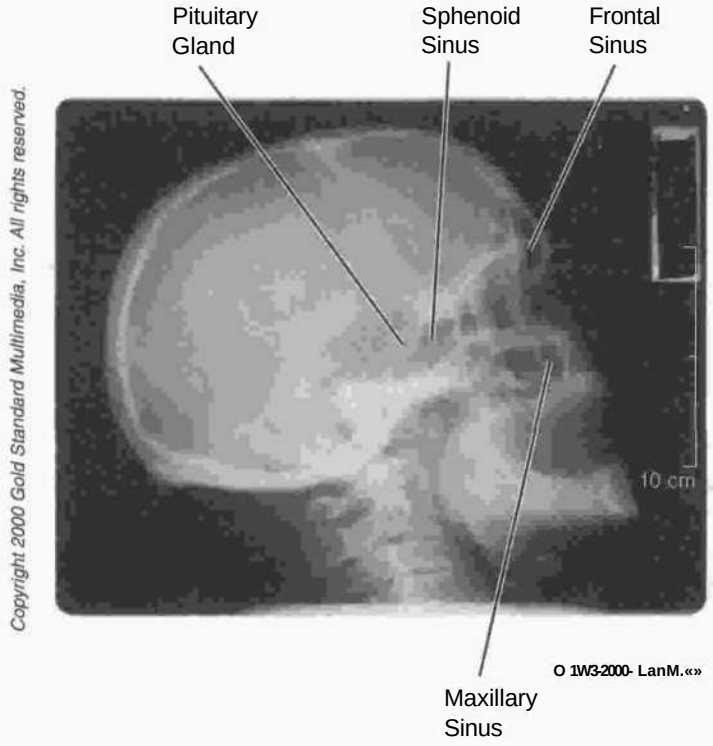


Figure 111-6-20. **Head and Neck: Lateral Skull**

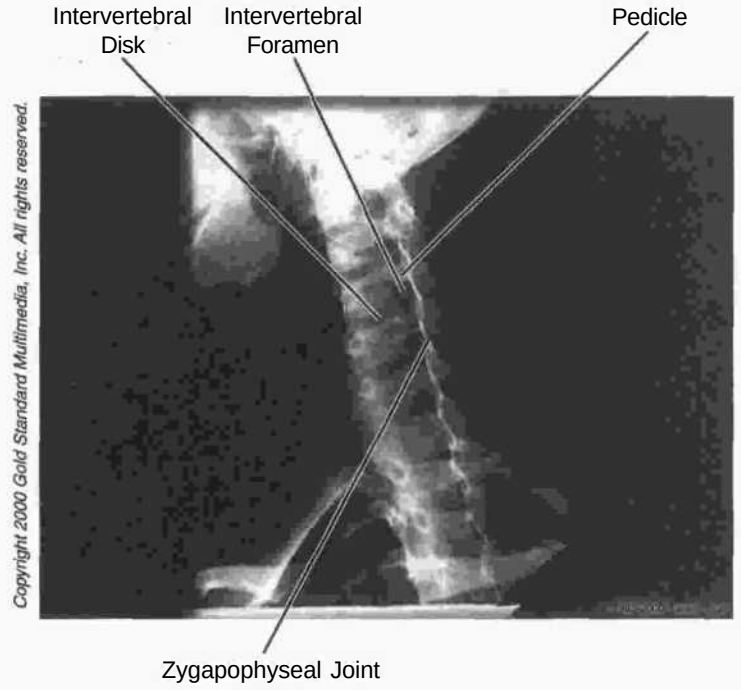


Figure 111-6-21. Head and Neck: Oblique Cervical Spine

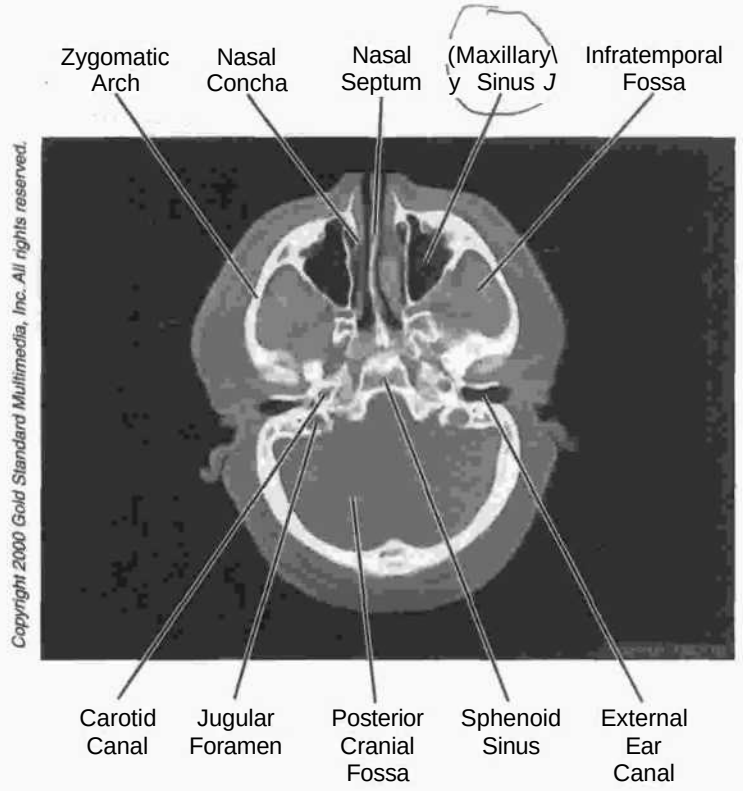


Figure III-6-22. Head and Neck: CT, Skull

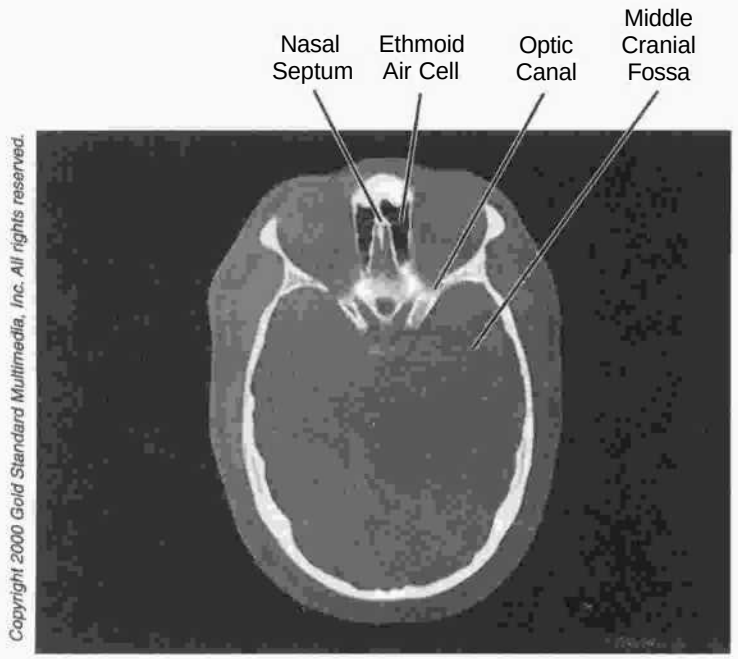


Figure 111-6-23. Head and Neck: CT, Skull

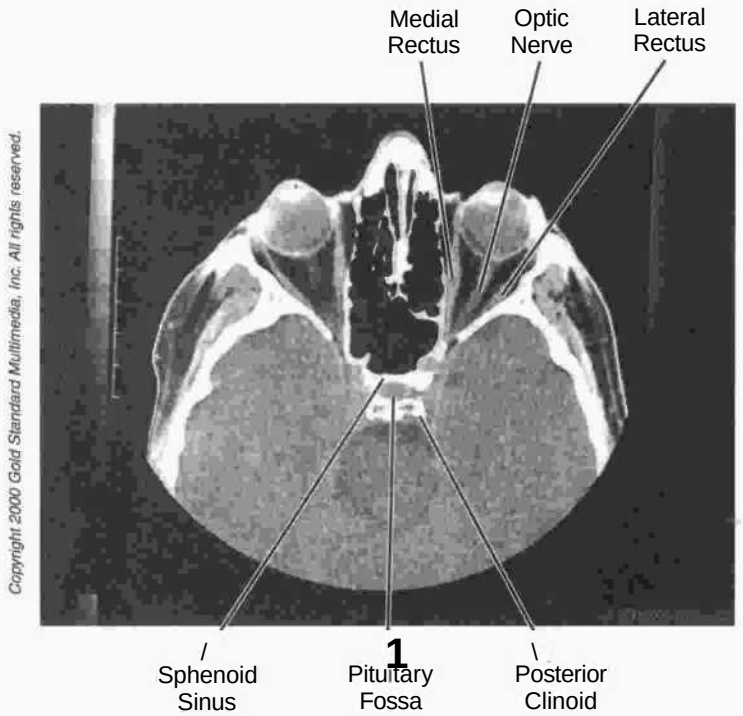


Figure 111-6-24. Head and Neck: CT, Orbit

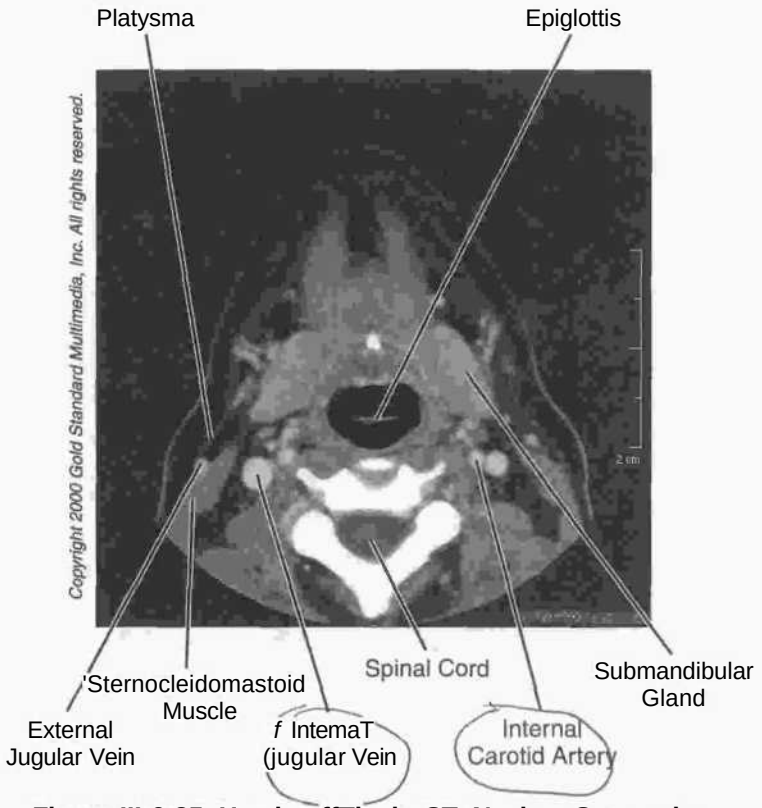


Figure III-6-25. Head anffTleck: CT, Neck at C_2 vertebra

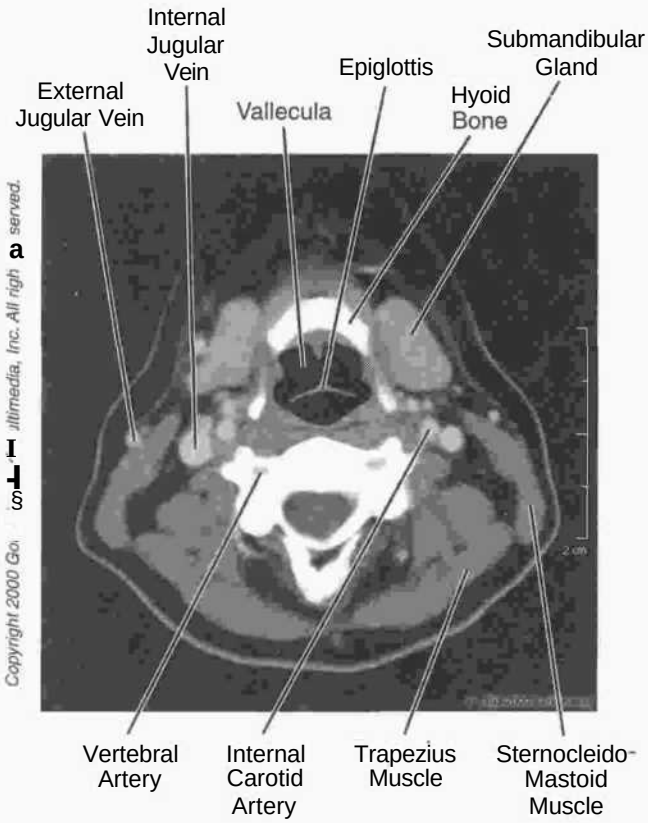


Figure 111-6-26. Head and Neck: CT, Neck at C_3

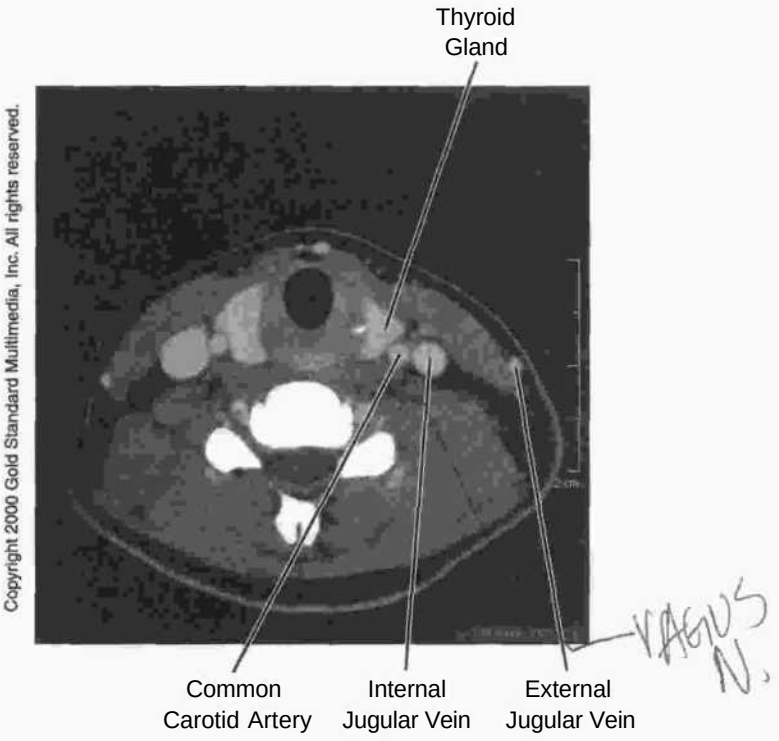


Figure IH-6-27. Head and Neck: CT, Neck at C_5

SECTION IV

Neuroscience

Peripheral Nervous System

1

Neural tube
Skeletal motor neurons
pregang. aut. neurons

Neural crest
sensory neurons
postganglionic autonomic neurons → all ganglia in PNS (either)
chromaffin
Schwann cells

CELLULAR ELEMENTS

The peripheral nervous system (PNS) contains cranial and spinal nerves that consist of neurons that give rise to axons, which grow out of the neural tube, and neurons derived from neural crest cells. Skeletal motor neurjQps and axons of preganglionic autonomic neurons are derived from the neural tube (Figs IV-1-1, IV-1-2, IV-1-3, IV-1-4, and IV-1-5).

Neural crest cells form sensory neurons and postganglionic autonomic neurons. The neuronal cell bodies of these neurons are found in ganglia. Therefore, all ganglia found in the PNS contain either sensory or postganglionic autonomic neurons and are derived from neural crest cells.

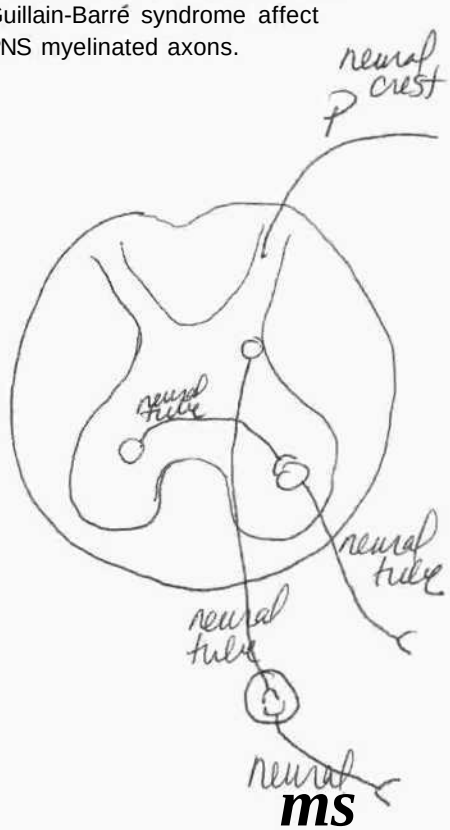
Chromaffin cells are neural crest cells, which migrate into the adrenal medulla to form postganglionic sympathetic neurons.

Schwann cells are glial cells that make myelin for PNS axons. Unlike oligodendrocytes, which make CNS myelin, individual Sclywann cells myelinate only a small part of a singkjxon. At the junction between two Schwann cells, there are dlscontinuitiesjn the myelin called nodes of Ranvier. Here, action potentials skip from node to node in saltatory conduction.

Clinical Correlate

Peripheral Neuropathies

Peripheral neuropathies such as Guillain-Barré syndrome affect PNS myelinated axons.



Clinical Correlate

BeducadJeveJs_ofalpha-fetojiro-lein are seen in mothers of fetuses with Down syndrome.

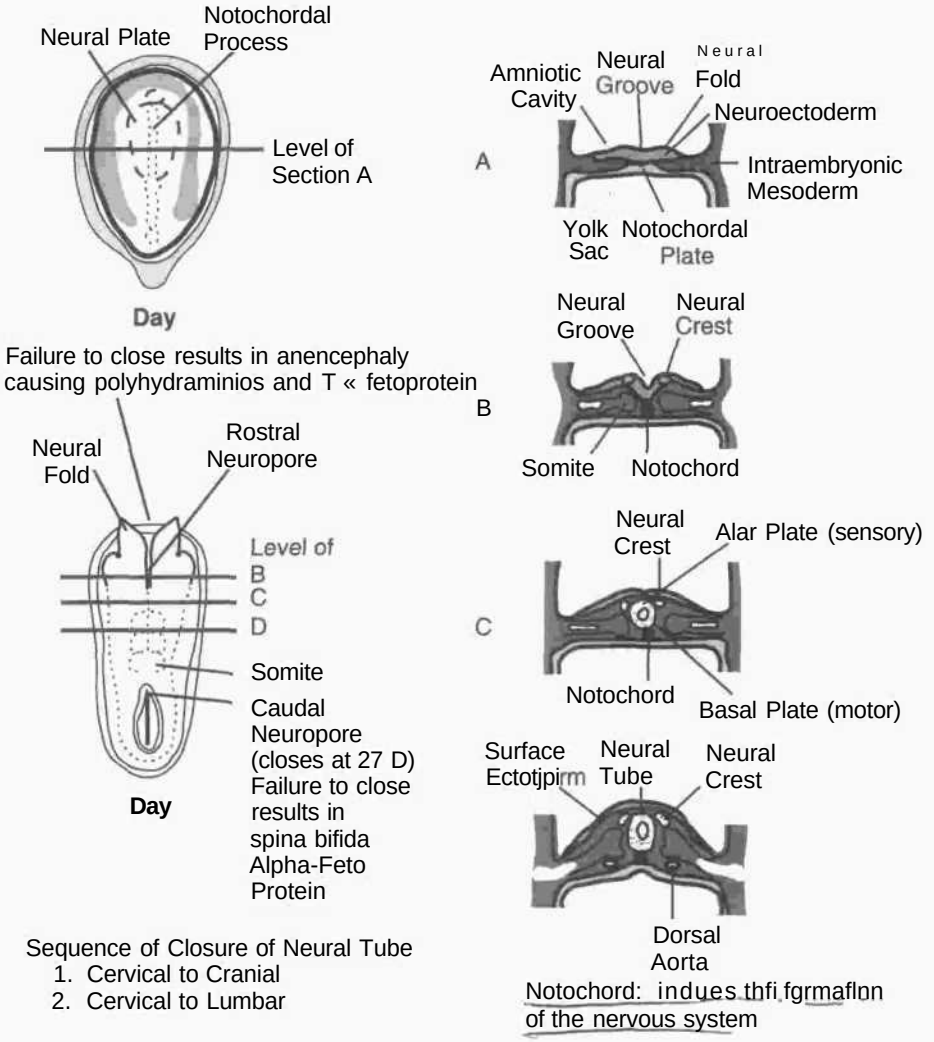


Figure IV-1-1. Third Week-Neurulation

Anencephaly: ↑AFP

any ↑AFP caused by neural tube defect

Table IV-1-1. Germ Layer Derivatives

Ectoderm	Mesoderm	Endoderm
Surface ectoderm	Muscle	**Forms Epithelial parts of:**
Epidermis	Smooth	Tonsils
Hair	Cardiac	Thymus
Nails	Skeletal	Pharynx
Inner ear	Connective tissue	Larynx
Enamel of teeth	All serous membranes	Trachea
Lens of eye	Bone and cartilage	Bronchi
Anterior pituitary	Blood, lymph, cardiovascular organs	Lungs
Parotid gland	Adrenal cortex	Urinary bladder
Neuroectoderm	Gonads and internal reproductive organs	Urethra
Neural tube	Spleen	Tympanic cavity
Central nervous system	Kidney and ureter	Auditory tube
Retina	Duramater	GI tract
Pineal gland		
Neurohypophysis		**Forms parenchyma of:**
dial Cells		Liver
		Pancreas
Neural crest		Tonsils
Adrenal Medulla		Thyroid gland
Ganglia		Parathyroid glands
Sensory		Glands of the GI tract
Autonomic		Submandibular gland
Pigment cells		Sublingual gland
Schwann cells		
Satellite cells		
Meninges		
Pia and arachnoid mater		
Pharyngealarch cartilage		
Odontoblasts		
Parafollicular (C) cells		
Aorticopulmonary septum		
Endocardial cushions		

Yolk sac derivatives:

Primordial germ cells
Early blood and blood vessels
Epitheiia of the gut not derived from endoderm

AUTONOMIC NERVOUS SYSTEM: GENERAL ORGANIZATION

The Autonomic Nervous System (ANS) is responsible for the motor innervation of smooth muscle, cardiac muscle, and glands of the body. The ANS is composed of two divisions: (1) Sympathetic and (2) Parasympathetic.

In both divisions there are two neurons in the peripheral distribution of the motor innervation.

1. Preganglionic neuron with cell body in CNS
2. Postganglionic neuron with cell body in a ganglion in the PNS.

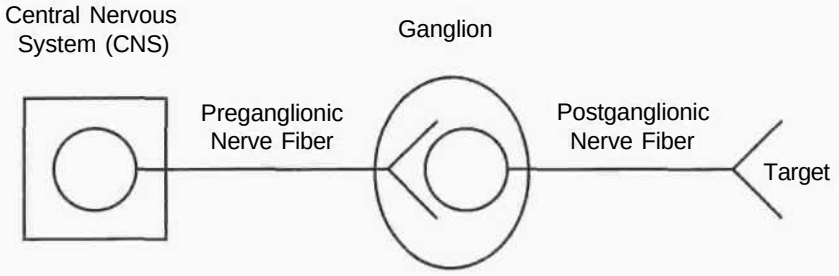


Figure IV-1-2. Autonomic Nervous System

Table IV-1-2. Sympathetic = ThoracolumbarOutflow

Origin	Site of Synapse	Innervation
Spinal cord levels T1-L2	Sympathetic chain ganglia (paravertebral ganglia)	Smooth muscle, cardiac muscle and glands of body wall and limbs, head and thoracic viscera.
Thoracic splanchnic nerves T5-12	Prevertebral ganglia, (e.g. celiac, aorticorenal superior mesenteric ganglia	Smooth muscle and glands of the foregut and midgut
Lumbar splanchnic nerves L1, 2	Prevertebral ganglia, e.g. inferior mesenteric and pelvic ganglia	Smooth muscle and glands of the pelvic viscera and hindgut

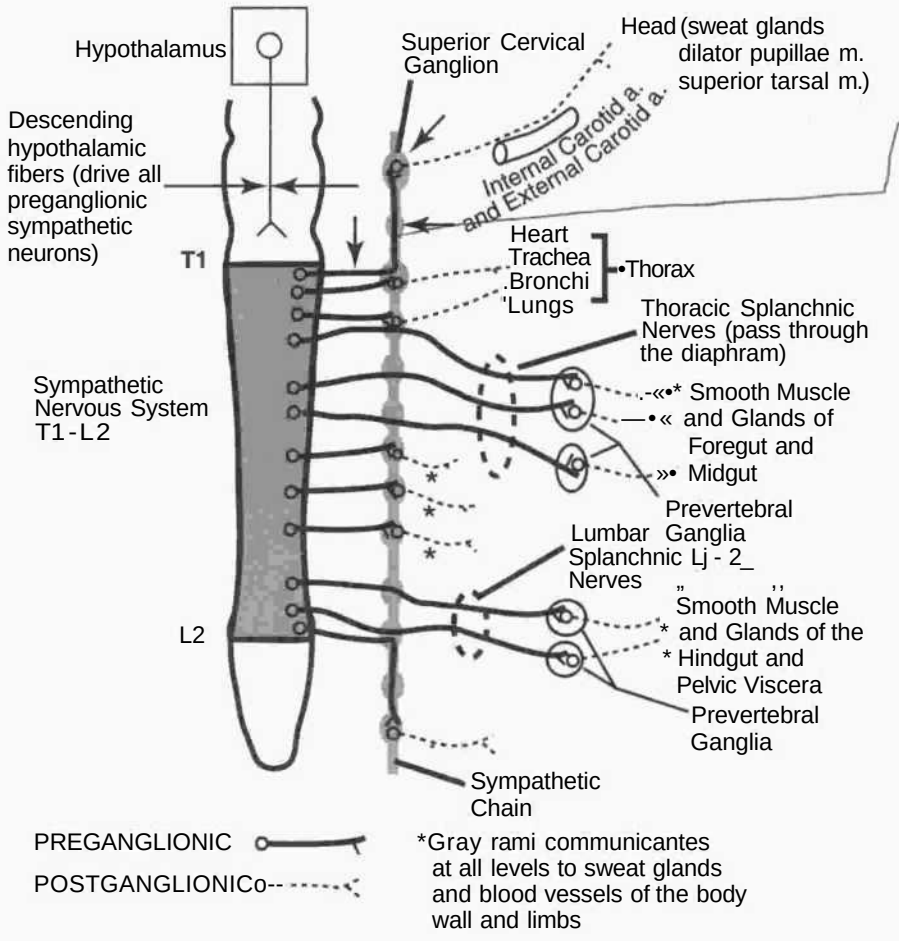


Figure IV-1-3. Overview of Sympathetic Outflow

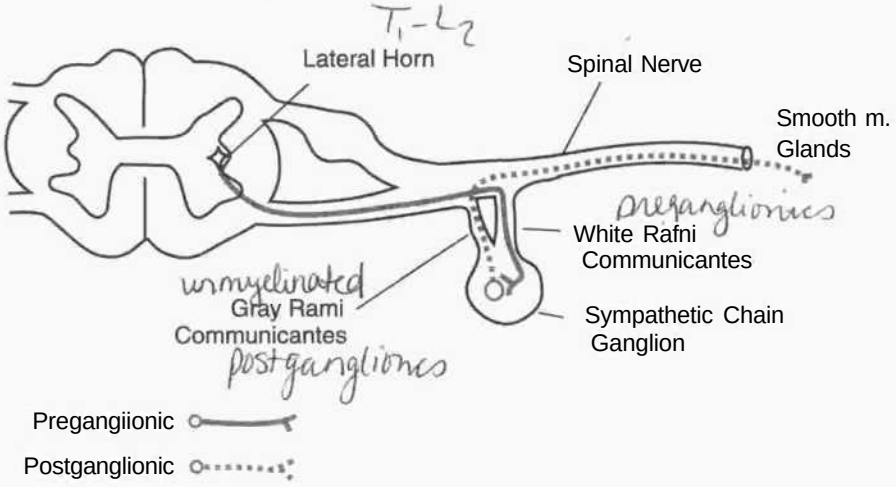


Figure IV-1-4. Spinal Cord Showing Sympathetic Outflow T1 ~ L2

Clinical Correlate

Lesions at arrows result in Homer's syndrome.
- partial ptosis
- miosis
- anhydrosis (w/o sweat)

lesion JJ\.dlDt- hypothalamic fibers → also can give Horners syndrome.

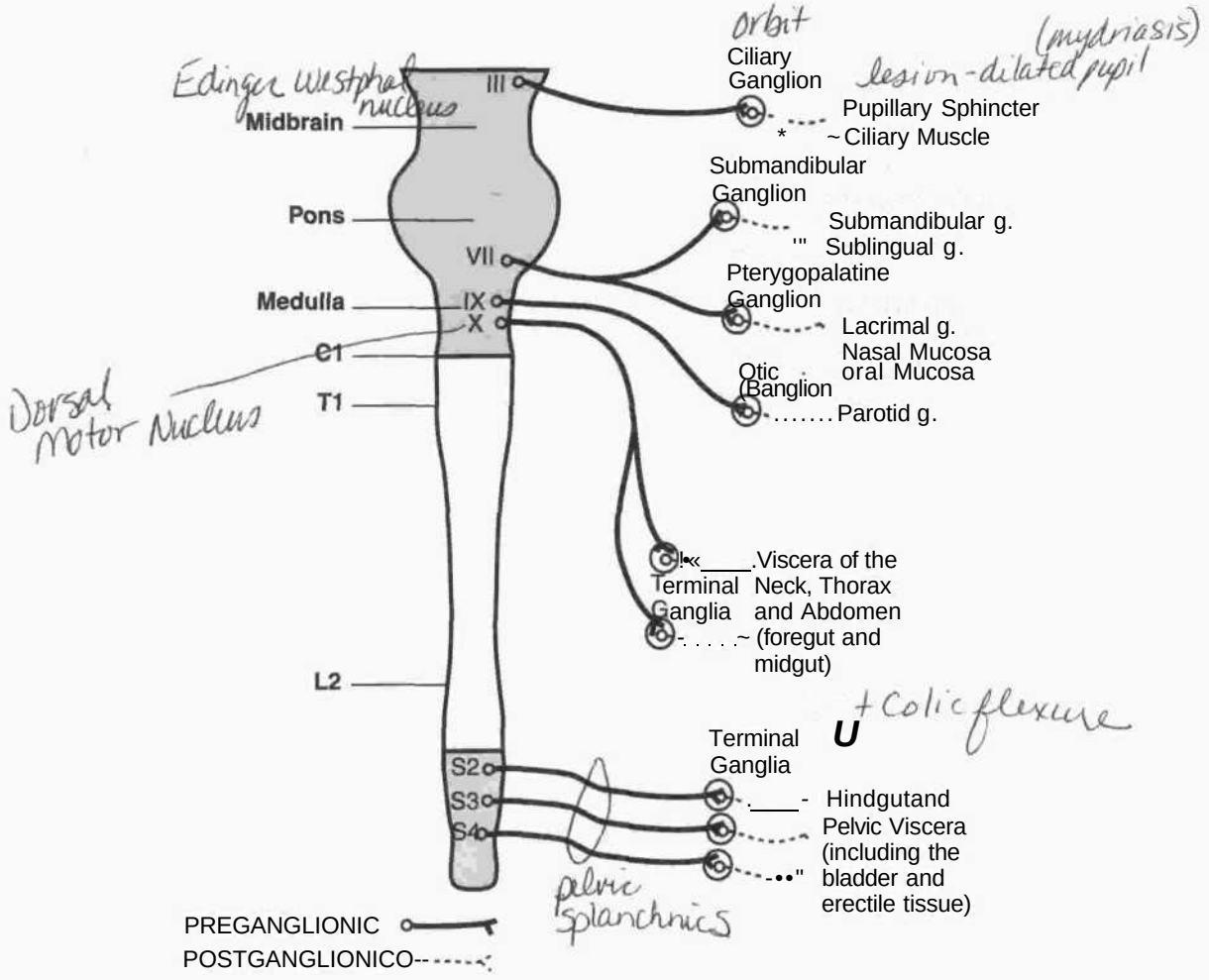


Figure IV-1-5. Overview of Parasympathetic Outflow

Table FV-1-3. Parasympathetic = Craniosacral Outflow

Origin	Site of synapse	Innervation
Cranial nerves III. VIIJX	4 cranial ganglia	Glands and smooth muscle of the head
Cranial nerve X	Terminal ganglia (in or near the walls of viscera)	Viscera of the neck, thorax, foregut, and midgut
Pelvic splanchnic nerves S 2, 3, 4	Terminal ganglia (in or near the walls of viscera)	Hindgut and pelvic viscera (including the bladder and erectile tissue)

Central Nervous System

2

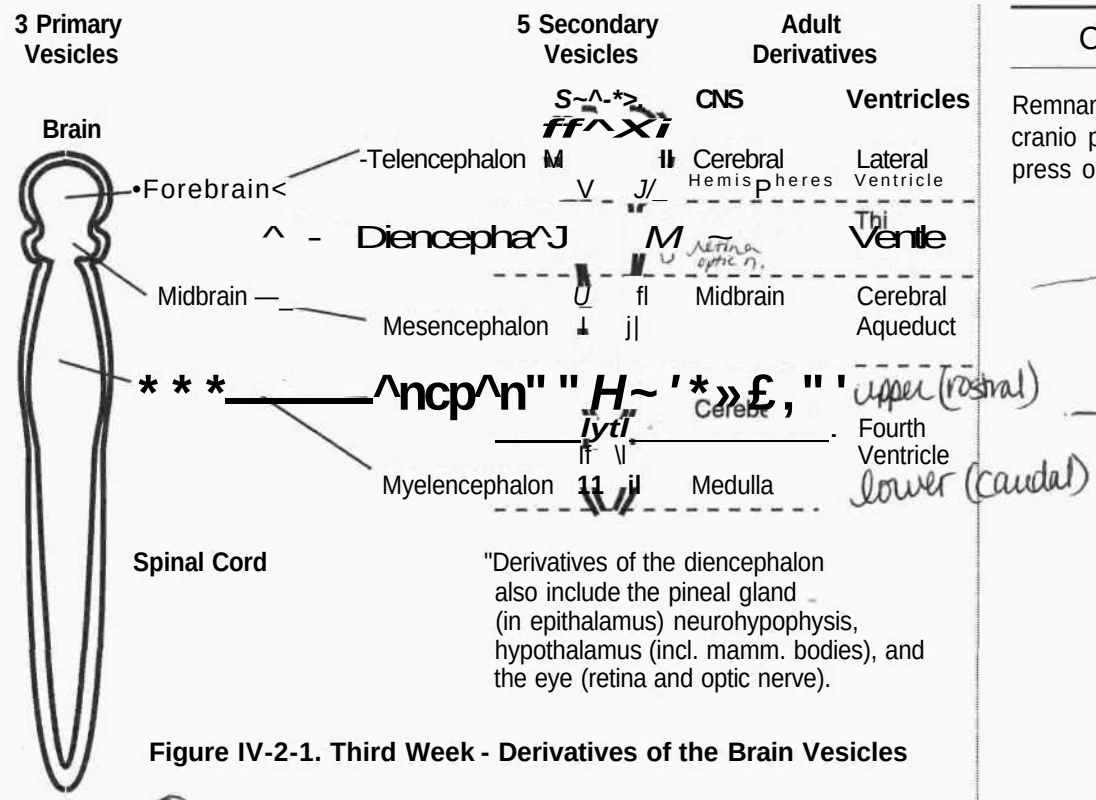


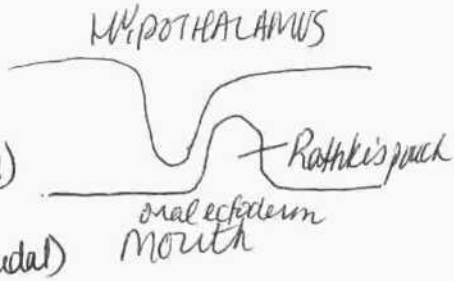
Figure IV-2-1. Third Week - Derivatives of the Brain Vesicles

The roots of spinal nerves enter or exit segmentally from the spinal cord.

The anterior pituitary (adenohypophysis) is an outgrowth of oral ectoderm (Rathke's pouch) and is not derived from the CNS.

Clinical Correlate

Remnants of Rathke's pouch form cranio pharyngiomas that compress optic chiasm.



Clinical Correlate

Axonal polyneuropathies produce distal "glove and stocking" weakness or sensory deficits, and are related to axonal transport failure. Diabetes mellitus patients present with sensory neuropathies.

Clinical Correlate

Axons utilize anterograde and retrograde axonal transport to move subcellular elements toward or away from the axon terminal. Anterograde transport utilizes microtubuTes, is mediated by (Sinesir), and moves vesicles and~protein to the axon terminal. Retrograde axonal transport also uses microtubules, is mediated by|6yneln) and transportsjyso-SQrueg and recycled membrane. Exogenous substances such as herpesyirus, polio virus, and tetanus toxin affect neuron cell bodies as a result of retrofitide axonal transport.

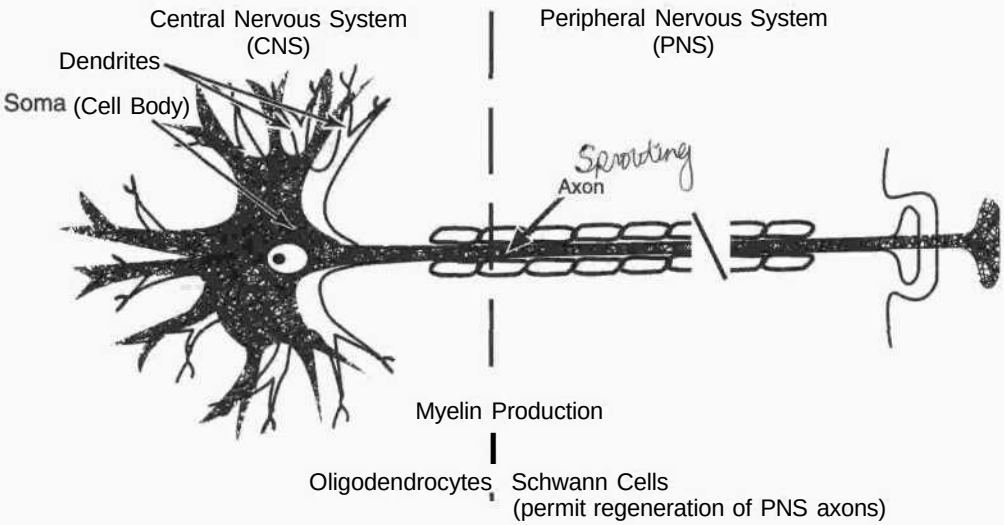
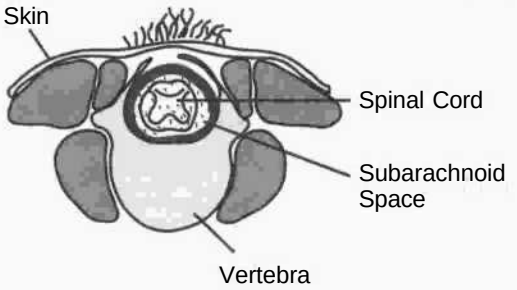
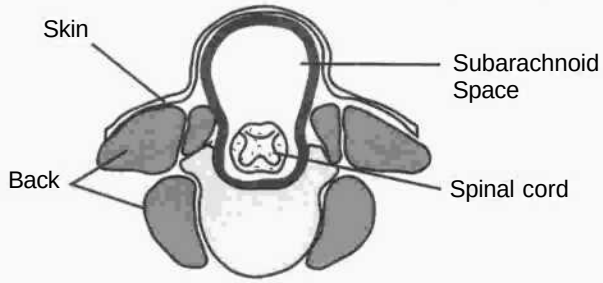


Figure IV-2-2.The **Neuron**

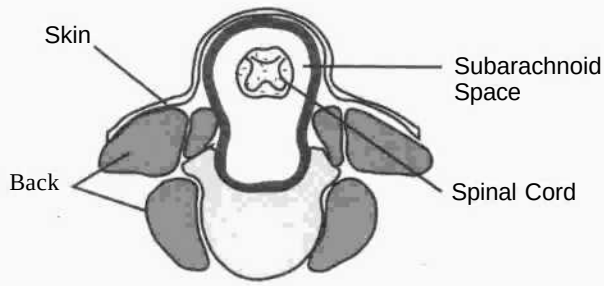
A. Spina Bifida Occulta: a defect in the vertebral arches; asymptomatic.



B. Spina Bifida with Meningocele: occurs when the meninges project through the vertebral defect; elevated alpha-feto protein levels.



C. Spina Bifida with Meningomyelocele: occurs when the meninges and spinal cord project through the vertebral defect; elevated alpha-feto protein levels.



D. Spina Bifida with Myeloschisis: results in an open neural tube that lies on the surface of the back; most severe variation; elevated alpha-feto protein levels.

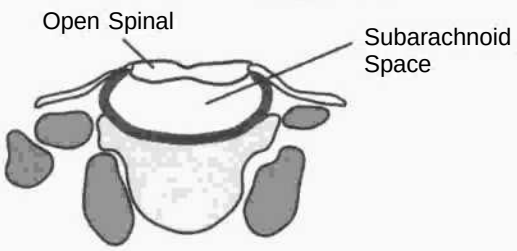


Figure IV-2-3. Malformations of the Vertebral Column or Spinal Cord

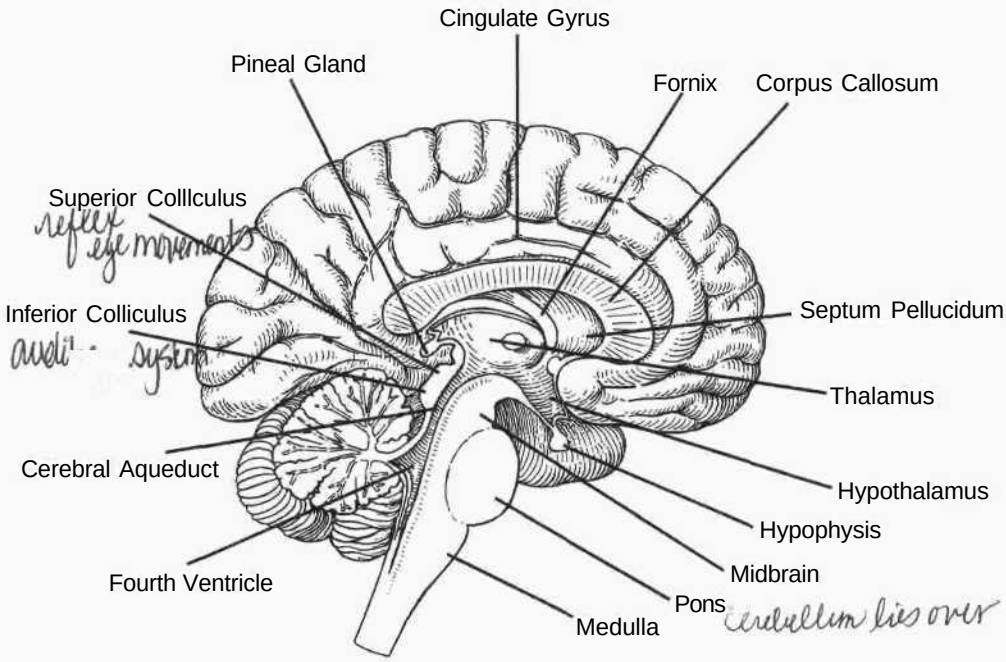


Figure IV-2-4 Brain: Sagittal Section

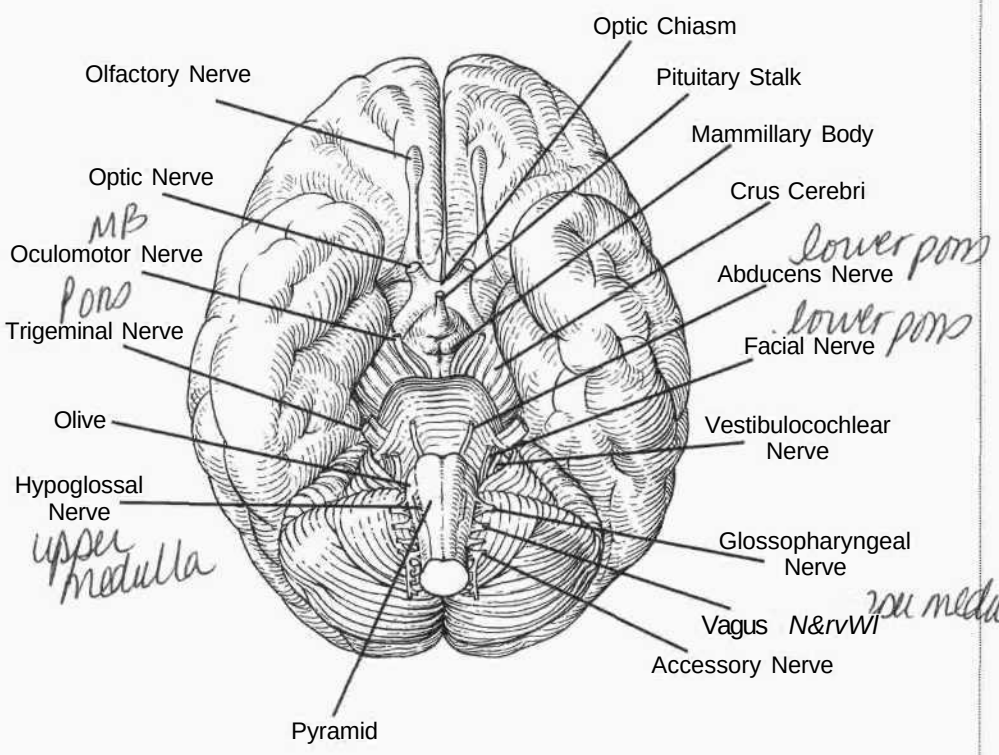


Figure IV-2-5. Brain: Inferior View

Cellular Elements

Neurons of the neural tube form all CNS interneurons, skeletal motoneurons, and preganglionic autonomic neurons.

Skeletal motoneurons and preganglionic autonomic neurons send their axons out of the CNS in cranial and spinal nerves.

Glial cells derived from the neural tube include ependymal cells, astrocytes, and oligodendrocytes.

Ependymal cells line the ventricles. Cilia on their luminal surfaces move CSF.

Astrocytes control the microenvironment of CNS neurons and participate in the blood-brain barrier. They also guide migrating cortical neurons in development and proliferate in response to CNS injury.

Oligodendrocytes form myelin for axons in the CNS. An individual oligodendrocyte is able to myelinate as many as 50 axons. In the CNS, myelination begins during the fourth month of development and continues into the second decade of life. Microglia are derived from mesoderm, migrate into the CNS, and act as scavengers to devour cellular debris after injury.

Clinical Correlate

Multiple Sclerosis

Multiple sclerosis is a demyelinating disease, which affects CNS axons including the optic nerve, but not other nerves.

The Ventricular System

3

The brain and spinal cord float within a protective bath of cerebrospinal fluid (CSF) which is produced continuously by the choroid plexus within the ventricles of the brain.

Each part of the CNS contains a component of the ventricular system. There are four interconnected ventricles in the brain: two lateral ventricles, a third ventricle, and a fourth ventricle. A lateral ventricle is located deep within each cerebral hemisphere. Each lateral ventricle communicates with the third ventricle via an interventricular foramen (foramen of Monro). The third ventricle is found in the midline within the diencephalon and communicates with the fourth ventricle via the cerebral aqueduct (of Sylvius), which passes through the midbrain. The fourth ventricle is located between the dorsal surfaces of the pons and upper medulla and the ventral surface of the cerebellum. The fourth ventricle is continuous with the central canal of the lower medulla and spinal cord (Fig IV-3-1).

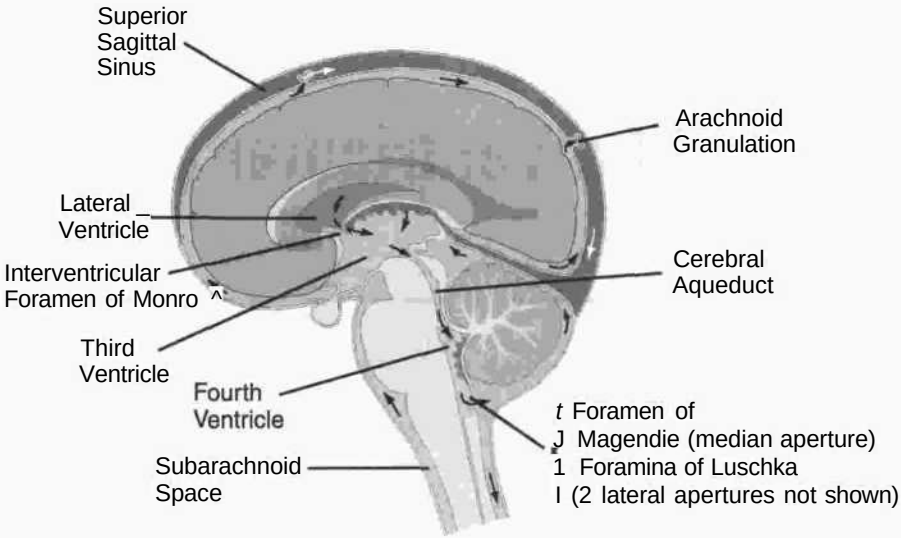


Figure IV-3-1. Sagittal Section of the Brain

CSF DISTRIBUTION, SECRETION, AND CIRCULATION

CSF fills the subarachnoid space and the ventricles of the brain. The average adult has 90 to 150 mL of total CSF, although 400 to 500 mL is produced daily. Only 25 mL of CSF is found in the ventricles themselves.

Approximately 70% of the CSF is secreted by the choroid plexus, which consists of glomerular tufts of capillaries covered by ependymal cells that project into the ventricles (the remaining 30% represents metabolic water production). The choroid plexus is located in parts of each lateral ventricle, the third ventricle, and the fourth ventricle.

CSF from the lateral ventricles passes through the interventricular foramina of Monro into the third ventricle. From there, CSF flows through the aqueduct of Sylvius into the fourth ventricle. The only sites where CSF can leave the ventricles and enter the subarachnoid space outside the CNS are through three openings in the fourth ventricle, two lateral foramina of Luschka and the median foramen of Magendie.

Within the subarachnoid space, CSF also flows up over the convexity of the brain and around the spinal cord. Almost all CSF returns to the venous system by draining through arachnoid granulations into the superior sagittal dural venous sinus.

Normal CSF is a **clear** fluid, isotonic with serum (290-295 mOsm/L).

The pH of CSF is 7J3 (arterial blood pH, 7.40; venous blood pH, 7.36).

Sodium ion (Na^+) concentration is equal in serum and CSF (=138 mEq/L).

CSF has a higher concentration of chloride (Cl~) and magnesium (Mg^{2+}) ions than does serum.

CSF has aJower. concentration of potassium JK^+), calcium (Ca^{2+}), and bicarbonate (HCOp ions, as well as glucose, than does serum.

The concentration of protein (including all immunoglobulins) is much lower in the CSF as compared with serum.

Normal CSF contains 0 to 4 lymphocytes or mononudear cells per cubic millimeter. Although the presence of a few monocytes or lymphocytes is normal, the presence of polymorphonuclear leukocytes is always abnormal, as in bacterial meningitis.

Red blood cells (RBCs) are not normally found in the CSF but may be present after traumatic spinal tap or subarachnoid hemorrhage.

Increased protein levels may indicate a CNS tumor.

Tumor cells may be present in the CSF in cases with meningeal involvement.

The Blood-Brain Barrier and the Blood-CSF Barrier

The chemical integrity of the brain is protected in a different way by two separate systems.

The Blood-Brain Barrier

The blood-brain barrier is formed by capillary endothelium connected by tight junctions. Astrocytes participate in the maintenance of the blood-brain barrier. They have numerous long processes with expanded vascular end-feet, or pedicels, which attach to the walls of capillaries.

Water diffuses across the blood-brain barrier readily, but glucose, the primary energy source of the brain, reguires carrier-mediated transport. Active transport systems are capable of pumping weak organic acids, halides, and extracellular K^+ out of the brain against their respective concentration gradients.

Clinical Correlate

CSF Abnormalities

Hydrocephalus is caused by an excess volume or pressure of CSF, producing ventricular dilatation.

Communicating hydrocephalus is caused by oversecretion of CSF without obstruction in the ventricles or by CSF circulation or absorption problems from the subarachnoid space. Choroid plexus papilloma is a possible cause of oversecretion, a tumor in the subarachnoid space limits circulation, or meningitis may jjmit absorption into the superior sagittal sinus.

Noncommunlcatlng hydrocephalus is caused by obstruction to the CSF flow inside the ventricular system at a foramen of Monro, in the cerebral aqueduct, or in the fourth ventricle. CSF is prevented from exiting through the foramina of Magendie or Luschka in the fourth ventricle into the subarachnoid space.

Normal pressure hydrocephalus results when CSF is not absorbed by arachnoid villi and the ventricles are enlarged, pressing the cortex against the skull. Patients present with £onfusion, ataxia, and urinary incontinence.

TheBlood-CSFBarrier

Tight junctions located along the egithelial cells of the choroid pkxus form the blood-CSF barrier. TransporTrnechanisms are similar to those described for the blood-brain barrier, although the ability of a substance to enter the CSF does not guarantee it will gain access to the brain.

The Spinal Cord

4

GENERAL FEATURES

The spinal cord is housed in the vertebral canal. It is continuous with the medulla, below the pyramidal decussation and terminates as the conus meidullaris at the second lumbar vertebra of the adult. The roots of 31 pairs of spinal nerves arise segmentally from the spinal cord.

Brachial Plexus C5-T1

There are eight cervical pairs of spinal nerves (C1 through C8). The cervical enlargement (C5 through T1) gives rise to the rootlets that form the brachial plexus, which innervates the upper limbs.

There are 12 thoracic pairs of spinal nerves (T1 through T12). Spinal nerves emanating from thoracic levels innervate most of the trunk.

There are five lumbar pairs of spinal nerves (L1 through L5). The lumbar enlargement (L1 through S2) gives rise to rootlets that form the lumbar and sacral plexuses, which innervate the lower limbs.

There are five sacral pairs of spinal nerves (S1 through S5). Spinal nerves at the sacral level innervate part of the lower limbs and the pelvis.

There is one coccygeal pair of spinal nerves. The cauda equina consists of the dorsal and ventral roots of the lumbar, sacral, and coccygeal spinal nerves.

Inside the spinal cord, gray matter is centrally located and shaped like a butterfly. It contains neuronal cell bodies, their dendrites, and the proximal parts of axons. White matter surrounds the gray matter on all sides. White matter contains bun-

dies of functionally similar axons called tracts or fasciculi, which ascend or descend in the spinal cord (Figs IV-4-1 and IV-4-2).

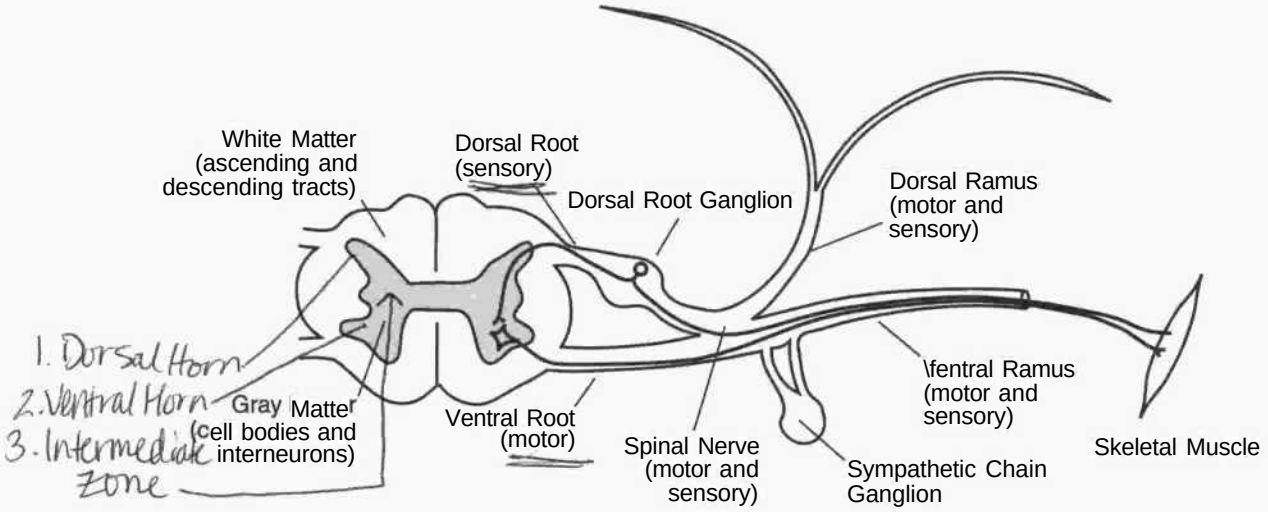


Figure IV-4-1. Cross Section of Spinal Cord and the Components of a Spinal Nerve

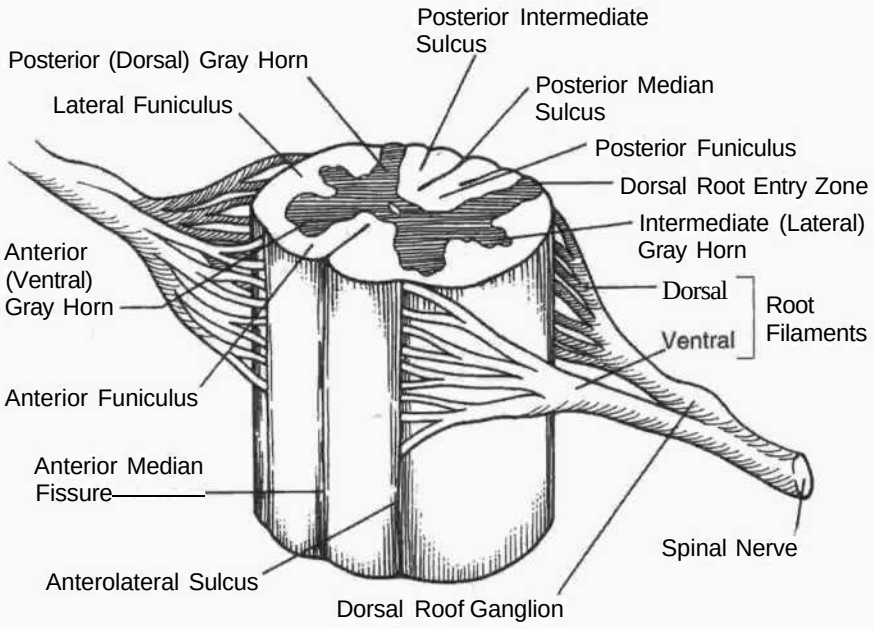


Figure IV-4-2. The Spinal Cord

The gray matter is organized into a dorsal horn, a ventral horn, and an intermediate zone.

Dorsal ***Horn***

The dorsal horn is dominated by neurons that respond to sensory stimulation. All incoming sensory fibers in spinal nerves enter the dorsolateral part of the cord adjacent to the dorsal horn in a dorsal root. Neurons in the dorsal horn project to higher levels of the CNS to carry sensations to the brain stem, cerebral cortex, or cerebellum. Other dorsal horn neurons participate in reflexes.

Ventral ***Horn***

The ventral horn contains alpha and gamma motoneurons. The alpha motoneurons innervate skeletal muscle (extrafusal fibers) by way of a specialized synapse at a neuromuscular junction, and the gamma motoneurons innervate the contractilejj^afusajjnuscle fibers of the muscle spindle. Within the ventral horn, alpha and gamma motoneurons that innervate flexors are dorsal to those that innervate extensors. Alpha and gamma motoneurons that innervate the proximal musculature are medial to those that innervate the distal musculature. Axons of alpha and gamma motoneurons and axons of preganglionic autonomir npiirnns leave the cord by way of a ventral root.

Intermediate Zone

The intermediate zone of the spinal cord from Tl to L2 contains preganglionic sympathetic neuron cell bodies and Clarke's nucleus, which sends unconscious proprioception to the cerebellum.

NEURAL SYSTEMS

There are three major neural systems in the spinal cord that use neurons in the gray matter and tracts or fasciculi of axons in the white matter. These neural systems have components that can be found at all levels of the CNS from the cerebral cortex to the tip of spinal cord. An understanding of these three neural systems is essential to understanding the effects of lesions in the spinal cord, brain stem, and at higher levels of the CNS.

Motor Systems

Voluntary *Innervation* ***of Skeletal Muscle***

Upper and Lower Motoneurons

Two motoneurons, an upper motoneuron and a lower motoneuron, together form the basic neural circuit involved in the voluntary contraction of skeletal muscle everywhere in the body. The lower motoneurons are found in the ventraj^

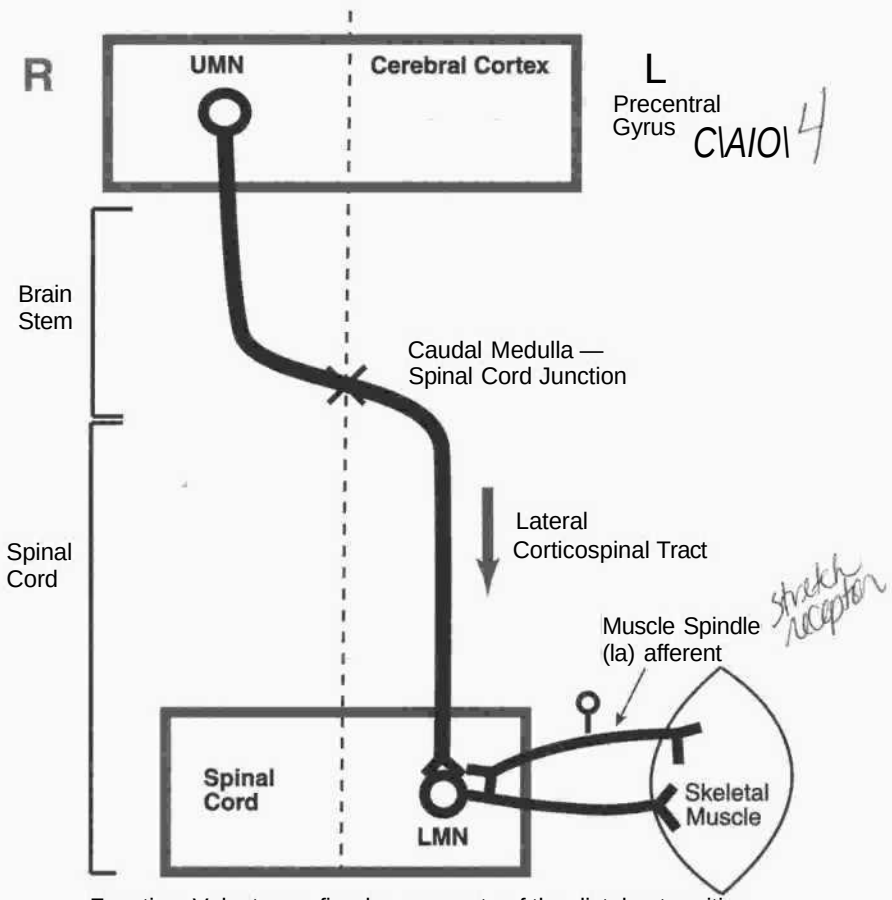
horn, of the spinal cord and in cranial nerve nuclei in the brain stem. Axons of lower motoneurons of spinal nerves exit in a ventral root, then join the spinal nerve to course in one of its branches to reach and synapse directly at a neuromuscular junction in skeletal muscle. Axons of lower motojoeurons in the brain stem exit in a cranial nerve.

To initiate a voluntary contraction of skeletal muscle, a lower motoneuron must be innervated by an upper motoneuron (Fig IV-4-3). The cell bodies of upper motoneurons are found in the brain stem and cerebral cortex, and their axons descend into the spinal cord in a tract to reach and synapse on lower motoneurons, or on interneurons, which then synapse on lower motoneurons. At a minimum, therefore, to initiate a voluntary contraction of skeletal muscle, two motoneurons, an upper and a lower, must be involved. The upper motoneuron innervates the lower motoneuron, and the lower motoneuron innervates the skeletal muscle.

The cell bodies of upper motoneurons are found in the red nucleus, reticular formation, and lateral vestibular nuclei of thebrainstem, but the most important location of upper motoneurons is in thevcerebral cortex} Axons of these cortical neurons course in the corticosBlnal tract.

Abbreviations

LMN = lower motoneuron
UMN = upper motoneuron



Function: Voluntary refined movements of the distal extremities.

Figure IV-4-3. Corticospinal Tract: Descending Motor Pathway

Corticospinal Tract

The primary motor cortex, located in the precentral gyrus of the frontal lobe, and the premotor area, located immediately anterior to the primary motor cortex, give rise to about 60% of the fibers of the corticospinal tract (Fig FV-4-4). Primary and secondary somatosensory cortical areas located in the parietal lobe give rise to about 40% of the fibers of the corticospinal tract.

Fibers in the corticospinal tract leave the cerebral cortex in the internal capsule, which carries all axons in and out of the cortex. Corticospinal fibers then descend through the length of the brain stem in the ventral portion of the midbrain, pons, and medulla.

In the lower medulla, 80 to 90% of corticospinal fibers cross at the decussation of the pyramids and continue in the contralateral spinal cord as the lateral corticospinal tract. The lateral corticospinal tract descends the full length of the cord in the lateral part of the white matter. As it descends, axons leave the tract and enter the gray matter of the ventral horn to synapse on lower motoneurons.

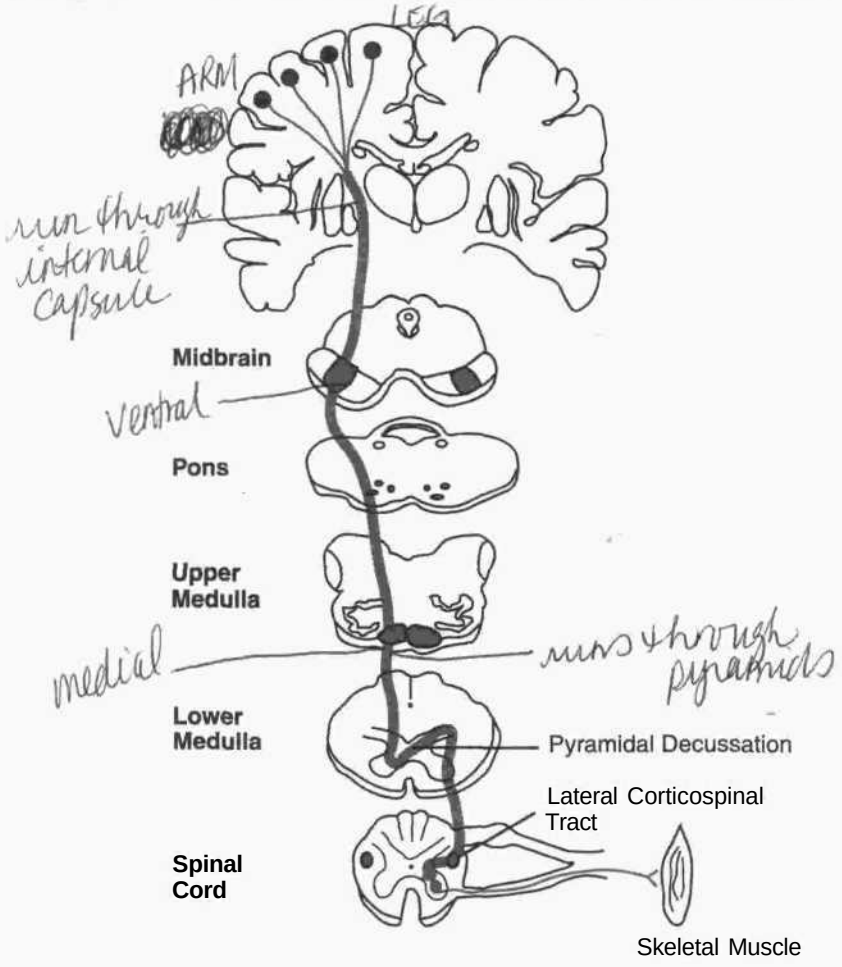


Figure IV-4-4. Corticospinal Tract

Clinical Correlate

Lesions of the Corticospinal Tract

The crossing or decussation of axons of the corticospinal tract at the medulla/spinal cord junction has significant clinical implications. If lesions of the corticospinal tract occur above the pyramidal decussation, a weakness is seen in muscles on the contralateral side of the body; lesions below this level produce an ipsilateral muscle weakness. In contrast to upper motoneurons, the cell bodies of lower motoneurons are ipsilateral to the skeletal muscles that their axons innervate. A lesion to any part of a lower motoneuron will resultin an ipsilateral muscle weakness, at the level of the lesion.

Clinical Correlate

Lesions to la afferent fibers or lower motoneurons produce areflexia.

Important muscle stretch reflexes to test are:

- knee (L_2 - L_4)
- ankle (S^
- biceps (C_5 - C_6)
- triceps (C_7 - C_8)

Reflex Innervation of Skeletal Muscle

A reflex is initiated by a stimulus of a sensory neuron, which in turn innervates a motoneuron and produces a motor response. In reflexes involving skeletal muscles, the sensory stimulus arises from receptors in the muscle, and the motor response is a contraction or relaxation of one or more skeletal muscles. In the spinal cord, lower motoneurons form the specific motor component of skeletal muscle reflexes. Upper motoneurons provide descending control over the reflexes.

Both alpha and gamma motoneurons arejojvexjnotoneiirons that participate in reflexes. Alpha motoneurons are large cells in the ventral 'rinrn that innervate extrafusaLmuscle fibers. A single alpha motoneuron innervates a group of musde fibers, which constitutes a motor unitTtfiFtTasifunit tor voluntary, postural, and reflex activity. Gamma motoneurons supply intrafusal muscle-fibers, which are modified skeletal muscle fibers. The intrafusal muscle fibers form the muscle spindle, which acts as a sensory receptor in skeletal muscle stretch reflexes.

Both ends of the muscle spindle are connected in parallel with the extrafusal fibers, so these receptors monitor the length and rate of change in length of extrafusal fibers. Muscles involved with fine movements contain a greater density of spindles than those used in coarse movements.

Muscle Stretch (Myotatic) Reflex

The muscle stretch (myotatic) reflex is the stereotyped contraction of a muscle in response to stretch of that muscle. The stretch reflex is a basic reflex that occurs in all muscles and is the primary mechanism for regulating musclgjone. Muscle tone is the tejisionjjresent in all resting muscle. Tension is controlled by the stretch reflexes. **

The best example of a muscle stretch or deep tendon reflex is the knee-jerk reflex. Tapping the patellar ligament stretches the quadriceps muscle and its muscle spindles. Stretch of the spindles activates sensory endings (la afferents), and afferent impulses are transmitted to the cord. Some impulses from stretch receptors carried by la fibers monosynaptically stimulate the alpha motoneurons that supply the quadriceps. This causes contraction of the muscle and a sudden extension of the leg at the knee. Afferent impulses simultaneously inhibit antagonist muscles through interneurons (in this case, hamstrings).

Inverse Muscle Stretch Reflex

The inverse muscle stretch reflex monitors muscle tension. This reflex uses Golgi tendon organs (GTOs). These are encapsulated groups of nerve endings that terminate between collagenous tendon fibers at the junction of muscle and tendon. GTOs are oriented in series with the extrafusal fibers and respond to increases in force or tension generated in that muscle. Increases in force in a muscle increase the firing rate of Ib afferent neurons that innervate the GTOs, which, in turn, polysynaptically facilitate antagonists and inhibit agonist muscles.

Muscle tone and reflex activity can be influenced by gamma motoneurons and by upper motoneurons. Gamma motoneurons directly innervate the muscle spindles and regulate their sensitivity to stretch. Upper motoneurons innervate gamma motoneurons and also influence the sensitivity ojjnuscle-spindles to, stretch. Stimulation ot gamma motoneurons causes intrafusal muscle fibers located at the pole^f^eacH muscle spindle to contract, which activates alpEa motoneurons, causing an increaSe~irrrnuscle rone.

FlexorWithdrawalReflex

The flexion withdrawal reflex is a protective reflex in which a stimulus (usually painful) causes withdrawal of the stimulated limb. This reflex may be accompanied by a crossed extension reflex in which the contralateral limb is extended to help support the body.

Clinical Correlate

Upper Motoneuron Versus Lower Motoneuron Muscle Lesions

A fundamental requirement of interpreting the cause of motor weakness in neuroscience cases is the ability to distinguish between a lesion of an upper versus a lower motoneuron. Because a lesion to either an upper or a lower motoneuron produces a weakness in the ability to voluntarily contract skeletal muscles, the key to distinguishing an upper from a lower motoneuron lesion will be the condition of reflexes of the affectedrnuscJesJFig IV-4-5).

A lesion of any part of a lower motoneuron will result in hypoactivejnusclfe-stretch reflexes and a^reduction in muscle tone (hypotonicity) because lower motoneurons form the motor component of the reflex. Therefore, lower motoneuron lesions result in a paresis combined with suppressed or absent muscle stretch reflexes. An early sign of a lower motoneuron lesion is muscle fasciculations, which are twitchesor_contractions of groups of muscle fibers, that may produce a movement visible on the skin. Later, lower motoneuron lesions produce fibrillations, which are invisible 1- to 5-ms potentials, detected with electromyography. Muscles denervated by a lower motoneuron lesion undergo pronounced wasting or atrophy. The constellation of lower motoneuron lesion signs combining paresis with suppressed or absent reflexes, fasciculations, and atrophy is known as a **flaccid paralysis.** With few exceptions, lower motoneuron (LMN) lesions produce a flaccid paralysis ipsilateral and at the level of the lesion.

Neurologically, upper motoneurons including the corticospinal tract have a net overall inhibitory effect on muscle stretch reflexes. As a result, upper motoneuron lesions combine paresis of skeletal muscles with muscle stretch or deep tendon reflexes that are hyperactive or hvpertonic. The hypertonia may be seen as decorticate rigidity (i.e., postural flexiorj_Qf_the arm and extension of the leg) or deCerebrate rigidity (i.e., postural exten^on_oObfi-axnQ-andJeg).depending on the locaF" ttorToF tlte lesion. Lesions above the midbrain produce decorticate rigidity; lesions below themidbrain produce decerebrate rigidity. Upper motoneuron lesions resUlt irTaTrophy of weakened muscles only as a result of disuse, because these muscles can still be contracted by stimulating muscle stretch reflexes.

almost always ipsilateral

Babinski sign

(continued next page)

Clinical Correlate *(continued)*

Upper motoneuron lesions are also accompanied by reversal of cutaneous reflexes, which normally yield a flexor motor response. The best known of the altered flexor reflexes is the Babinski reflex. The test for the Babinski reflex is performed by stroking the lateral surface of the sole of the foot with a slightly painful stimulus. Normally, there is plantar flexion of the big toe. With a lesion of the corticospinal tract, the Babinski reflex is present, which is characterized by extension of the great toe and fanning ot the other toes. Two other flexor reflexes, the abdominal and cremasteric, are also lost in upper motoneuron lesions. The constellation of upper motoneuron lesion signs combining paresis with increases or hyperactive reflexes, djsuse atrophy *nf* skgistai musri<>s, and altered cutaneous reflexes is known as a spastic paresis.

In contrast to lower motoneuron lesions, lesions of upper motoneurons result in a **spastic paresis** that is ipsilateral or contralateral and below the site of the lesion. Upper motoneuron lesions anywhere in the spinal cord.will result in an jjDSiJaleial spastic paresis below the level of the lesion. Upper motoneuron lesions between the cerebral cortex and the medulla above the decussation of the pyramids will result in a cgntralateral spastic paresis below the level of the lesion.

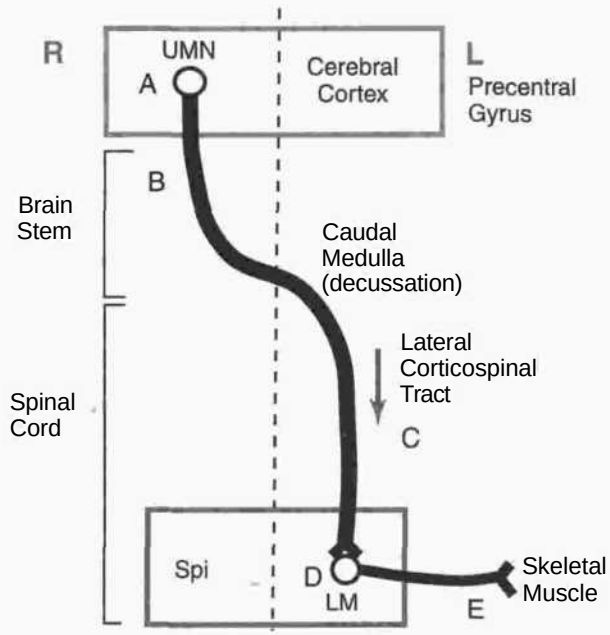


Figure IV-4-5. Upper versus Lower Motoneuron Lesions

Table IV-4-1. Upper versus Lower Motoneuron Lesions

Upper Motor Neuron Lesion	Lower Motor Neuron Lesion
Spastic paralysis	Flaccid paralysis
Hyperreflexia	Areflexia
Babinski sign present	No Babinski
Increased muscle tone	Fasiculations
Muscle weakness	Decreased muscle tone
Disuse atrophy of muscles	Atrophy of muscle(s)
Decreased speed of voluntary movements	Loss of voluntary movements
Large area of the body involved	Small area of body affected

Sensory Systems

Two sensory systems, the dorsal column-medial lemniscal system and the anterolateral (spinothalamic) system, use three neurons to convey sensory information from peripheral sensory receptors to conscious levels of cerebral cortex. In both systems, the first sensory neuron that innervates a sensory receptor has a cell body in the dorsal root ganglion and carries the information into the spinal cord in the dorsal root of a spinal nerve. The first neuron synapses with a second neuron in the brain stem or the spinal cord, and the axon of the second neuron crosses the midline and is carried in a tract in the CNS. The axon of the second neuron then synapses on a third neuron that is in the thalamus. The axon of the third neuron projects to primary somatosensory cortex (Fig IV-4-6).

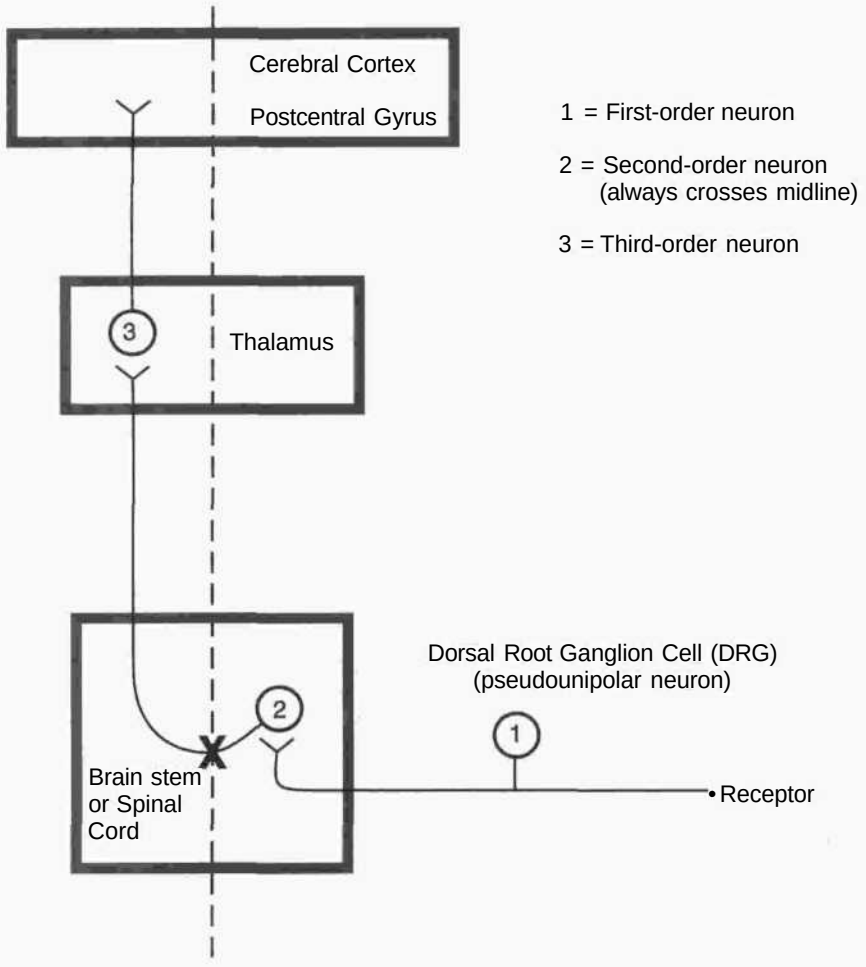
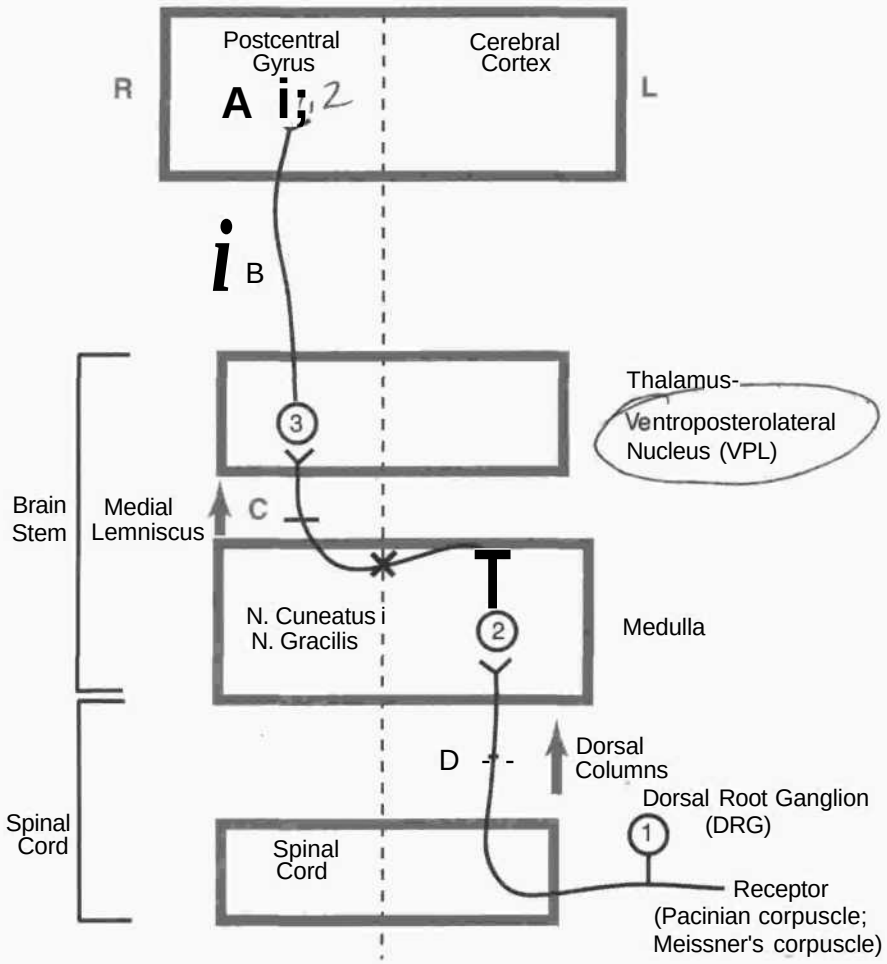


Figure IV-4-6. General Sensory Pathways

Dorsal Column-Medial Lemniscal System

The dorsal column-medial lemniscal system carries sensory information for discriminative touch, joint position (WjnpsjjipiHr nr r;gnscious p_mp_riocepjiye) sense, vibratory, and pressure sensations from the trunk and limbs (Fig IV-4-7). The primary afferent neurons in this system have their cell bodies in the dorsal root ganglia, enter the cord via class II or A-beta dorsal root fibers, and then coalesce in the fasciculus gracilis or fasciculus cuneatus in the dorsal funiculus of the spinal cord. The fasciculus gracilis, found at all spinal cord levels, is situated closest to the midline and carries input from jhg lower extremities and lower trunk. The fasciculus ^ungaius, found only at upper thoracic and cervical spinal cord levels, is lateral to the fasciculus_gracilis and carries input fronTthe upper "extremities and upper trunk. These two fasciculi form the dorsal columns of the spinal cord tKaFcarry the central processes of dorsal root ganglion cells and ascend the length of the spinal cord to reach their second neurons in the lower part of the medulla.

In the lower part of the medulla, fibers in the fasciculus gracilis and fasciculus cuneatus synapse with the second neurons found in the nucleus gracilis and nucleus cuneatus, respectively. Cells in these medullary nuclei give rise to fibers that cross the midline as internal arcuate fibers and ascend through the brain stem in the medial lemniscus. Fibers of the medial lemniscus terminate on cells of the ventral posterolateral (VPL) nucleus of the thalamus. From the VPL nucleus, thalamocortical fibers project to the primary somesthetic (somatosensory) area of the postcentral gyrus, located in the most anterior portion of the parietal lobe.



Function: Conscious proprioception, fine touch, vibration, pressure two point discrimination,

Lesion: loss of above senses
Site of lesion: affected side of body
A, B, and C: contralateral
D: Ipsilateral

Figure IV-4-7. Dorsal Column Pathway—Medial Lemniscal System

Clinical Correlate

Lesions of the dorsal columns result in a loss of joint position sensation, vibratory and pressure spnsatinns, and two-point discrimination. There is loss of the ability to identify the characteristics of an object, called astereognosis (e.g., size, consistency, form, shape), using only the sense of touchT lyplcally, dorsal column-medial lemniscal lesions are evaluated by testing vibratory sense using a 128-Hz tuning fork. Romberg's sign is also used to distinguish between lesions of the dorsal columns and the midline (vermal area) of the cerebellum.

Romberg's sign is tested b^askingjhe.patients to place theirfegt together. If there is a marked .delsxioiation of posture (if the patient sways) with the eyes closed, this is a positive Romberg sign, suggesting that the lesion is in the dorsal columns (or dorsal roots of spinal nerves). With the eyes open, interruption of proprioceptive input carried by the dorsal columns can be compensated for by visual input to the cerebellum. Therefore, if the patient JTasbalange-ocoblems and tends to sway with theirey_esopen(this is indicatiygof cerebellar damage.

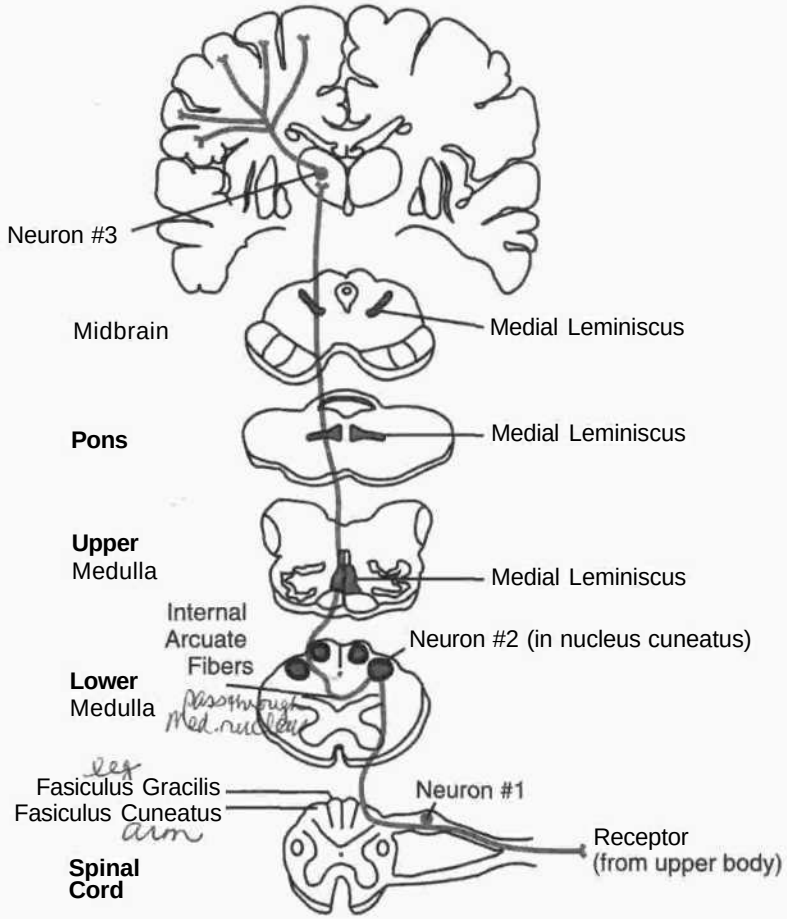
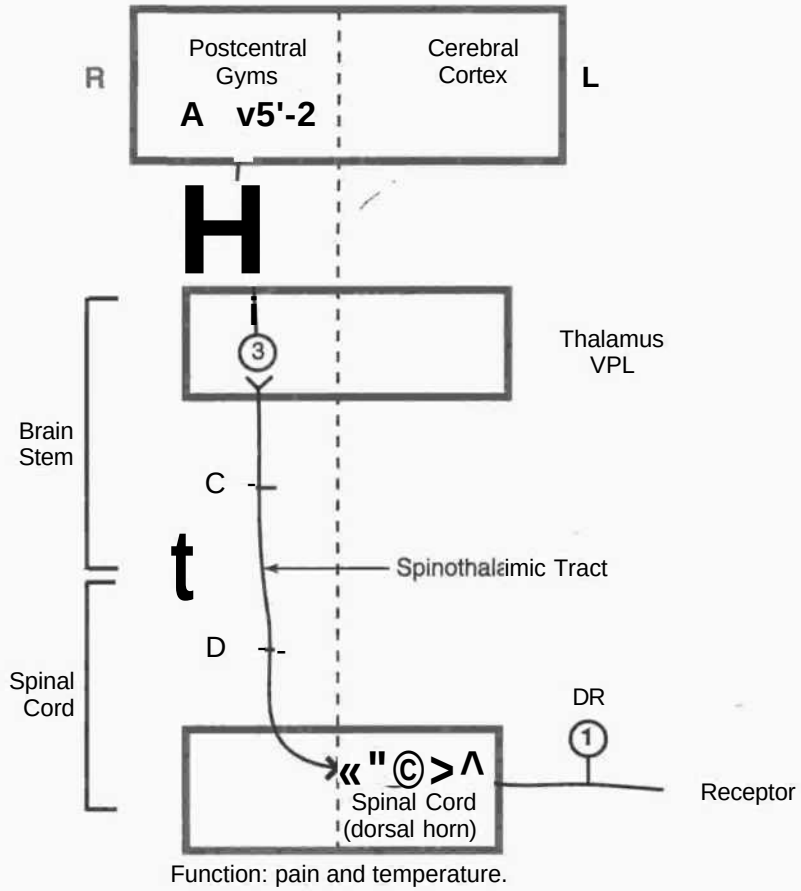


Figure IV-4-8. Dorsal Column Pathway—Medial Lemniscal Pathway

Anterolateral (Spinothalamic ***Tract) System***

The anterolateral system carries pain, temperature, and crude touch sensations from the extremities and trunk.

Pain and temperature fibers have cell bodies in the dorsal root ganglia and enter the spinal cord via A-delta and C or class III and class IV dorsal root fibers (Fig IV-4-9). Their fibers ascend or descend a couple of segments in the dorsolateral tract of Lissauer before entering and synapsing in the dorsal horn. The second neuron cell bodies are located in the dorsal horn gray matter. Axons from these cells cross in the ventral white commissure just below the central canal of the spinal cord and coalesce to form the spinothalamic tract in the ventral part of the lateral funiculus. The spinothalamic tract courses through the entire length of the spinal cord and the brain stem to terminate in the VPL nucleus of the thalamus. Cells in the VPL nucleus send pain and temperature information to the primary somatosensory cortex in the postcentral gyms.



Function: pain and temperature.

Lesion: anesthesia (loss of pain and temperature sensations)
Site of lesion: affected side of body
A, B, C, D: contralateral below the lesion; tract intact rostral to the lesion

Figure IV-4-9. Spinothalamic Tract (Anterolateral System)

Clinical Correlate

Because the pain and temperature information crosses almost as soon as it enters the spinal cord, any unilateral **lesion of the spinothalamic tract** in the spinal cord or brain stem will result in a contralateral loss of pain and temperature. This is an extremely useful clinical sign because it means that if a patient presents with analgesia on one side of the trunk or limbs, the location of the lesion must be on the contralateral side of the spinal cord or brain stem. The analgesia begins 1 to 2 segments below the lesion and includes everything below that level (Fig IV-4-10).

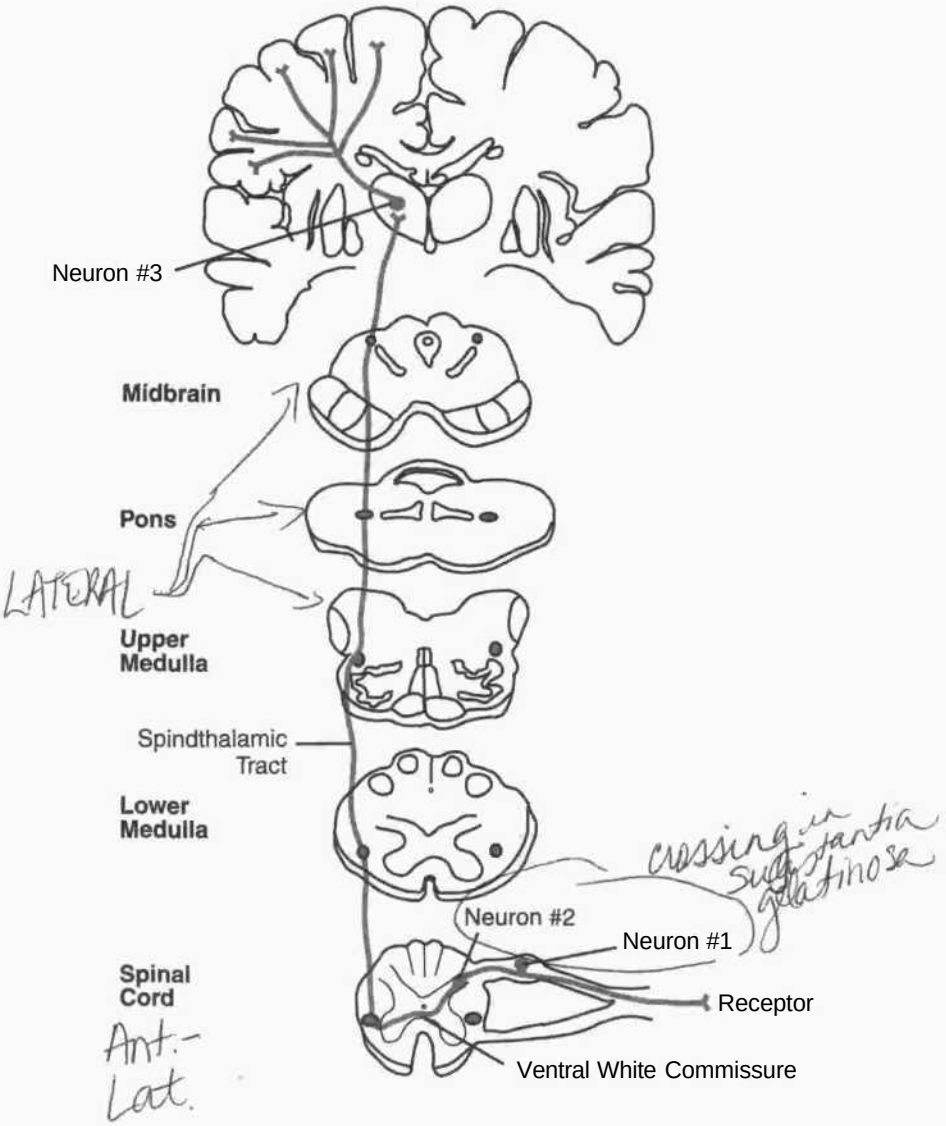


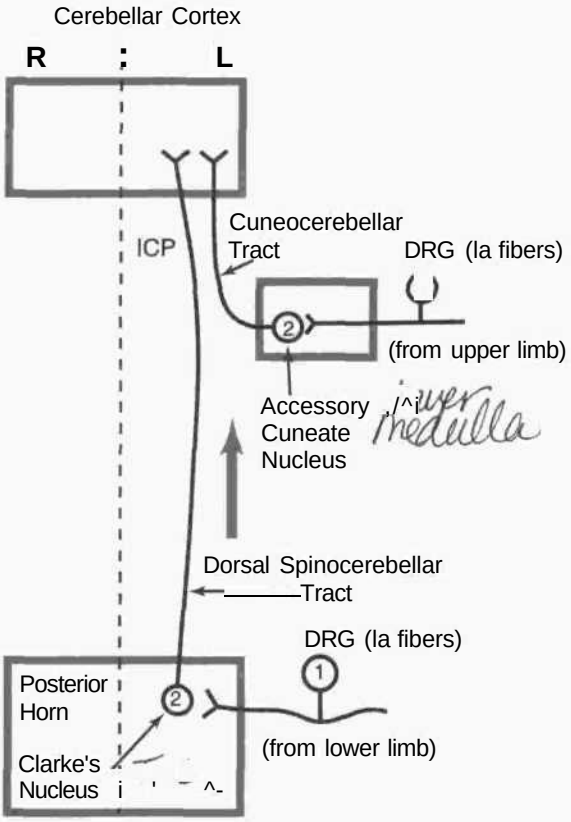
Figure IV-4-10. **Lesions of the Spinothalamic Tract (Anterolateral System)**

SpinocerebellarPathways

The spinocerebellar tracts mainly carry unconscious proprioceptive input from muscle spindles and GTOs to the cerebellum, where this information is used to help monitor and modulate movements. There are two major spinocerebellar pathways:

- Dorsal spinocerebellar tract—carries input from the lower extremities and lower trunk.
- Cuneocerebellar tract—carries proprioceptive input to the cerebellum from the upper extremities and upper trunk.

The cell bodies of the djjrsal spinocerebellar tract are found in Clarke's nucleus, which is situated in the spinal cord rrom 11 to L2. The cell bodies oFtEe cuneocerebellar tract are found in the medulla in the external cuneate nucleus (Fig IV-4-11).



ICP = Inferior Cerebellar Peduncle
SCP = Superior Cerebellar Peduncle

Figure IV-4-11. Spinocerebellar Tracts: Unconscious Proprioception

Clinical Correlate

Lesions that affect only the spinocerebellar tracts are uncommon, but there are a group of hereditary diseases in which degeneration of spinocerebellar pathways is a prominent feature. The most common of these is Friedreich's ataxia, which is usually inherited as an autosomal recessive trait. The spinocereBeTlartracTs, dorsal columns, corticospinal tracts, and cerebellum may be involved. Ataxia of gait is the most common initial symptom of this disease.

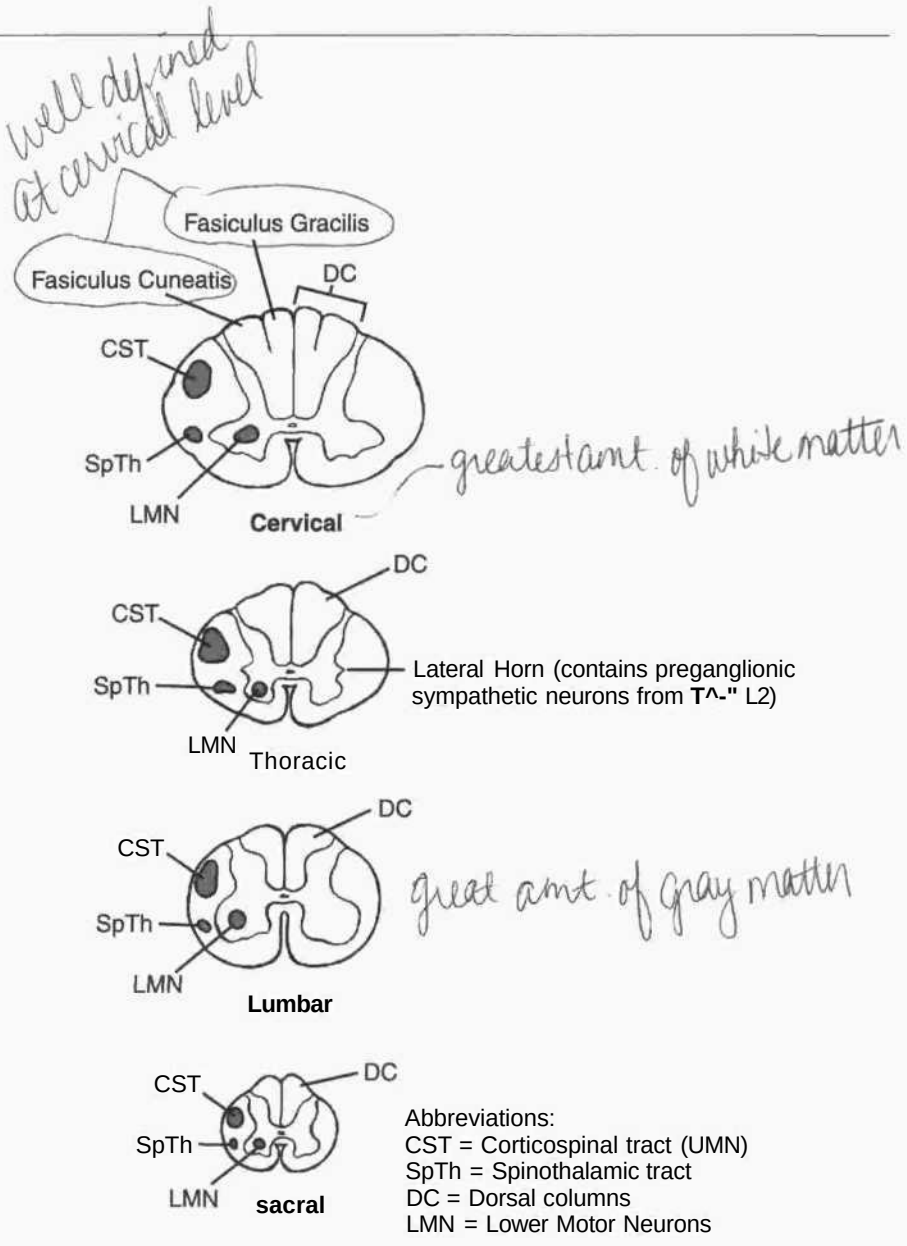
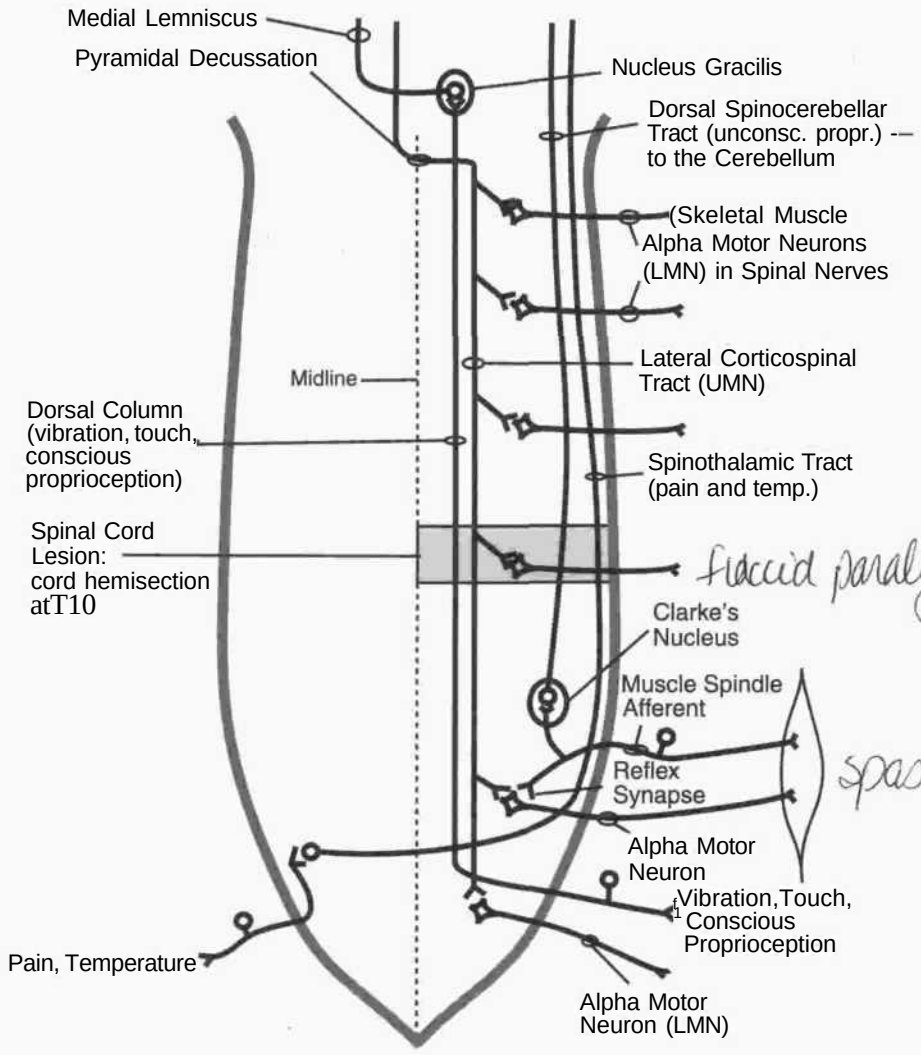


Figure IV-4-12. Spinal Cord: Levels

Spinal Cord Lesions

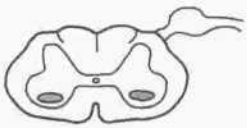
Figure IV-4-13 provides an overview of the spinal cord tracts, and Figures IV-4-14 and IV-4-15 show lesions at different sites, which are discussed below.



flaccid paralysis

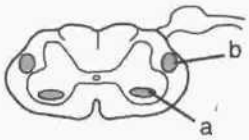
spastic paralysis

Figure IV-4-13. An Overview of the Spinal Cord Pathways

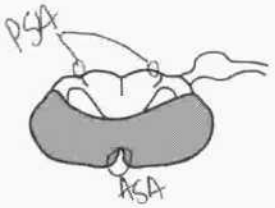


Polio
a. Flaccid paralysis
b. Muscle atrophy
c. Fasiculations
d. Areflexive

Tabes Dorsalis
a. Bilateral dorsal column (DC) signs below lesions
b. Associated with late-stage syphilis
+ Romberg sign: sways with eyes closed



Amyotrophic **Lateral Sclerosis (ALS) at Cervical Enlargement**
a. Progressive spinal muscular atrophy (ventral horn)
b. Primary lateral sclerosis (corticospinal tract)
- Spastic paralysis in lower limbs
- Increased tone and reflexes
- Flaccid paralysis in upper limbs

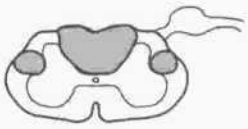


Anterior Spinal Artery (ASA) Occlusion
a. DC spared
b. All else bilateral signs

Figure IV-4-14. Lesions of the Spinal Cord—1

Brown-Séquard Syndrome

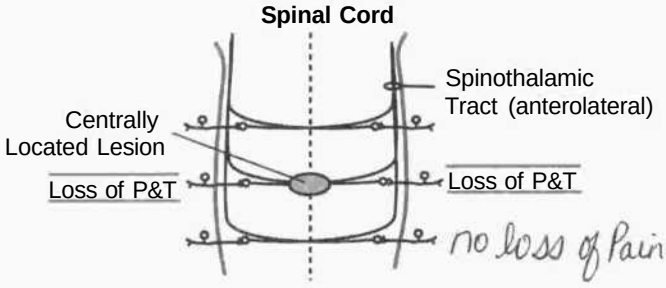
Brown-Se"quard syndrome results from a hemisection of the cord along the transverse plane. Hemisection of the cord results in a lesion of each of the three main neural systems: the principal upper motoneuron pathway of the corticospinal tract, one or both dorsal columns, and the spinothalamic tract. The hallmark of a lesion to these three long tracts is that the patient presents with two ipsilateral signs and one contralateral sign. Lesion of the corticospinal tract results in an ipsilateral spastic paresis below the level of the injury. Lesion to the fasciculus gracilis or cuneatus results in an ipsilateral loss of joint position sense, tactile discrimination, and vibratory sensations below the lesion. Lesion of the spinothalamic tract results in a contralateral loss of pain and temperature sensation starting one or two segments below the level of the lesion. At the level of the lesion, there will be an ipsilateral loss of all sensation, including touch modalities as well and pain and temperature, and an ipsilateral flaccid paralysis in muscles supplied by the injured spinal cord segments (Fig IV-4-15).



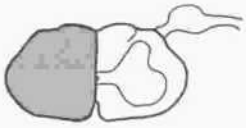
Subacute Combined Degeneration

a. Vitamin B_{12}, pernicious anemia; (AIDS)
b. Demyelination of the
- Dorsal columns ataxia
- Spinocerebellar tracts
- Corticospinal tracts (CST) spastic paralysis

Syringomyelia
a. Cavitation of the cord; usually cervical
b. Bilateral loss of pain and temperature at the level of the lesion



c. As the disease progresses, there is muscle weakness: eventually flaccid paralysis and atrophy of the upper limb muscles, due to destruction of ventral horn cells



Hemisectlon: Brown-Séquard **Syndrome**

a. DC: ipsilateral loss of position and vibratory senses at and below level of the lesion
b. Spinothalamic tract: contralateral loss of P&T below lesion and bilateral loss at the level of the lesion
c. CST: ipsilateral paresis below the level of the lesion
d. LMN: Flaccid paralysis at the level of the lesion
e. Descending hypothalamics: ipsilateral Homer s Syndrome (if cord lesion above T2)
- Facial hemianhydrosis
- Ptosis (slight)
- Miosis

Figure IV-4-15. Lesions of the Spinal Cord—2

Poliomyelitis

Poliomyelitis results from a relatively selective destruction of lower motoneurons in the ventral horn by the poliovirus. The disease causes a flaccid paralysis of muscles with the accompanying hyporeflexia and hypotonicity. Some patients may recover most function, whereas others progress to muscle atrophy and permanent disability (Fig IV-4-14).

AmyotrophicLateralSclerosis

Amyotrophic lateral sclerosis (ALS, Lou Gehrig's disease) is a relatively pure motor system disease that affects both upper and lower motoneurons. The disease typically begins at cervical levels of the cord and progresses either up or down the cord. Patients present with bilateral flaccid weakness of the upper limbs

and bilateral spastic weakness of the lower limbs. Lower motoneurons in the brain stem nuclei may be involved later (Fig IV-4-14).

Occlusion of the Anterior Spinal Artery

This artery lies in the anterior median sulcus of the spinal cord. Occlusion of the anterior spinal artery interrupts blood supply to the ventrolateral parts of the cord, including the corticospinal tracts and spinothalamic tracts. Below the level of the lesion, the patient exhibits a bilateral spastic paresis and a bilateral loss of pain and temperature (Fig IV-4-14).

Clinical Correlate

Syringomyelia may present with hydrocephalus and Arnold Chiari (I) malformation.

Syringomyelia

Syringomyelia is a disease characterized by progressive cavitation of the central canal, usually in the cervical spinal cord but may involve other cord regions or the medulla. Early in the disease, there is a bilateral loss of pain and temperature sensation in the hands and forearms as a result of the destruction of spinothalamic fibers crossing in the anterior white commissure. When the cavitation expands, lower motoneurons in the ventral horns are compressed, resulting in bilateral flaccid paralysis of upper limb muscles. A late manifestation of cavitation is **Horner's syndrome,** which occurs as a result of involvement of descending hypothalamic fibers innervating preganglionic sympathetic neurons in the Tl through T4 cord segments. Horner's syndrome consists of miosis (pupillary constriction), ptosis (drooping eyelids), and anhidrosis (lack of sweating) in the face (FigIV-4-15).

Clinical Correlate

Tabes patients present with paresthesias (pins and needles sensations), pain, polyuria, Romberg sign.

Tabes Dorsalis

Tabes dorsalis is one possible manifestation of neurosyphilis. It is caused by bilateral degeneration of the dorsal roots and secondary degeneration of the dorsal columns. There may be impaired vibration and position sense, astereognosis, paroxysmal pains, and ataxia, as well as diminished stretch reflexes or incontinence. Owing to the loss of proprioceptive pathways, individuals with tabes dorsalis are unsure of where the ground is and walk with a characteristic and almost diagnostic "high step stride" (Fig IV-4-14). Tabetic patients may also present with abnormal pupillary responses (Argyll Robertson pupils).

Clinical Correlate

Subacute combined degeneration patients present paresthesias bilateral spastic weakness, Babinski signs, and antibodies to instrinsic factor.

Subacute Combined Degeneration

Subacute combined degeneration is seen most commonly in cases of vitamin B_{12} deficiency, sometimes related to pernicious anemia. The disease is characterized by patchy losses of myelin in the dorsal columns and lateral corticospinal tracts, resulting in a bilateral spastic paresis and a bilateral alteration of touch, vibration, and pressure sensations below the lesion sites (Fig IV-4-15). Myelin in both CNS and PNS is affected.

Multiple Sclerosis

Multiple sclerosis is a demyelinating disease of the CNS in which certain myelinated pathways, such as the optic nerve, dorsal columns, corticospinal tract, and medial longitudinal fasciculus (MLF) are affected. The illness is characterized by episodes of focal neurologic deficits that are separated in place and in time. The disease course is characterized by exacerbations and remissions. Patients may develop the following symptoms:

- Weakness or spastic paresis occurring from damage to the corticospinal tract.
- Monocular blindness or scotoma resulting from optic nerve damage.
- Paresthesias occurring from damage to the dorsal columns.
- Ataxia resulting from damage to cerebellar connections in the brain stem, dorsal columns, or spinocerebellar tracts.
- Diplopia most often occurring after damage to the MLF, a brain stem pathway connecting the cranial nerve nuclei that control extraocular movement with each other and with the cerebellum, vestibular nuclei, and cervical proprioceptive input.

The Brain Stem

5

The brain stem is divisible into three continuous parts, the midbrain, the pons, and the medulla. The midbrain is most rostral and begins just below the diencephalon. The pons is in the middle and is overlain by the cerebellum.

The medulla is caudal to the pons and is continuous with the spinal cord.

The brain stem is the home of the origins or sites of termination of fibers in 9 of the 12 cranial nerves (CN).

CRANIAL NERVES

Two cranial nerves, the oculomotor and trochlear (CN III and IV), arise from the midbrain (Fig IV-5-1).

Four cranial nerves, the trigeminal, abducens, facial, and vestibulocochlear nerves (CN V, VI, VII, and VIII), enter or exit from the pons.

Three cranial nerves, the glossopharyngeal, vagus, and hypoglossal nerves (CN IX, X, and XII), enter or exit from the medulla. Fibers of the accessory nerve arise from the cervical spinal cord.

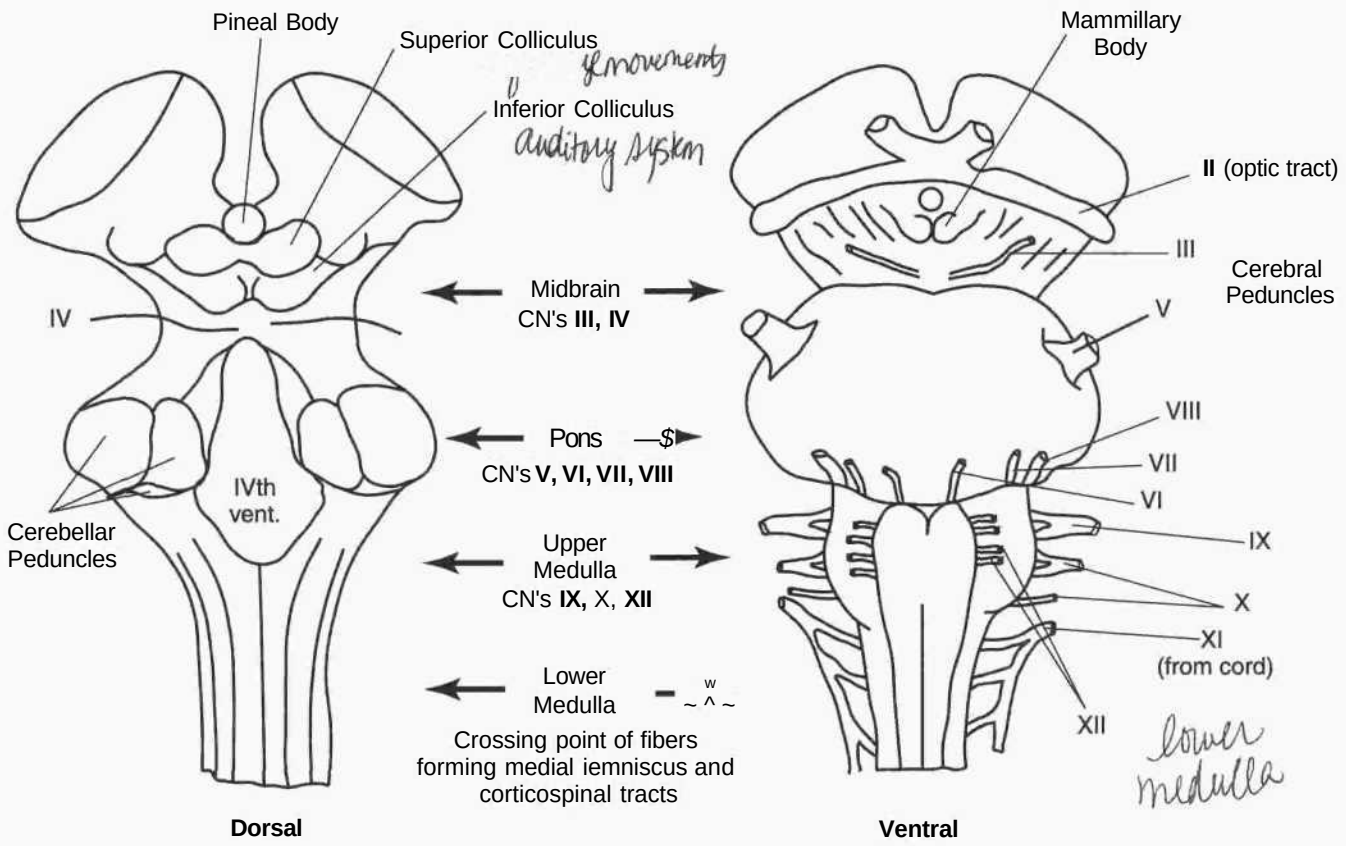


Figure IV-5-1. Brainstem and Cranial Nerve-Surface Anatomy

Clinical Correlate

Pineal tumors result in Parinaud's syndrome: paralysis of upward gaze and noncommunicating hydrocephalus.

Clinical Correlate

Schwannomas typically affect VIII nerve fibers seen in neurofibromatosis type 2.

Afferent fibers of cranial nerves enter the CNS and terminate in relation to aggregates of neurons in sensory nuclei. Motor or efferent components of cranial nerves arise from motor nuclei. All motor and sensory nuclei that contribute fibers to cranial nerves are organized in a series of discontinuous columns according to the functional component that they contain. Motor nuclei are situated medially, closest to the midline, and sensory nuclei are situated lateral to the motor nuclei. A cranial nerve nucleus or nerve will be found at virtually every transverse sectional level of the brain stem (Fig IV-5-2).

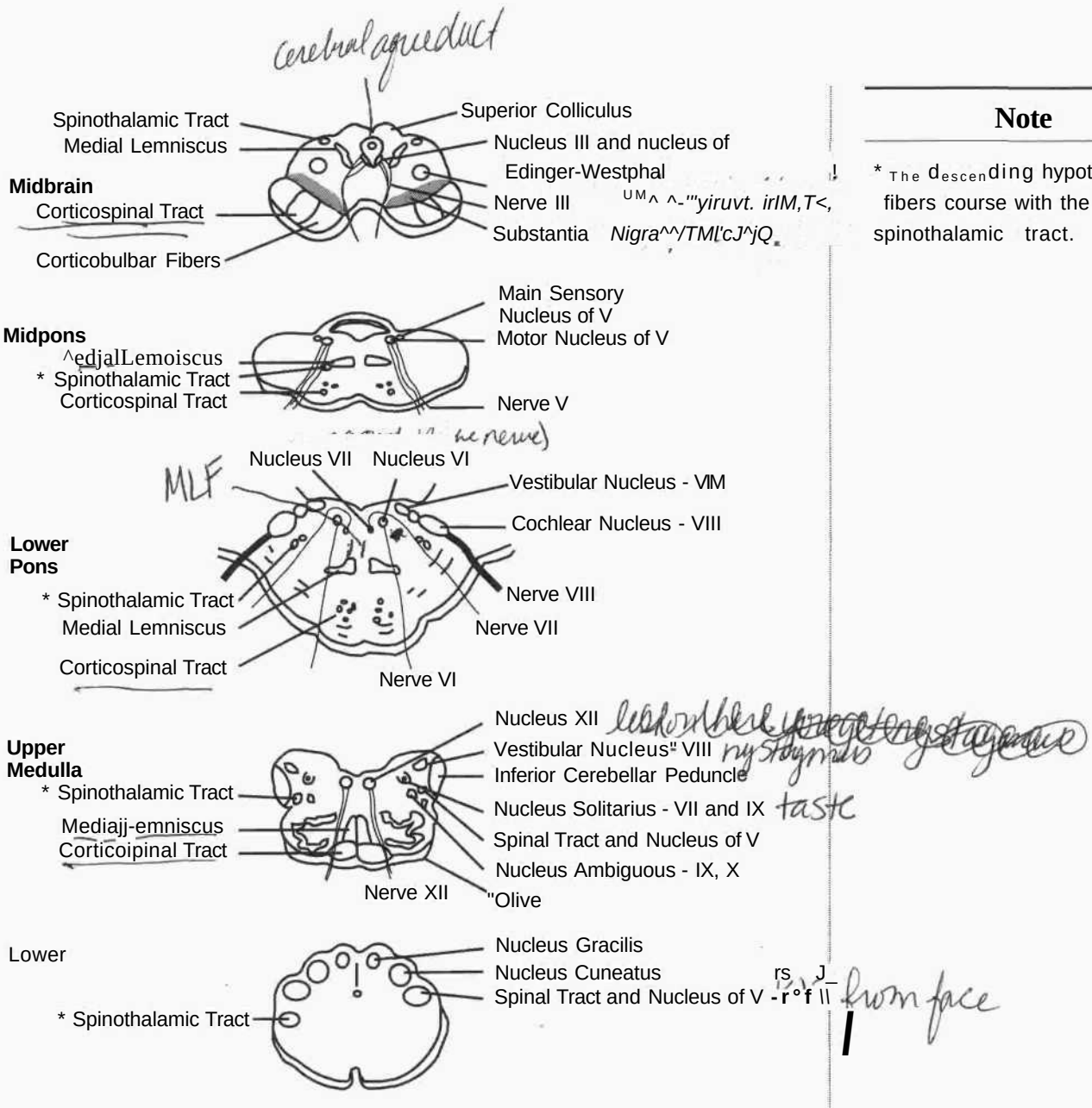


Figure IV-5-2. Brainstem: Cranial Nerves and Identification of Sections

Note

* The descending hypothalamic fibers course with the spinothalamic tract.

Table FV-5-1. Cranial Nerves: Functional Features

CN	Name	Type	Function	Lesions Result in	Exits/Enters Cranium	Region Innervated
I	Olfactory	Sensory	Smells	Anosmia	Cribriform plate	Nasal cavity
II	Optic	Sensory	Sees (optic nerve is really a tract of CNS with meninges)	Visual field deficits (anopsia) Loss of light reflex with HI Only nerve to be affected by MS (swinging flashlight test)	Optic canal	Orbit
VIII	Vestibulocochlear	Sensory	Hears Linear acceleration (gravity) Angular acceleration (head turning)	Sensorineural hearing loss Loss of balance, nystagmus	Internal auditory meatus	Inner ear
III	Oculomotor	Motor	Moves eyeball in all directions Adduction (medial reetus) most important action Constricts pupil (sphincter pupillae) Accommodates (ciliary muscle) Raises eyelid (levator palpebrae superioris)	Diplopia—external strabismus Loss of parallel gaze Dilated pupil, loss of light reflex **with II** Loss of near response Ptosis	Superior orbital fissure	Orbit
IV	Trochlear	Motor	Superior oblique—depresses and abducts eyeball (makes eyeball look down and out) Intorts	Weakness looking down and in Trouble going down stairs Head tilts away from lesioned side	Superior orbital fissure	Orbit
VI	Abducens	Motor	Lateral reetus—abducts eyeball	Diplopia—internal strabismus Loss of parallel gaze, "pseudoptosis"	Superior orbital fissure	Orbit
XI	Accessory	Motor	Turns head to opposite side (sternocleidomastoid) Elevates and rotates scapula (trapezius)	Weakness turning head to opposite side Shoulder droop	Jugular foramen	Neck
XII	Hypoglossal	Motor	Moves tongue (styloglossus, hyoglossus, genioglossus, and intrinsics—palatoglossus is by X)	Tongue pointing toward same (affected) side on protrusion	Hypoglossal canal	Tongue
V	Trigeminal Ophthalmic (VI)	Mixed	General sensation (touch, pain, temperature) of forehead/scalp/ cornea	VI—loss of general sensation in skin of forehead/scalp Loss of blink reflex with VH	VI—superior orbital fissure (ophthalmic division)	Orbit and scalp
	Maxillary (V2)		General sensation of palate, nasal cavity, maxillary face, maxillary teeth	V2—loss of general sensation in skin over maxilla, maxillary teeth	V2—foramen rolundum (maxillary division)	Pterygopalaline fossa (leave by openings to face, oral and nasal cavity)
	Mandibular (V3)		General sensation of anterior two thirds of tongue, mandibular face, mandibular teeth Motor to muscles of mastication (temporalis, masseter, medial and lateral pterygoids) and anterior belly of digastric, mylohyoid, tensor tympani, tensor palati	V3—loss of general sensation in skin over mandible, mandibular teeth, tongue, weakness in chewing Jaw deviation toward weak side Trigeminal neuralgia—intractable pain in V2 or V3 territory	V3—foramen ovale (mandibular division)	Infratemporal Fossa

(continued)

Table IV-5-1. Cranial Nerves: Functional Features *(continued)*

CN	Name	Type	Function	Lesions Result in	Exits/Enters Cranium	Region Innervated
VII	Facial	Mixed	To muscles of facial expression, posterior belly of digastric, stylohyoid, stapedius Tastes anterior two thirds of tongue/palate Salivates (submandibular, sublingual glands) Tears (lacrimal gland) Makes mucus (nasal and palatine glands)	Corner of mouth droops, can't dose eye, can't wrinkle forehead, loss of blink reflex, hyperacusis Alteration or loss of taste (ageusia) Eye dry and red Bell's palsy-lesion of nerve in facial canal	Internal auditory raeatu	Face, nasal, and oral cavity (branches leave skull in stylomastoid foramen, petrotympanic fissure, or hiatus of facial canal)
IX	Glossopharyngeal	Mixed	Senses pharynx, carotid sinus/ body Salivates (parotid gland) Tastes and senses posterior one third oftongue Motor to one muscle—stylopharyngeus	Loss of gag reflex with X	Jugular foramen	Neck **Pharynx/tongue**
X	Vagus	Mixed	To muscles of palate and pharynx for swallowing except tensor palati (V) and stylopharyngeus (IX) To all muscles of larynx (phonates) Senses larynx and laryngopharynx Senses larynx and GI tract To GI tract smooth muscle and glands in foregut and midgut	Nasal speech, nasal regurgitation Dysphagia, palate droop Uvula pointing away from affected side Hoarseness/fixed vocal cord Loss of gag reflex with DC Loss of cough reflex	Jugular forame	Neck Pharynx/larynx Thorax, abdomen
	Sympatheticsto head	**Motor**	Raises eyelid (superior tarsal muscle) Dilates pupil Innervates sweat glands of face and scalp Constricts blood vessels in head	Homer's syndrome: eyelid droop (ptosis), constricted pupil (miosis), loss of sweating (anhydrosis), flushed face	**Carotid canal on internal carotid artery**	Orbit, face, scalp

NEURAL SYSTEMS

Each of the following five ascending or descending neural tracts, fibers, or fasciculi course through the brain stem and will be found at every transverse sectional level.

Medial Lemniscus

The medial lemniscus (ML) contains the axons from cell bodies found in the dorsal column nuclei (gracilis and cuneatus) in the caudal medulla and represents the second neuron in the pathway to the thalamus and cortex for discriminative touch, vibration, pressure, and conscious proprioception. The axons in the ML cross the midline of the medulla immediately after emerging from the dorsal column nuclei. Lesions in the ML, in any part of the brain stem, result in a loss of discriminative touch, vibration, pressure, and conscious proprioception from the **contralateral** side of the body.

Spinothalamic Tract (part of anterolateral system)

The spinothalamic tract has its cells of origin in the spinal cord and represents the crossed axons of the second neuron in the pathway conveying pain and temperature to the thalamus and cortex. Lesions of the spinothalamic tract, in any part of the brain stem, results in a loss of pain and temperature sensations from the **contralateral** side of the body.

Corticospinal Tract

The corticospinal tract controls the activity of lower motoneurons, and interneuron pools for lower motoneurons course through the brain stem on their way to the spinal cord. Lesions of this tract produce a spastic paresis in skeletal muscles of the body **contralateral** to the lesion site in the brain stem.

Descending Hypothalamic Fibers

The descending hypothalamic fibers arise in the hypothalamus and course without crossing through the brain stem to terminate on preganglionic sympathetic neurons in the lateral horn of the spinal cord. Lesions of this pathway produce ipsilateral **Horner's syndrome.** Horner's syndrome consists of miosis (pupillary constriction), ptosis (drooping eyelid), and anhidrosis (lack of sweating) in the face ipsilateral to the side of the lesion.

Descending hypothalamic fibers course with the spinothalamic fibers in the lateral part of the brain stem. Therefore, brain stem lesions producing Horner's syndrome may also result in a contralateral loss of pain and temperature sensations from the limbs and body.

Medial Longitudinal Fasciculus

The medial longitudinal fasciculus is a fiber bundle interconnecting centers for horizontal gaze, the vestibular nuclei, and the nerve nuclei of CN III, IV, and VI, which innervate skeletal muscles that move the eyeball. This fiber bundle courses close to the dorsal midline of the brain stem and also contains vestibulospinal fibers, which course through the medulla to the spinal cord. Lesions of the fasciculus produce internuclear ophthalmoplegia and disrupt the vestibulo-ocular reflex.

MEDULLA

In the caudal medulla, two of the neural systems, the corticospinal and dorsal column-medial lemniscal pathways, send axons across the midline. The nucleus gracilis and nucleus cuneatus give rise to axons that decussate in the caudal medulla (the crossing axons are the internal arcuate fibers), which then form and ascend in the medial lemniscus.

The corticospinal (pyramidal) tracts, which are contained in the pyramids, course ventromediaUy through the medulla. Most of these fibers decussate in the caudal medulla just below the crossing of axons from the dorsal column nuclei, and then travel down the spinal cord as the (lateral) corticospinal tract.

The olives are located lateral to the pyramids in the rostral two thirds of the medulla. The olives contain the convoluted inferior olivary nuclei. The olivary nuclei send climbing (olivocerebellar) fibers into the cerebellum through the inferior cerebellar peduncle. The olives are a key distinguishing feature of the medulla.

The spinothalamic tract and the descending hypothalamic fibers course together in the lateral part of the medulla below the inferior cerebellar peduncle and near the spinal nucleus and tract of CN V.

Cranial Nerve Nuclei

Spinal Nucleus of V

The spinal nucleus of the trigeminal nerve (CN V) is located in a position analogous to the dorsal horn of the spinal cord. The spinal tract of the trigeminal nerve lies just lateral to this nucleus and extends from the upper cervical cord (C2) to the point of entry of the fifth cranial nerve in the pons. Central processes from cells in the trigeminal ganglion conveying pajn anrTtpmpprai-iirp sensations from the face enter the brain stem in the rostral pons butdescend in the spmal tract of CN V and synapse on cells in the spinal nucleus (Fig IV-5-3).

Solitary Nucleus

The solitary nucleus receives the axons of all general and special visceral afferent fibers carried into the CNS by CN VII, IX, and X. These include both taste and visceral sensations carried by these cranial nerves. Taste and visceral sensory neurons all have their cell bodies in ganglia associated with CN VII, IX, and X outside the CNS.

Nucleus Ambiguus

The nucleus ambiguus is a column of large motoneurons situated dorsal to the inferior olive. Axons arising from cells in this nucleus course in the ninth and tenth cranial nerves. The component to the ninth nerve is insignificant. In the tenth nerve, these fibers supply muscles of the soft palate, larynx, pharynx, and upper esophagus. A unilateral lesion will produce ipsilateral paralysis of the soft palate causing the uvula to deviate away from the lesioned nerve and nasal regurgitation of liquids, weakness of laryngeal muscles causing hoarseness, and pharyngeal weakness resulting in difficulty in swallowing.

Dorsal Motor Nucleus of CN X

These visceral motoneurons of CN X are located lateral to the hypoglossal nucleus in the floor of the fourth ventricle. This is a major parasympathetic nucleus of the brain stem, and it supplies preganglionic fibers innervating terminal ganglia in the thorax and the foregut and midgut parts of the gastrointestinal tract.

Hypoglossal Nucleus

The hypoglossal nucleus is situated near the midline just beneath the central canal and fourth ventricle. This nucleus sends axons into the hypoglossal nerve to innervate all of the tongue muscles except the palatoglossus.

The Accessory Nucleus

The accessory nucleus is found in the cervical spinal cord. The axons of the spinal accessory nerve arise from the accessory nucleus, pass through the foramen magnum to enter the cranial cavity, and join the fibers of the vagus to exit the cranial cavity through the jugular foramen. As a result, intramedullary lesions do not affect fibers of the spinal accessory nerve. The spinal accessory nerve supplies the sternocleidomastoid and trapezius muscles.

The rootlets of the glossopharyngeal (CN IX) and vagus (CN X) nerves exit between the olive and the fibers of the inferior cerebellar peduncle. The hypoglossal nerve (CN XII) exits more medially between the olive and the medullary pyramid.

PONS

The pons is located between the medulla (caudally) and the midbrain (rostrally). The cerebellum overlies the pons. It is connected to the brain stem by three pairs of cerebellar peduncles. The fourth ventricle is found between the dorsal surface of the pons and the cerebellum. The ventral surface of the pons is dominated by fibers, which form a large ventral enlargement that carries fibers from pontine nuclei to the cerebellum in the middle cerebellar peduncle. This ventral enlargement is the key distinguishing feature of the pons.

The corticospinal tracts are more diffuse in the pons than in the medulla and are embedded in the transversely coursing fibers that enter the cerebellum in the middle cerebellar peduncle.

The medial lemniscus is still situated near the midline but is now separated from the corticospinal tracts by the fibers forming the middle cerebellar peduncle. The medial lemniscus has changed from a dorsoventral orientation in the medulla to a more horizontal orientation in the pons.

The spinothalamic tract and the descending hypothalamic fibers continue to course together in the lateral pons.

The lateral lemniscus, an ascending auditory pathway, is lateral and just dorsal to the medial lemniscus. The lateral lemniscus carries the bulk of ascending auditory fibers from both cochlear nuclei to the inferior colliculus of the midbrain.

The medial longitudinal fasciculus (MLF) is located near the midline just beneath the fourth ventricle.

Cranial Nerve Nuclei

Abducens Nucleus

The abducens nucleus is found near the midline in the floor of the fourth ventricle just lateral to the MLF.

Facial Motor Nucleus

The facial motor nucleus is located ventrolateral to the abducens nucleus. Fibers from the facial nucleus curve around the posterior side of the abducens nucleus (the curve forms the internal genu of the facial nerve), then pass ventrolaterally to exit the brain stem at the pontomedullary junction.

Superior Olivary Nucleus

The superior olivary nucleus lies immediately ventral to the nucleus of CN VII and receives auditory impulses from both ears by way of the cochlear nuclei. The

Clinical Correlate

The abducens nucleus is coexistent with the PPRF, the center for ipsilateral horizontal gaze. Lesions have resulted in an inability to look to the lesion side, and may include a complete ipsilateral facial paralysis of the VIIth nerve fibers.

cochlear nuclei are found at the pontomedullary junction just lateral to the inferior cerebellar peduncle.

Vestibular Nuclei

The vestibular nuclei are located near the posterior surface of the pons lateral to the abducens nucleus, and extend into the medulla.

Cochlear Nuclei

The dorsal and ventral cochlear nuclei are found at the ponto medullary junction. All of the fibers of the cochlear part of the Vlllth nerve terminate here.

Trigeminal Nuclei

Motor Nucleus

The motor nucleus of CN V is located in the pons just medial to the main sensory nucleus of the trigeminal and adjacent to the point of exit or entry of the trigeminal nerve fibers. These motor fibers supply the muscles of mastication (masseter, temporalis, and medial and lateral pterygoid; Fig FV-5-3).

Sensory Nucleus

The main sensory nucleus is located just lateral to the motor nucleus.

The main sensory nucleus receives tactile and pressure sensations from the face, scalp, oral cavity, nasal cavity, and dura.

Spinal Trigeminal Nucleus

The spinal trigeminal nucleus is a caudal continuation of the main sensory nucleus, extending from the mid pons through the medulla to the cervical cord. Central processes from cells in the trigeminal ganglion conveying pain and temperature sensations from the face descend in the spinal tract of V and synapse on cells in the spinal nucleus.

Mesencephalic Nucleus

The mesencephalic nucleus of CN V is located at the point of entry of the fifth nerve and extends into the midbrain. It receives proprioceptive input from joints, muscles of mastication, extraocular muscles, teeth, and the periodontium. Some of these fibers synapse monosynaptically on the motoneurons, forming the sensory limb of the jaw jerk reflex.

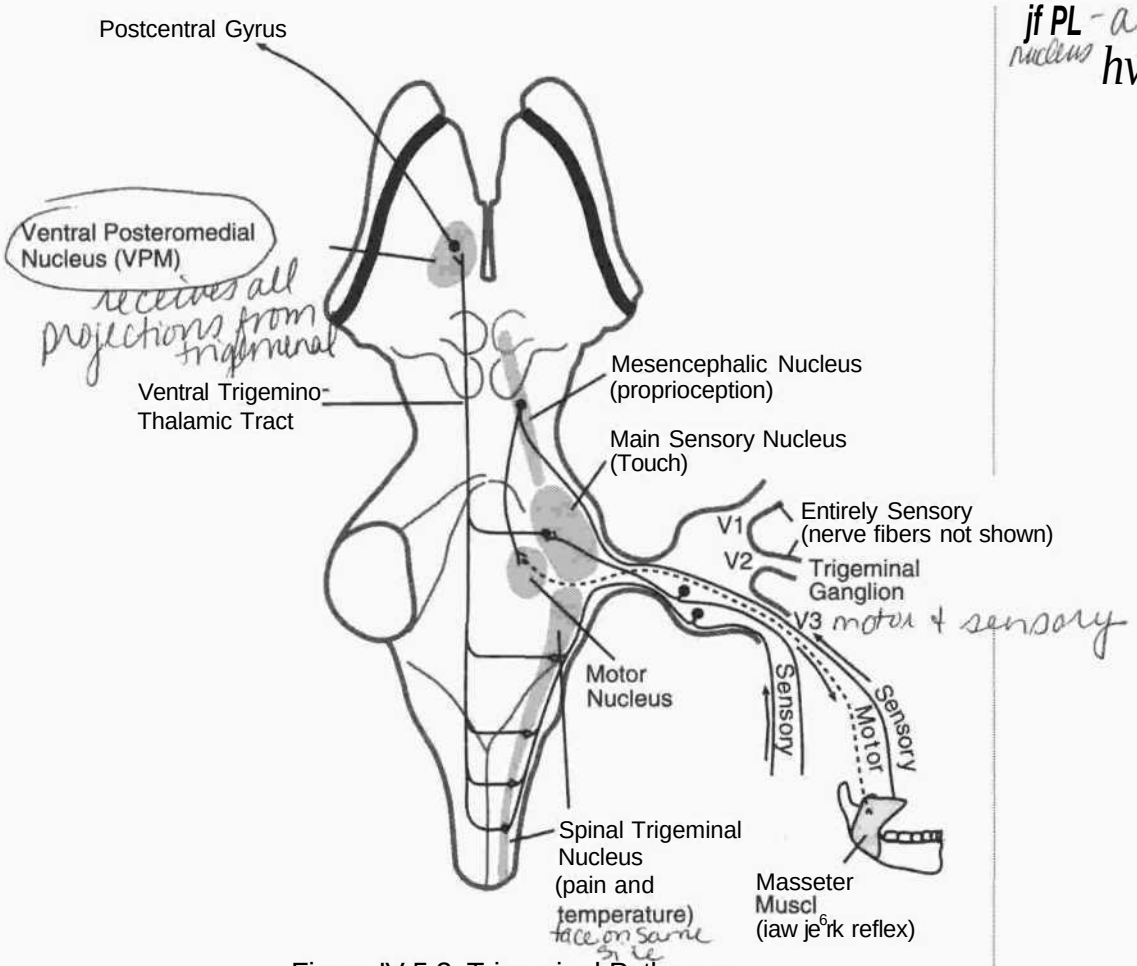


Figure IV-5-3. Trigeminal Pathways

Cranial Nerves V, VI, VII, and VIII

Four cranial nerves emerge from the pons. Cranial nerves VI, VII, and VIII emerge from the pontomedullary junction. The facial nerve is located medial to the vestibulocochlear nerve. The abducens nerve (CN VI) emerges near the midline medial to the corticospinal tract. The trigeminal nerve (CN V) emerges from the middle of the pons.

MIDBRAIN

The midbrain (mesencephalon) is located between the pons and diencephalon. The cerebral aqueduct, a narrow channel that connects the third and fourth ventricles, passes through the midbrain. The inferior colliculi and superior colliculi are found on the dorsal aspect of the midbrain above the cerebral aqueduct. The inferior colliculus processes auditory information received bilaterally from the cochlear nuclei by axon fibers of the lateral lemniscus. The superior colliculi help direct movements of both eyes in gaze. The pretectal region is located just

beneath the superior colliculi and in front of the oculomotor complex. This area contains interneurons involved in the pupillary light reflex The massive cerebral peduncles extend ventrally from the midbrain. The cerebral peduncles contain corticospinal and corticobulbar fibers. The interpeduncular fossa is the space between the cerebral peduncles.

The substantia nigra is the largest nucleus of the midbrain. It appears black to dark brown in the freshly cut brain because nigral cells contain melanin pigments. Neurons in the substantia nigra utilize Dopamine and GABA as neurotransmitters.

The medial lemniscus and spinothalamic tract and descending hypothalamic fibers course together ventrolateral to the periaqueductal gray.

The MLF continues to be located near the midline, just beneath the cerebral aqueduct.

The mesencephalic nuclei of the trigeminal nerve are located on either side of the central gray.

Cranial Nerve Nuclei

The trochlear nucleus is located just beneath the periaqueductal gray near the midline between the superior and inferior colliculi. The oculomotor nucleus and the nucleus of Edinger-Westphal are found just beneath the periaqueductal gray near the midline at the level of the superior colliculi.

Two cranial nerves emerge from the midbrain: the oculomotor (CN III) and the trochlear (CN IV) nerves.

The **oculomotor nerve** arises from the oculomotor nucleus and exits ventrally from the midbrain in the interpeduncular fossa. CN III also contains preganglionic parasympathetic axons that arise from the nucleus of Edinger-Westphal, which lies adjacent to the oculomotor nucleus.

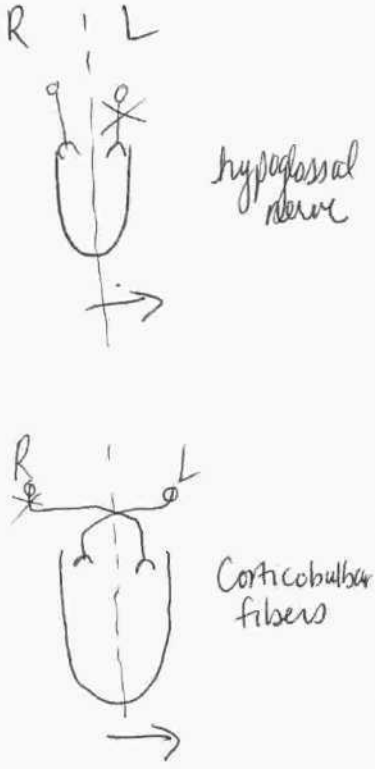
Axons of the **trochlear nerve** decussate in the superior medullary velum and exit the brain stem near the posterior midline just inferior to the inferior colliculi.

Corticobulbar Innervation of Cranial Nerve Nuclei

Corticobulbar fibers serve as the source of upper motoneuron innervation of lower motoneurons in cranial nerve nuclei (Fig IV-5-4). Corticobulbar fibers arise in the motor cortex and influence lower motoneurons in all brain stem nuclei that innervate skeletal muscles. This includes:

- Muscles of mastication (CN V)
- Muscles of facial expression (CN VII)
- Palate, pharynx, and larynx (CN X)
- Tongue (CN XII)
- Sternocleidomastoid and trapezius muscles (CN XI)

The corticobulbar innervation of cranial nerve lower motoneurons ispredonjinantly bilateral, in that each lower motoneuron in a cranial nerve nucleus receives input from corticobulbar axons arising from both the right and the left cerebral cortex.



Clinical Correlate

Facial Paralysis

The upper motoneuron innervation of lower motoneurons in the facial motor nucleus is different and clinically significant. Like most cranial nerve lower motoneurons, the corticobulbar innervation of facial motoneurons to muscles of the upper face (which wrinkle the forehead and shut the eyes) is bilateral. The corticobulbar innervation of facial motoneurons to muscles of the mouth, however, is contralateral only. Clinically, this means that one can differentiate between a lesion of the seventh nerve and a lesion of the corticobulbar fibers to the facial motor nucleus. A facial nerve lesion (as in **Bell's Palsy)** will result in a complete ipsilateral paralysis of muscles of facial expression, including an inability to wrinkle the forehead or shut the eyes and a drooping of the corner of the mouth. A corticobulbar lesion will result in only a drooping of the corner of the mouth on the contralateral side of the face and no other facial motor deficits. Generally, no other cranial deficits will be seen with corticobulbar lesions because virtually every other cranial nerve nucleus is bilaterally innervated. In some individuals, the hypoglossal nucleus may receive mainly contralateral corticobulbar innervation. If these corticobulbar fibers are lesioned, the tongue muscles undergo transient weakness without atrophy or fasciculations and may deviate away from the injured corticobulbar fibers. If, for example, the lesion is in corticobulbar fibers on the left, there is transient weakness of the right tongue muscles, causing a deviation of the tongue toward the right side upon protrusion.

Abbreviations

LF= lower face innervation
UF= upper face innervation
UMN = upper motoneuron

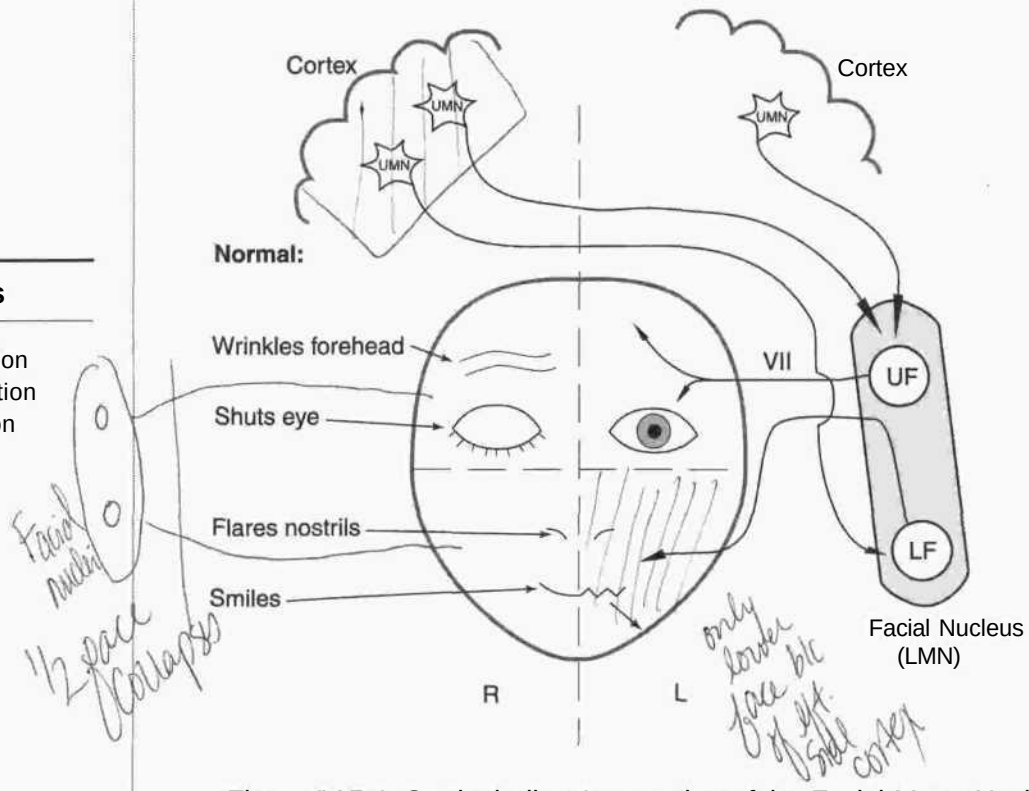


Figure IV-5-4. Corticobulbar Innervation of the Facial Motor Nucleus

COMPONENTS OF THE EAR, AUDITORY, AND VESTIBULAR SYSTEMS

Each ear consists of three components: twxLajr^fijled spaces, the external ear and the middle ear, and the fluid-filled spaces of the inner ear (Fig IV-5-5).

The external ear includes the pinna and the external auditory meatus, which extends to the tympanic membrane. Sound waves travel through the external auditory canal and cause the tympanic membrane (eardrum) to vibrate. Movement of the eardrum causes vibrations of the ossicles in the middle ear (i.e., the malleus, incus, and stapes). Vibrations of the ossicles are transferred through the oval window and into the inner ear.

The middle ear lies in the temporal bone, where the chain of three ossicles connect the tympanic membrane to the oval window. These auditory ossicles amplify the vibrations received by the tympanic membrane and transmit them to the fluid of the inner ear with minimal energy loss. The malleus is inserted in the tympanic membrane, and the stapes is inserted into the membrane of the oval window. Two small skeletal muscles, the tensor tympani and the stapedius, contract to prevent damage to the inner ear when the ear is exposed to loud sounds. The middle ear cavity communicates with the nasopharynx via the eustachian

tube, which allows air pressure to be equalized on both sides of the tympanic membrane.

The inner ear consists of a labyrinth of interconnected sacs (utricle and saccule) and channels (semicircular ducts and the cochlear duct) that contain patches of receptor or hair cells that respond to airborne vibrations or movements of the head. Both the cochlear duct and the sacs and channels of the vestibular labyrinth are filled with endolymph, which bathes the hairs of the hair cells. Endolymph is unique because it has the inorganic ionic composition of an intracellular fluid but it lies in an extracellular space. The intracellular ionic composition of endolymph is important for the function of hair cells. Perilymph, ionically like a typical extracellular fluid, lies outside the endolymph-filled labyrinth (Fig FV-5-6).

Clinical Correlate

Middle Ear Diseases

Middle ear diseases (otitis media, otosclerosis) result in a conductive hearing loss because of a reduction in amplification provided by the ossicles.

Lesions of the facial nerve in the brain stem or temporal bone (Bell's palsy) may result in hyperacusis, an increased sensitivity to loud sounds.

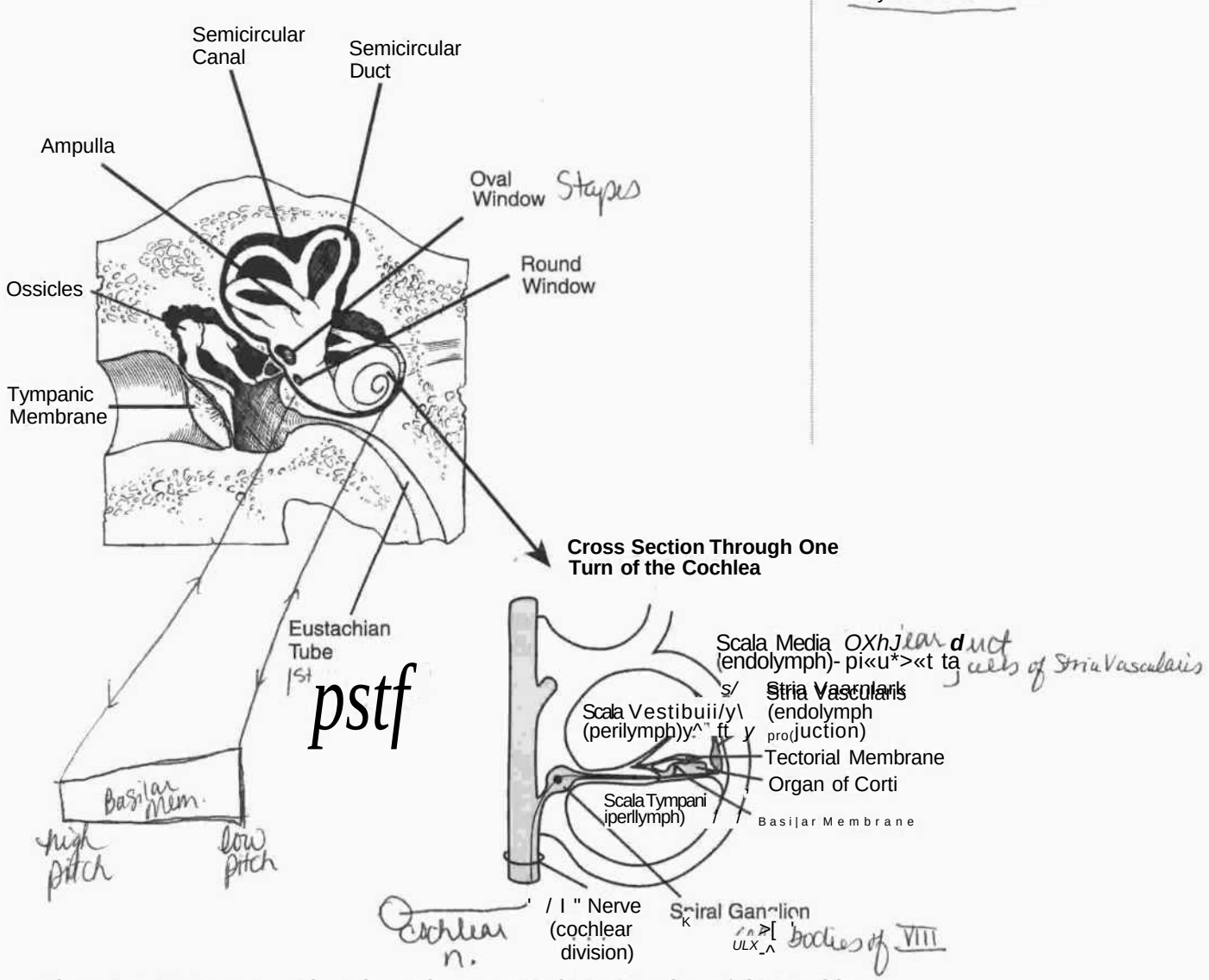


Figure IV-5-5. Cross Section Through an Ear and One Section of the Cochlea

endolymph ↑K+
perilymph ↑Na+
(similar to CSF)

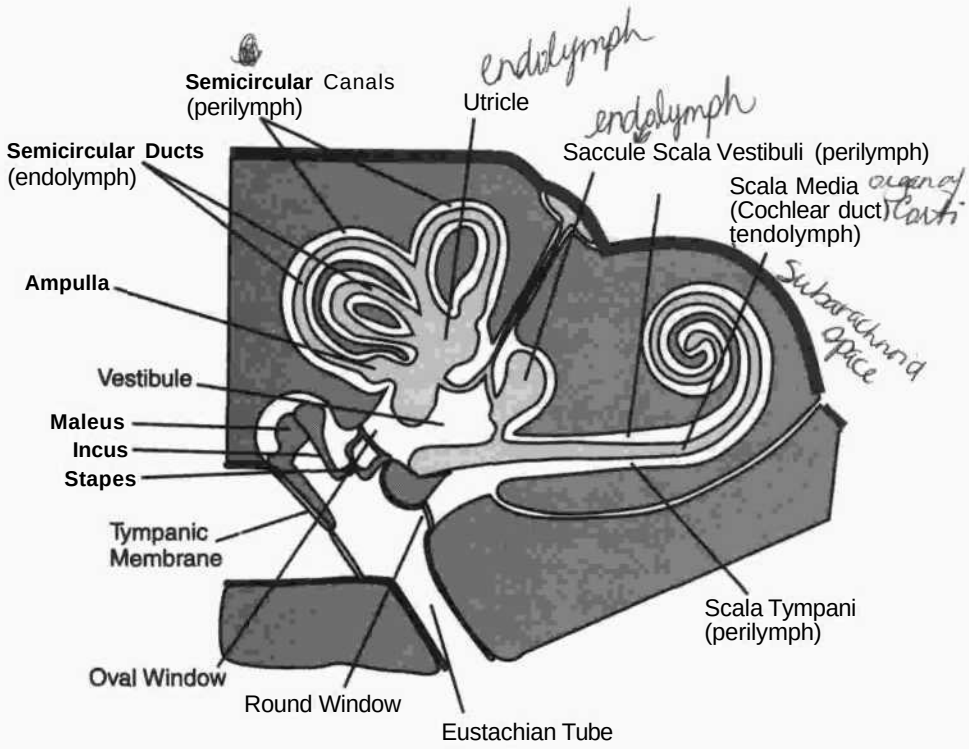


Figure IV-5-6. Distribution of Endolymph and Perilymph in the Inner Ear

Clinical Correlate

Presbycusis results from a loss of hair cells at the base of the cochlea.

Auditory System

CochlearDuct

The cochlear duct is the auditory receptor of the inner ear. It contains hair cells, which respond to airborne vibrations transmitted by the ossicles to the oval window. The cochlear duct coils two and a quarter turns within the bony cochlea and contains hair cells situated on an elongated, highly flexible, basilar membrane. High-frequency sound waves cause maximum displacement of the basilar membrane and stimulation of hair cells at the base of the cochlea, whereas low-frequency sounds maximally stimulate hair cells at the apex of the cochlea.

Spiral Ganglion

The spiral ganglion contains cell bodies whose peripheral axons innervate auditory hair cells of the organ of Corti. The central axons from these bipolar cells form the cochlear part of the eighth cranial nerve. All of the axons in the cochlear part of the eighth nerve enter the pontomedullary junction and synapse in the ventral and dorsal cochlear nuclei. Axons of cells in the ventral cochlear nuclei bilaterally innervate the superior olivary nuclei in the pons. The superior olivary nuclei are the first auditory nuclei to receive binaural input and use the binaural input to localize sound sources. The lateral lemniscus carries auditory input from

the cochlear nuclei and the superior olivary nuclei to the inferior colliculus in the midbrain. Each lateral lemniscus carries information derived from both ears; however, input from the contralateral ear predominates (Fig IV-5-7).

Inferior Colliculus

The inferior colliculus sends auditory information to the medial geniculate body (MGB) of the thalamus. From the MGB, the auditory radiation projects to the primary auditory cortex located on the posterior portion of the transverse temporal gyrus (Heschl's gyrus; Brodmann areas 41 and 42). The adjacent auditory association area makes connections with other parts of the cortex, including Wernicke's area, the cortical area for the comprehension of language.

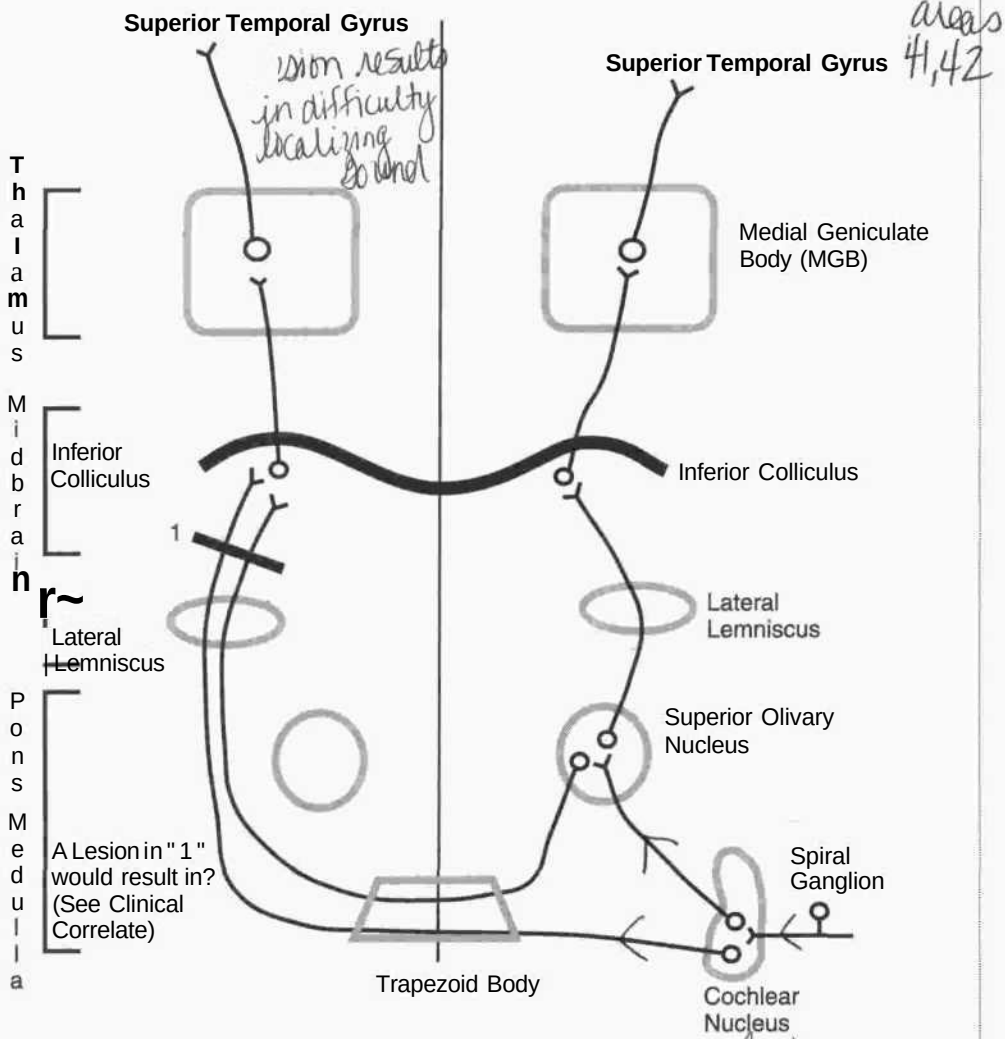


Figure IV-5-7. Auditory System

Vestibular System

SensoryReceptors

The vestibular system contains two kinds of sensory receptors, one kind in the utricle and the saccule and the other in the semicircular ducts.

The utricle and the saccule are two large sacs, each containing a patch of hair cells in a macula. Each macula responds to linear acceleration and detects positional changes in the head relative to gravity. There are three semicircular ducts in the inner ear, each lying in a bony semicircular canal. Each semicircular duct contains an ampullary crest of hair cells that detect changes in angular acceleration resulting from circular movements of the head. The three semicircular ducts, anterior, posterior, and horizontal, are oriented such that they lie in the three planes of space. Circular movements of the head in any plane will depolarize hair cells in a semicircular duct in one labyrinth and hyperpolarize hair cells in the corresponding duct in the opposite labyrinth.

VestibularNuclei

There are four vestibular nuclei located in the rostral medulla and caudal pons. The vestibular nuclei receive afferents from the vestibular nerve, which innervates receptors located in the semicircular ducts, utricle, and saccule. Primary vestibular fibers terminate in the vestibular nuclei and the flocculonodular lobe of the cerebellum.

VestibularFibers

Secondary vestibular fibers, originating in the vestibular nuclei, join the MLF and supply the motor nuclei of CN III, IV, and VI. These fibers are involved in the production of conjugate eye movements. These compensatory eye movements represent the efferent limb of the vestibulo-ocular reflex, which enables the eye to remain focused on a stationary target during movement of the head or neck. Most of our understanding of the vestibulo-ocular reflex is based on horizontal head turning and a corresponding horizontal movement of the eyes in the direction opposite to that of head turning. For example, when the head turns horizontally to the right, both eyes will move to the left using the following vestibulo-ocular structures. Head turning to the right stimulates hairs cells in the right semicircular ducts. The right eighth nerve increases its firing rate to the right vestibular nuclei. These nuclei then send axons by way of the MLF to the right oculomotor nucleus and to the left abducens nucleus. The right oculomotor nerve to the right medial rectus adducts the right eye, and the left abducens nerve to the left lateral rectus abducts the left eye. The net effect of stimulating these nuclei is that both eyes will look to the left (Figs IV-5-8 and IV-5-9).

Clinical Correlate

Lesions Causing Hearing Loss

Lesions of the cochlear part of the eighth nerve or cochlear nuclei inside the brain stem at the pontomedullary junction result in a profound unilateral sensorineural hearing loss. All other lesions to auditory structures in the brain stem, thalamus, or cortex result in a bilateral suppression of hearing and a decreased ability to localize a sound source. If a patient presents with a significant hearing loss in one ear, the lesion is most likely in the middle ear, inner ear, eighth nerve, or cochlear nuclei, and not at higher levels of the auditory system.

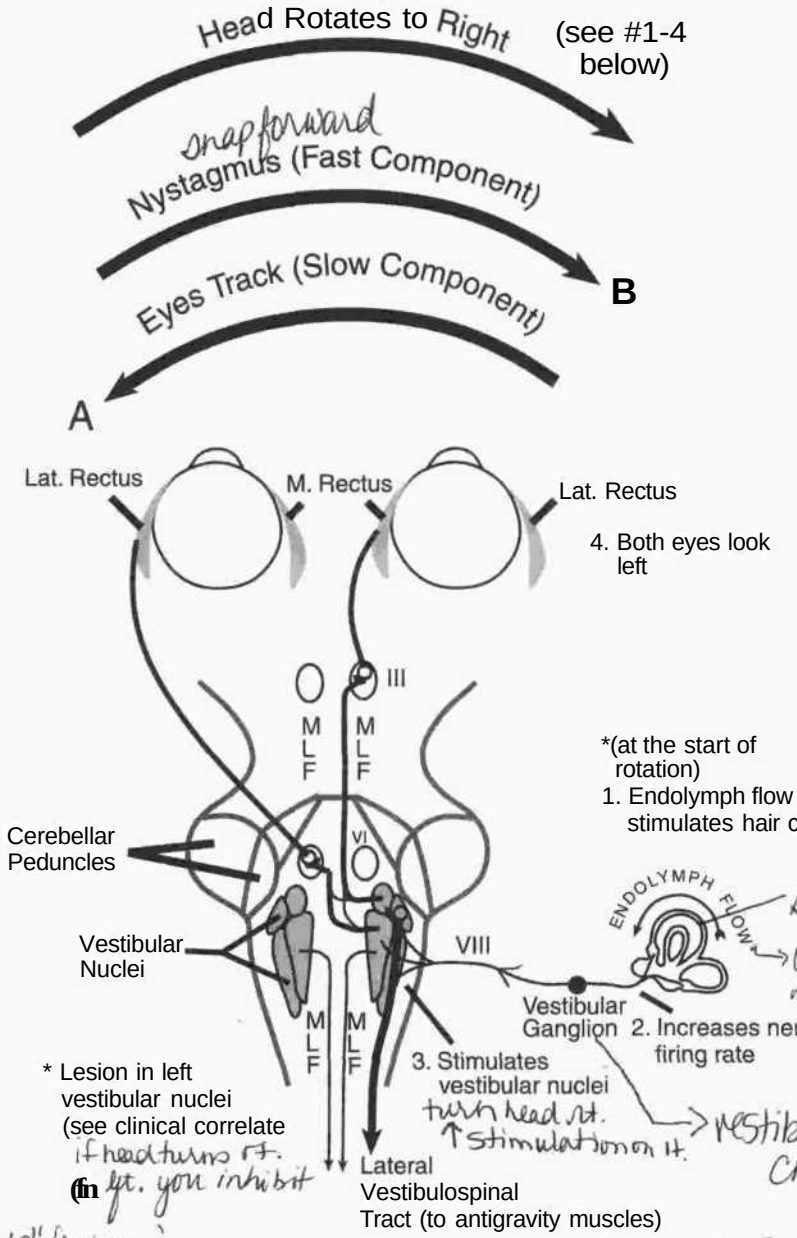


Figure IV-5-8. The Vestibulo-Ocular Reflex

Clinical Correlate

A lesion of the vestibular nuclei or nerve (in this example on the left) produces a vestibular nystagmus with a slow deviation of the eyes toward the lesion (A) and a fast correction back to the right (B).

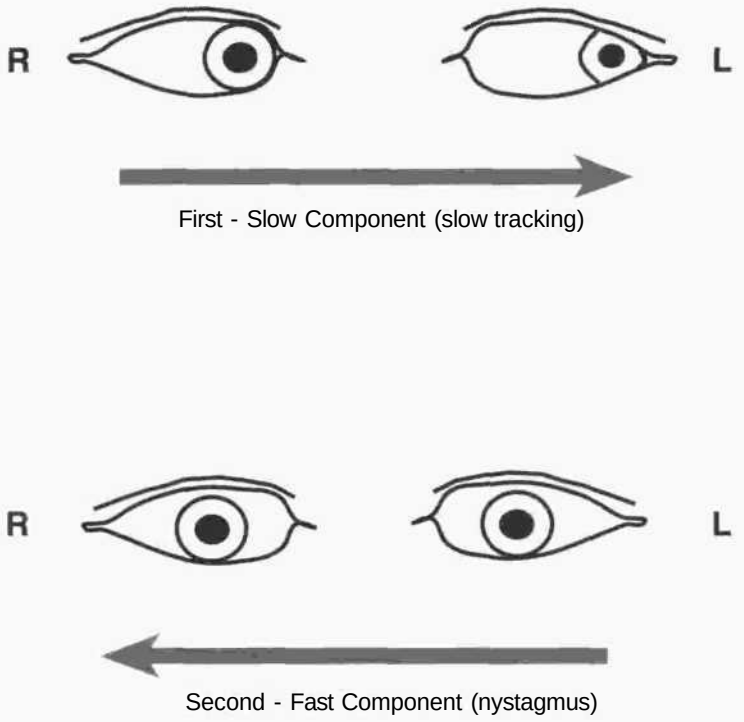


Figure IV-5-9. Vestibular System: Part 2

Clinical Correlate

Vestibular Dysfunction

Vestibular dysfunction may result from either peripheral or central lesions.

Vertigo

Vertigo may result from a lesion of either the peripheral (end organ, nerve) or central (nuclear, brain stem pathways) vestibular structures. Vertigo refers to the perception of rotation, which may involve either the subject or the external space. The vertigo is usually severe in peripheral disease and mild in brain stem disease. Chronic vertigo (i.e., persisting longer than 2-3 weeks) strongly suggests a central lesion.

Vertigo may also be caused by a variety of drugs, including anticonvulsants, aspirin, alcohol, and certain sedatives and antibiotics. Ménière's disease is characterized by abrupt, recurrent attacks of vertigo lasting minutes to hours accompanied by tinnitus or deafness and usually involving only one ear. Nausea and vomiting and a sensation of fullness or pressure in the ear also are common during the acute episode. The attacks often are severe, and the patient may be unable to stand. The disease usually occurs in middle age and results from distention of the fluid spaces in the cochlear and vestibular parts of the labyrinth.

Nystagmus

Nystagmus refers to rhythmic oscillations of the eyes slowly to one side followed by a rapid reflex movement in the opposite direction. Nystagmus is defined by the direction of the rapid reflex movement or the fast phase. It is usually horizontal, although rotatory or vertical nystagmus may also occur.

Unilateral vestibular nerve or vestibular nucleus lesions may result in a vestibular nystagmus. In a pathologic vestibular nystagmus, the initial slow phase is the response to the pathology, and the fast phase is the correction attempt made by the cortex in response to the pathology. Consider this example: if the left vestibular nerve or nuclei are lesioned, because of the loss of balance between the two sides, the right vestibular nuclei are unopposed and act as if they have been stimulated, causing both eyes to look slowly to the left. This is the slow phase of a pathologic vestibular nystagmus. Because the head did not move, the cortex responds by moving both eyes quickly back to the right, the direction of the fast phase of the nystagmus.

Tests for Nystagmus

The integrity of the vestibulo-ocular reflex can be an indicator of brain stem integrity in comatose patients. To test this reflex, a vestibular nystagmus is induced by performing a **caloric test** in which an examiner introduces warm or cool water into an external auditory meatus. Warm water introduced into the external ear stimulates the horizontal semicircular duct and causes the eyes to move slowly in the opposite direction. Because the head did not turn, the eyes are moved quickly back by the cortex (if intact) toward the same ear where the warm water was introduced, producing a fast phase of nystagmus to the same side. Introduction of cool water into the external ear mimics a lesion; the horizontal duct activity is inhibited on the cool water side, and the opposite vestibular complex moves the eyes slowly toward the cool water ear. The corrective or fast phase of the nystagmus moves the eyes quickly away from the ear where the cool water was introduced. A mnemonic which summarizes the direction of the fast phase of vestibular nystagmus in a caloric test toward the warm water side and away from the cool water side is COWS; cool, opposite, warm, same.

HORIZONTAL CONJUGATE GAZE

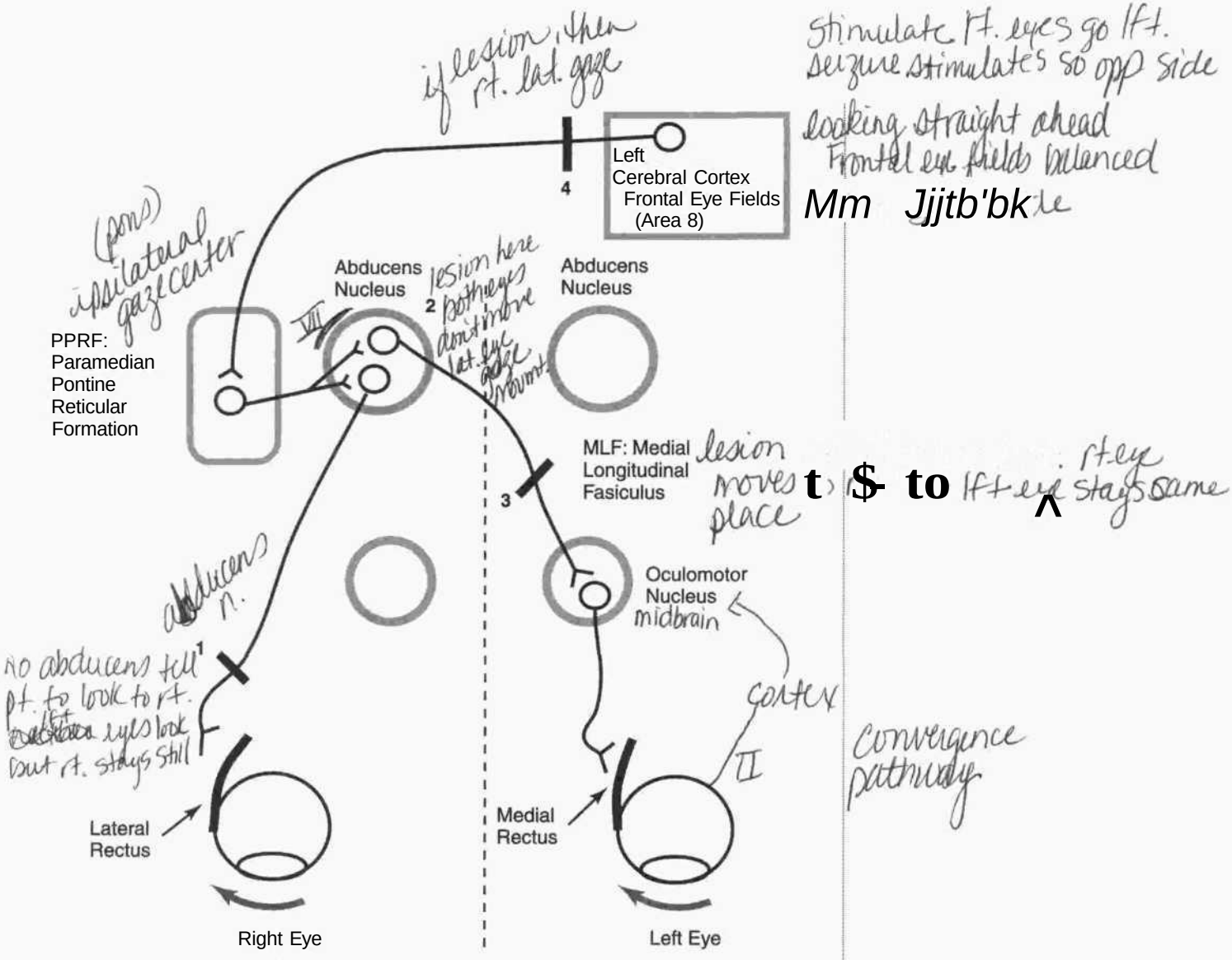
The eyeballs move together in conjugate gaze. The ocular muscles function to move and position both eyes as a unit so that an image falls on a corresponding spot on the retina of each eye. The slightest weakness in the movements of one eye causes diplopia, the presence of a double image, indicating that the image has been shifted to a different position on the retina of the affected side. Although gaze in all planes is possible, the muscles and cranial nerves involved in horizontal conjugate gaze, or abduction and adduction of both eyes together, are the most important eye movements (Fig IV-5-10).

Abduction of each eyeball is performed largely by the lateral rectus muscle, which is innervated by the abducens nerve (CN VI). Adduction of the eyeball is performed by the medial rectus muscle, which is innervated by the oculomotor nerve (CN III). Therefore, for both eyes to look to the right in horizontal gaze, the right abducens nerve and the right lateral rectus muscle must be active to abduct the right eye, and the left oculomotor nerve and the left medial rectus muscle must be active to adduct the left eye. The net effect is that both eyes will look to the right.

In the brain stem, the abducens nucleus (CN VI) and the oculomotor nucleus (CN III) are situated close to the midline just beneath the fourth ventricle or the cerebral aqueduct, in the pons and midbrain. These nuclei are interconnected by the fibers in the MLF. It is the fibers in the MLF that permit conjugate gaze, either when the target moves or when the head moves, through their interconnections to gaze centers and the vestibular system.

Control of Horizontal Gaze

Horizontal gaze is controlled by two interconnected gaze centers. One control center is in the frontal lobe, the frontal eye field (Brodmann area 8). This area acts as a center for **contralateral** horizontal gaze. In the pons is a second gaze center, known as the pontine gaze center or the PPRF, the paramedial pontine reticular formation. This is a center for ipsilateral horizontal gaze. When activated by neurons in the frontal eye field, the pontine gaze center neurons send axons to synapse with cell bodies in the abducens nucleus, which is actually contained within the pontine gaze center. The pontine gaze center also sends axons that cross immediately and course in the contralateral MLF to reach the contralateral oculomotor nucleus. The net effect of stimulation of the left frontal eye field, therefore, is activation of die pontine gaze center on the right and a saccadic horizontal eye movement of both eyes to the right. Horizontal gaze to the right results from activation of the right abducens nucleus and the left oculomotor nucleus by fibers in the MLF. Lesions in the MLF result in an internuclear ophthalmoplegia in which there is an ability to adduct one eye on attempted gaze to the opposite side. For example, a lesion in the right MLF results in an inability to adduct the right eye on an attempted gaze to the left. The left eye abducts normally but exhibits a nystagmus. If the MLF is lesioned bilaterally (as might be the case in multiple sclerosis), neither eye adducts on attempted gaze (Figs IV-5-11 and IV-5-12), and the abducting eye exhibits a nystagmus.



(Lesion sites are indicated by 1-4.)

Figure IV-5-10. Voluntary Horizontal Conjugate Gaze

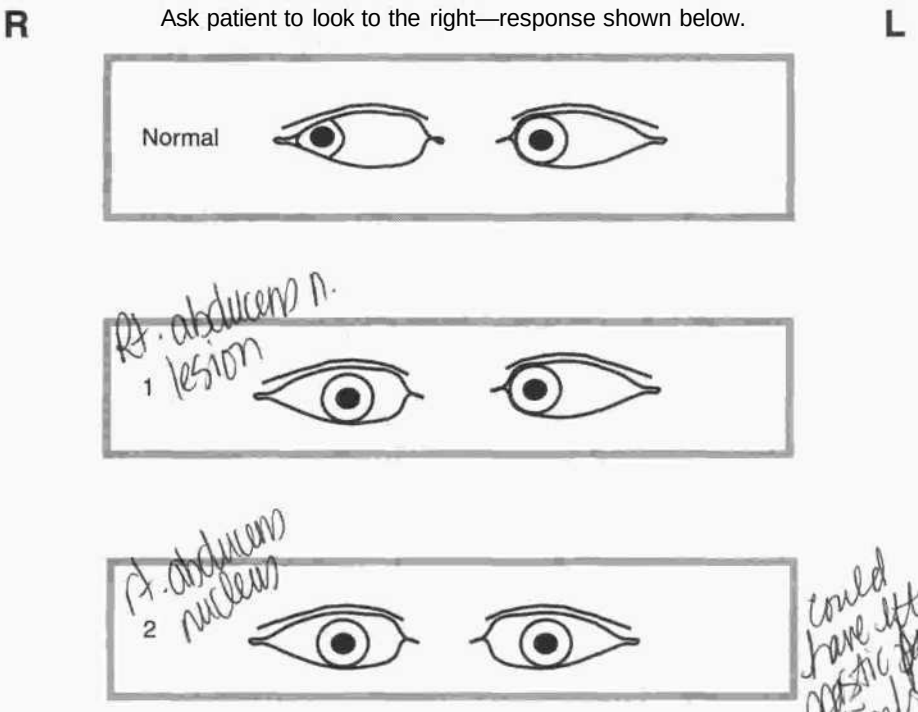


Figure IV-5-11. Normal and Abnormal Responses to the Horizontal Gaze

Table IV-5-2. Normal and Abnormal Responses to the Horizontal Conjugate Gaze: Part 1

Lesion location	Symptoms (Results)
Right Abducens nerve, **#1**	Right eye cannot look right (abduct)
Right Abducens nucleus, #2	Neither eye can look right (lateral gaze paralysis)—may be slow drift left and right facial paralysis

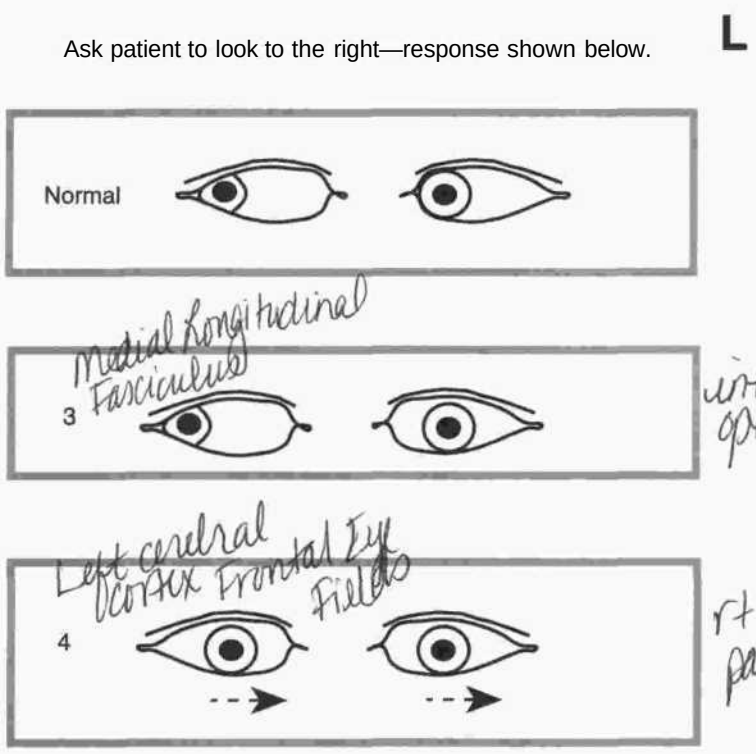


Figure 1V-5-12. **Normal and Abnormal Responses to the Horizontal Conjugate Gaze Test: Part 2**

Table IV-5-3. Normal and Abnormal Responses to the Horizontal Gaze: Part 2

Location	Symptoms
Left MLF, #3	Left eye cannot look right; convergence intact; right eye exhibits nystagmus
Left cerebral cortex, #4	Neither eye can look right: but slow drift to left

BLOOD SUPPLY TO THE BRAIN STEM

Vertebral Artery

This artery is a branch of the subclavian that ascends through the foramina of the transverse processes of the upper six cervical vertebrae. It enters the posterior fossa by passing through the foramen magnum. The vertebral arteries continue up the ventral surface of the medulla and, at the caudal border of the pons, join to form the basilar artery (Fig IV-5-13).

Abbreviations

AICA = anterior inferior cerebellar artery

PICA = posterior inferior cerebellar artery

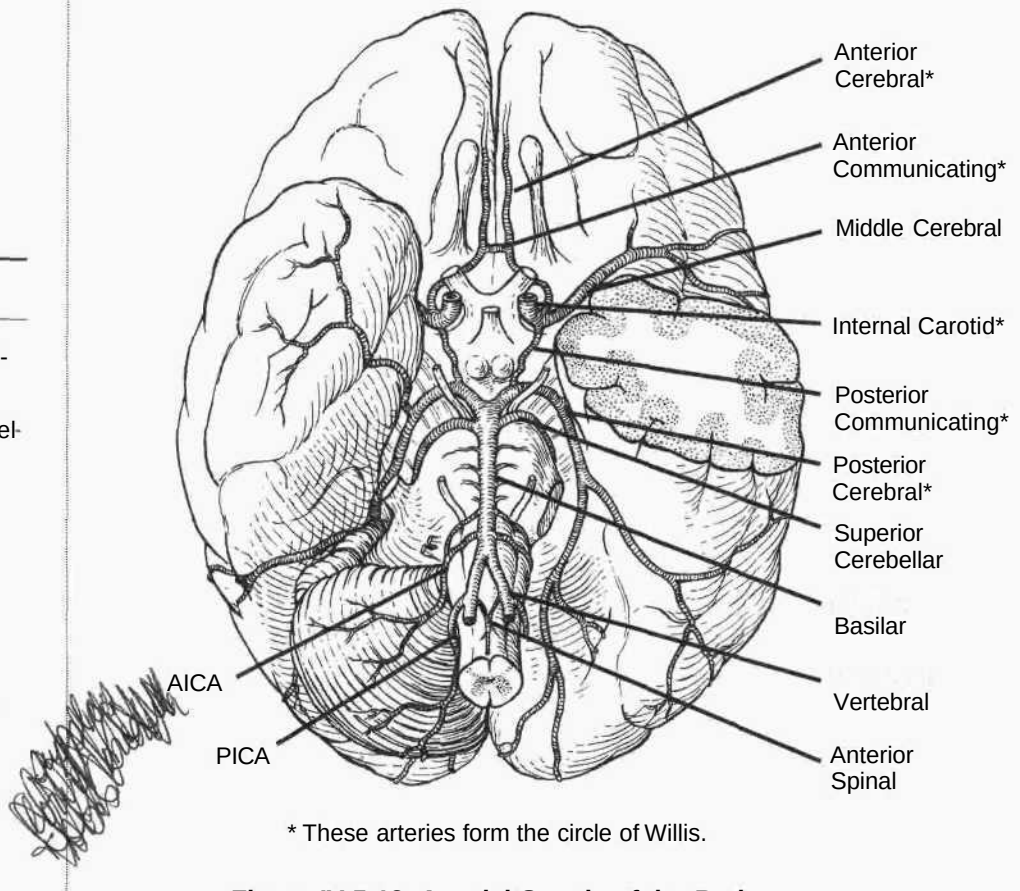


Figure IV-5-13. Arterial Supply of the Brain

Branches of the vertebral artery include: the anterior spinal artery, which supplies the ventrolateral two thirds of the cervical spinal cord and the ventrolateral part of the medulla; the posterior inferior cerebellar artery (PICA), which supplies the cerebellum and dorsolateral part of the medulla.

Basilar Artery

The basilar artery is formed by the joining of the two vertebral arteries at the pontomedullary junction. It ascends along the ventral midline of the pons and terminates near the rostral border of the pons by dividing into the two posterior cerebral arteries.

Branches of the basilar artery include: The labyrinthine artery, which follows the course of the eighth cranial nerve and supplies the inner ear; the anterior inferior cerebellar artery, which supplies part of the pons and the anterior and inferior regions of the cerebellum; the superior cerebellar artery, which supplies part of the rostral pons and the superior region of the cerebellum; pontine branches, which supply much of the pons via paramedian and circumferential vessels.

At the rostral end of the midbrain, the basilar artery divides into a pair of posterior cerebral arteries. Paramedian and circumferential branches of the posterior cerebral artery supply the midbrain.

BRAIN STEM LESIONS

There are two keys to localizing brain stem lesions. First, it is uncommon to injure parts of the brain stem without involving one or more cranial nerves. The cranial nerve signs will localize the lesion to the midbrain (CN III or IV), upper pons (CN V), lower pons (CN VI, VII, or VIII), or upper medulla (CN IX, X, or XII). Second, if the lesion is in the brain stem, the cranial nerve deficits will be seen with a lesion to one or more of the descending or ascending long tracts (corticospinal, medial lemniscus, spinothalamic, descending hypothalamic fibers). Lesions in the brain stem to any of the long tracts except for the descending hypothalamic fibers will result in a contralateral deficit. A unilateral lesion to the de^c^ndm^Jrypothalamicfibersthat resujtsjnjjorner's syndrome is always seen ipsilateral to the side of the lesion.

Medial Medullary Syndrome

Medial medullary syndrome is most frequently the result of occlusion of the vertebral artery or the anterior spinal artery (Fig rV-5-14). Medial medullary syndrome presents with a lesion of the hypoglossai nerve as the cranial nerve sign and lesions to both the medial lemniscus and the corticospinal tract. Corticospinal tract lesions produce contralateral spastic hemiparesis of both limbs.

Medial lemniscus lesions produce a contralateral deficit of propjioception and touch, pressure, and vibratory sensations in the limbs and body.

Lesions of the hypoglossal nerve in the medulla produce an ipsilateral paralysis of halfrKeTongue with atrophy. The tongue deviates toward the side of the lesion upon protrusion.

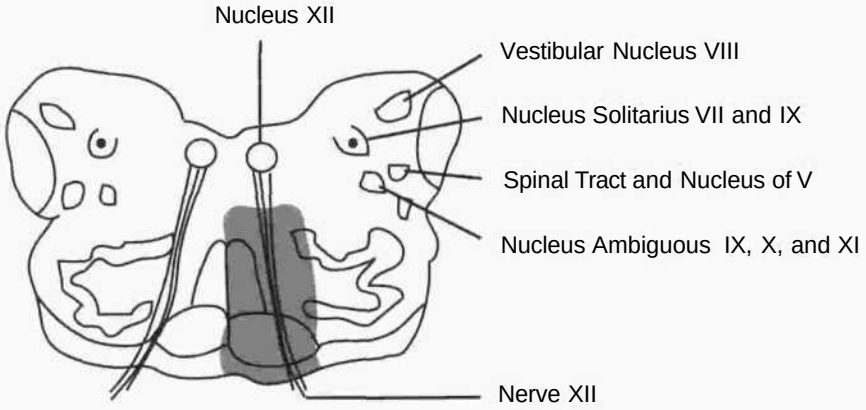


Figure IV-5-14. Medial Medullary Syndrome

Table IV-5-4. Medial Medullary Syndrome

Structure	Sign
Pyramid	Contralateral spastichemiparesis of body
Medial lemniscus	Contralateralloss of position and vibration sense on the body
Fibers ofXII	Tongue deviates to lesion side

Lateral Medullary (Wallenberg's) Syndrome (PICA syn.)

Lateral medullary syndrome results from occlusion of\ke PICA (Fig IV-5-15).

The cranial nerves or nuclei involved in the lesion are the vestibular or the cochlear parts of CN VIII, the glossopharyngeal and the vagus nerves, and the spinal nucleus or tract of V. The long tracts involved are the spinothalamic tract and the descending hypothalamic fibers.

Spinothalamic tract lesions produce a pain and temperature sensation deficit in the contralateral limbs and body.

Lesions of descending hypothalamic fibers produce an ipsilateral Homer's syndrome (i.e., miosis, ptosis, and anhidrosis).

Lesions of the vestibular nuclei and pathways may produce nystagmus, vertigo, nausea, and vomiting. If there is a vestibular nystagmus, the fast component will be away from the side of the lesion.

Lesions of the cochlear nucleus or auditory nerve produce an ipsilateral sensorineural hearing loss.

Lesions of the vagus nerves exiting the medulla may produce dysphagia (difficulty in swallowing) or hoarseness. The palate will droop on the affected side, and the uvula will deviate away from the side of the lesion.

Lesions of the glossopharyngeal nerve result in a diminished or absent gag reflex.

Lesions of the spinal tract and nucleus of the trigeminal nerve produce a loss of just pain and temperature sensations on the ipsilateral side of half the face. Touch sensations from the face and the corneal blink reflex will be intact. In lateral medullary syndrome, the pain and temperature losses are alternating; these sensations are lost from the face and scalp ipsilateral to the lesion but are lost from the contralateral limbs and trunk.

Taste sensations may be altered if the solitary nucleus is involved.

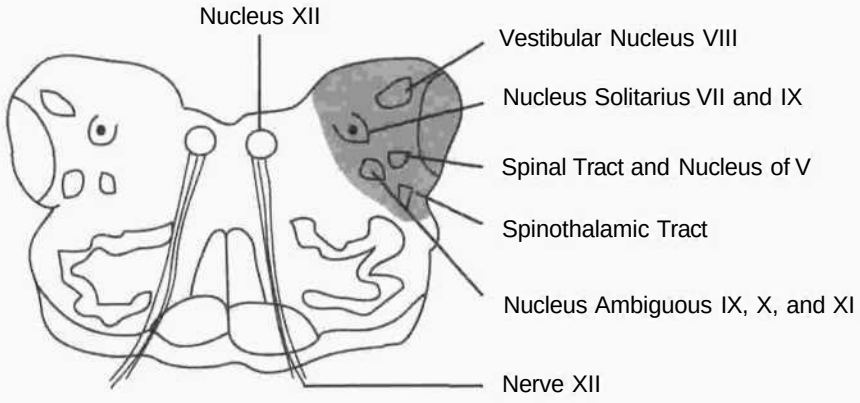


Figure IV-5-15. Lateral Medullary Syndrome (Wallenberg's Syndrome)

Table FV-5-5. Lateral Medullary Syndrome (Wallenberg's Syndrome)

Structure	Sign
Inferior cerebellar peduncle (ICP)	Ipsilateral limb ataxia
Spinal V	Ipsilateral pain and temperature loss—face
Spinothalamic tract	Contralateral pain and temperature loss—body
Vestibularnudei	Vomiting, vertigo, nystagmus—away from lesion side
Descending hypothalamics	y^rnpr's SYDlirillHf (fl‹wa y<! ip«i]s>tPra1)
Nucleusambiguus (fibers of IX, X)	Ipsilateral paralysis of the vocal cord, dysphagia, palate droop

occulomotor nerve damage - pupil dilate (unequal size) + ptosis

Medial Pontine Syndrome

Medial pontine syndrome results from occlusion of paramedian branches of the basilar artery (Fig IV-5-16).

At a minimum, this lesion affects the exiting fibers of the abducens nerve and the corticospinal tract. The medial lemniscus may be affected if the lesion is deeper into the pons, and the facial nerve may be affected if the lesion extends laterally.

The long tract signs will be the same as in medial medullary syndrome, involving the corticospinal and medial lemniscus, but the abducens nerve and the facial nerve lesions localize the lesion to the caudal pons.

Corticospinal tract lesions produce contralateral spastic hemiparesis of both limbs.

Medial lemniscus lesions produce a contralateral deficit of proprioception and touch, pressure, and vibratory sensations in the limbs and body.

Lesions of the abducens nerve exiting the caudal pons produce an internal strabismus of the ipsilateral eye (from paralysis of the lateral rectus). This results in diplopia on attempted lateral gaze to the affected side.

Lesions of the facial nerve exiting the caudal pons produce complete weakness of the muscles of facial expression on the side of the lesion.

Lesions of the facial nerve may also include an alteration of taste from the anterior two thirds of the tongue, loss of lacrimation (eye dry and red), and loss of the motor limb of the corneal blink reflex.

If a lesion extends dorsally to include the abducens nucleus (which includes the horizontal gaze center in the PPRF), there may be a lateral gaze paralysis in which both eyes are forcefully directed to the side contralateral to the lesion.

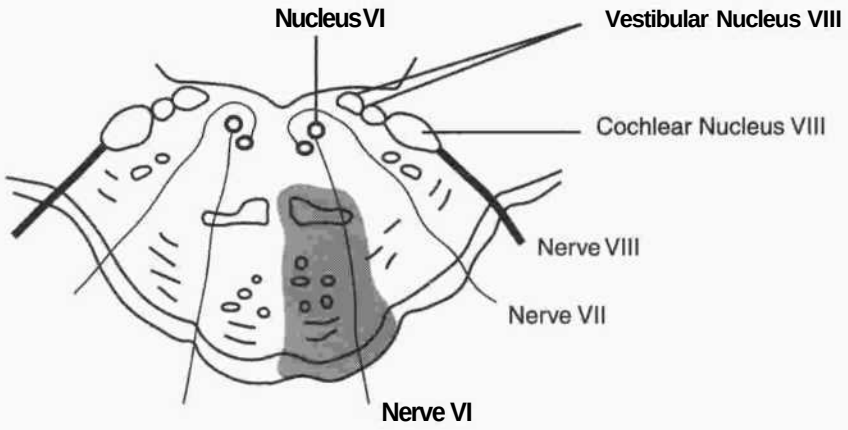


Figure IV-5-16. Medial Pontine Syndrome

Table IV-5-6. Medial Pontine Syndrome

Structure	Sign
CST	Contralateral spastic hemiparesis of the body
Mediallemniscus	Contralateral loss of position and vibration on the body
FibersofVI	Medial strabismus

Lateral Pontine Syndrome

Lesions of the dorsolateral pons usually result from occlusion of the anterior inferior cerebellar artery (caudal pons) or superior cerebellar artery (rostral pons). The long tracts involved will be the same as in lateral medullary syndrome, the spinothalamic tract and the descending hypothalamic fibers. The cranial nerves involved will be the facial and vestibulocochlear in the caudal pons, the trigeminal nerve in the rostral pons, and the spinal nucleus and tract of V in both lesions (FigIV-5-17).

Spinothalamic tract lesions produce a pain and temperature sensation deficit in the contralateral limbs and body.

Lesions of descending hypothalamic fibers produce an ipsilateral Horner's syndrome (i.e., miosis, ptosis, and anhidrosis).

Lesions of the vestibular nuclei and pathways (caudal pons) produce nystagmus, vertigo, nausea, and vomiting. Again, the fast phase of the nystagmus will be away from the side of the lesion. Lesions of the cochlear nucleus or auditory nerve produce an ipsilateral sensorineural hearing loss.

Lesions of the spinal tract and nucleus of the trigeminal nerve result only in a loss of pain and temperature sensations on the ipsilateral side of half the face.

Lesions of the facial nerve and associated structures produce ipsilateral facial paralysis, loss of taste from the anterior two thirds of the tongue, loss of lacrimation and salivation, and loss of the corneal reflex.

Lesions of the trigeminal nerve (rostral pons) result in complete anesthesia of the face on the side of the lesion, weakness of muscles of mastication, and deviation of the jaw toward the lesioned side.

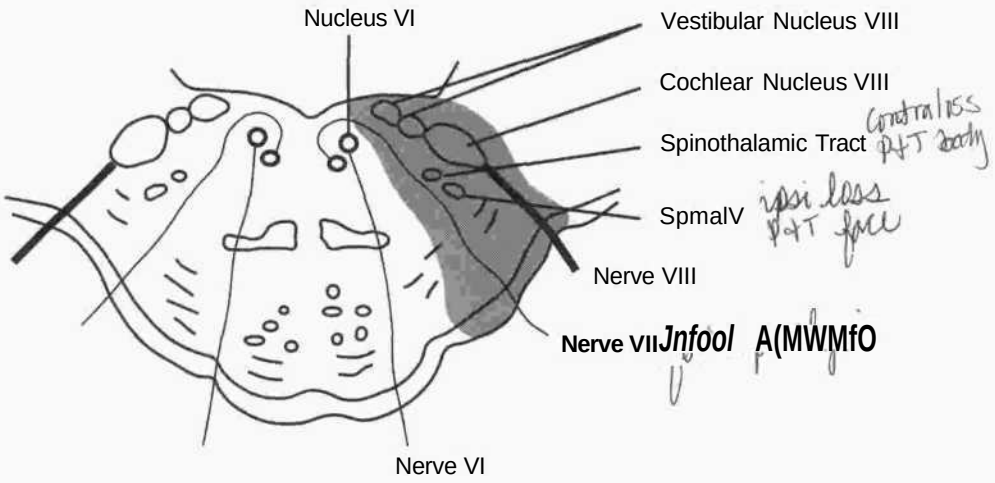


Figure IV-5-17. Lateral Pontine Syndrome

Table IV-5-7. Lateral Pontine Syndrome

Structure	Sign
ICP	Ipsilateral limb ataxia
Spinal V	Ipsilateral pain and temperature loss-face
Spinothalamic	Contralateral pain and temperature loss-body
Vestibular nuclei	Vomiting, vertigo, nystagmus-away from lesion side
Descending hypothalamics	Horner's syndrome (Ipsilateral)
Fibers of VII	Ipsilateral facial paralysis
Fibers of VIII	Hearing loss

Pontocerebellar Angle Syndrome

Pontocerebellar angle syndrome is usually caused by an acoustic neuroma (schwannoma) of CN VIII. This is a slow-growing tumor, which originates from Schwann cells in the veltibular nerve (or less commonly the auditory nerve). As the tumor grows, it exerts pressure on the lateral part of the caudal pons where CN VTI^emerges and may expand anteriorly to compress the fifth nerve. The cranial nerve deficits seen together localize the lesion totEebrain stem, but the absence of long tract signs indicates that the lesion must be outside of the brain stem.

Medial Midbrain (Weber's, Syndrome

Medial midbrain (Weber's) syndrome results from occlusion of branches of the posterior cerebral artery (Figs IV-5-18 and FV-5-19).

In medial midbrain syndrome, exiting fibers of CN **III** are affected, along with corticobulbar and corticobulbar fibers in the medial aspect of the cerebral peduncle. Third nerve lesions result in a ptosis, mydriasis (dilated pupil), and an external strabismus. As with any brain stem lesion affecting corticospinal fibers, accommodation and convergence will also be affected. Corticospinal tract lesions produce contralateral spastic hemiparesis of both limbs. The involvement of the corticobulbar fibers results in a contralateral lower face weakness seen as a drooping of the corner of the mouth. The patient will be able to shut the eye (blink reflex is intact) and wrinkle the forehead.

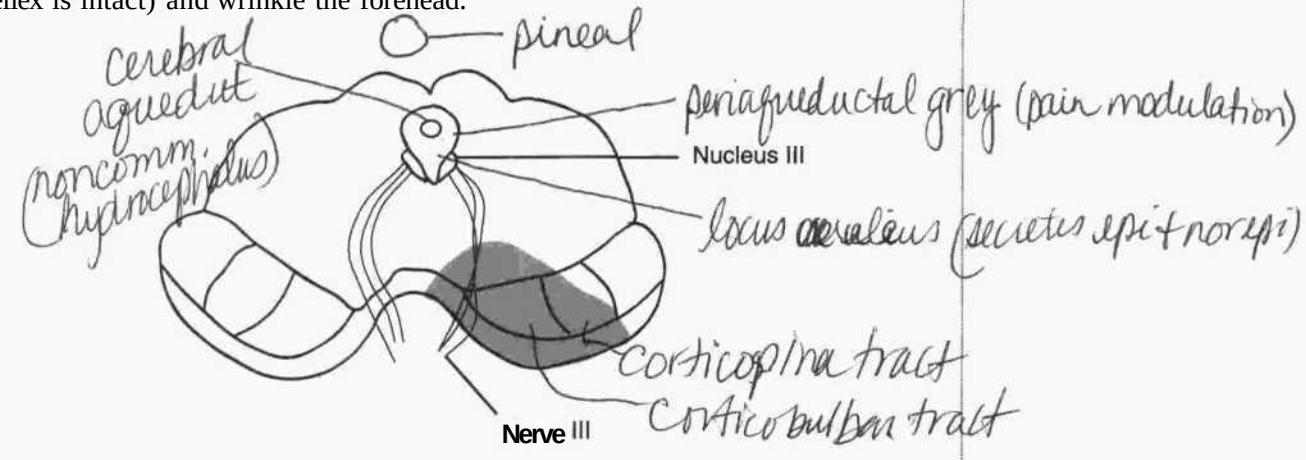
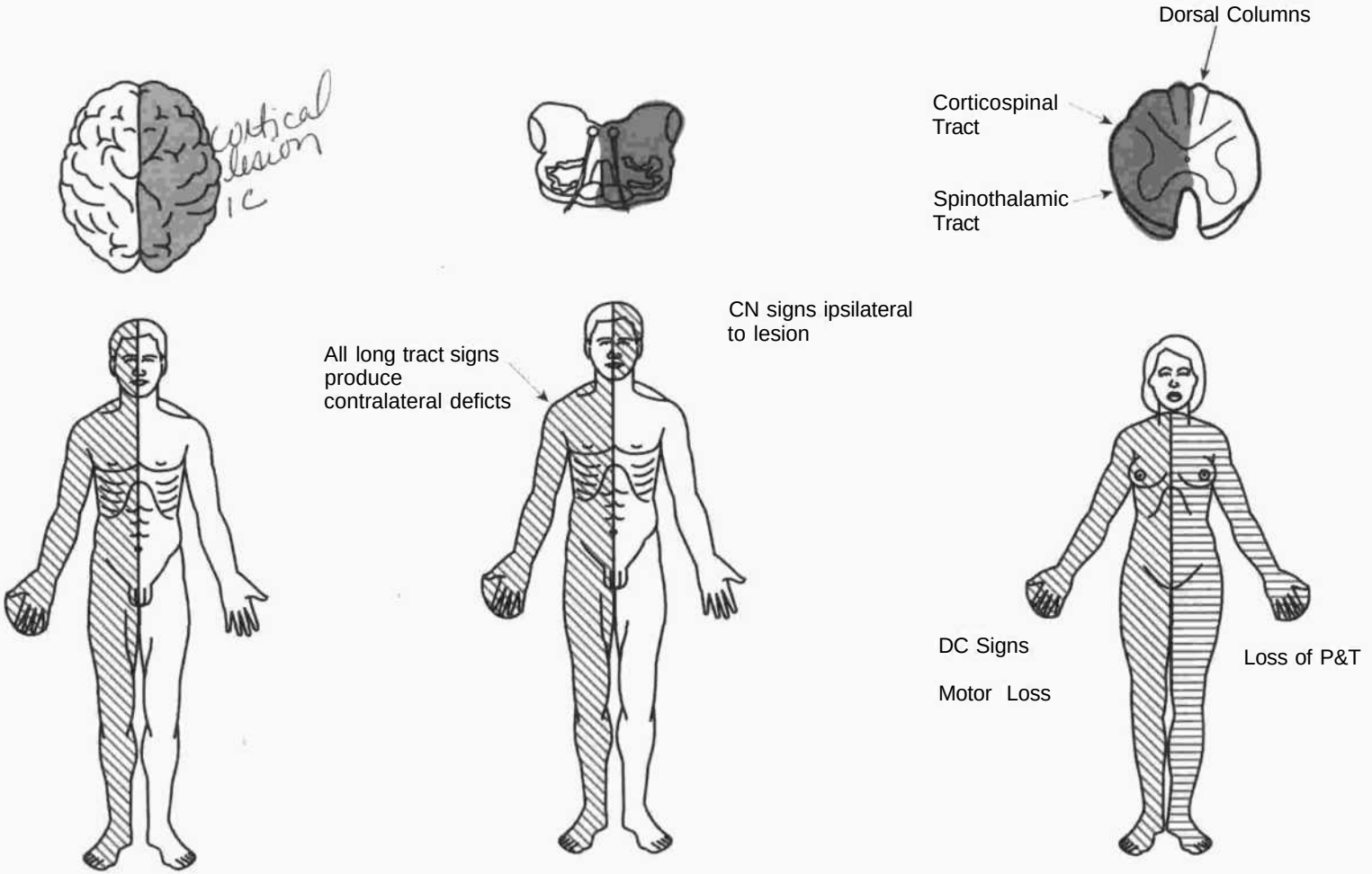


Figure IV-5-18. Ventral Midbrain Syndrome (Weber's Syndrome)

Structure	Sign
CST	Contralateral spastic hemiparesis, mostly upper limb
Corticobulbar tract	Contralateral spastic hemiparesis of lower half of FACE
Fibers of **III**	Ipsilateral oculomotor palsy 1. Dilated pupil 2. Ptosis 3.Eye pointing down and out (Lateral strabismus)



Cortex Lesions:

All sensory system lesions from face or body produce contralateral deficits. Lesion of corticobulbar fibers produces contralateral lower face weakness.

Brain Stem Lesions:

Long Track Findings - ALL give rise to contralateral deficts.

Lesion is in brainstem - at level of cranial nerve affected and on same side of cranial nerve findings

Spinal Cord Hemisection:

Long Track Findings - NOT ALL on one side; loss of P&T separate from others

Lesion is at spinal cord level on side opposite P&T loss

PT&T = Pain and temperature

Figure IV-5-19. Strategy for the Study of Lesions

Parinaud's Syndrome

Parinaud's syndrome usually occurs as a result of a pineal tumor compressing the superior colliculi. The most common sign is paralysis of upward or vertical gaze, combined with bilateral pupillary abnormalities (e.g., slightly dilated pupils, which may show an impaired light or accommodation reaction) and signs of elevated intracranial pressure. Compression of the cerebral aqueduct can result in noncomrnunicating hydrocephalus.

RETICULAR FORMATION

The reticular formation is located in the brain stem and functions to coordinate and integrate the actions of different parts of the CNS. It plays an important role in the regulation of muscle and reflex activity and control of respiration, cardiovascular responses, behavioral arousal, and sleep.

Reticular Nuclei

RapheNuclei

The raphe nuclei are a narrow column of cells in the midline of the brain stem, extending from the medulla to the midbrain. Cells in some of the raphe nuclei (e.g., the dorsal raphe nucleus) synthesize serotonin (5-hydroxytryptamine [5-HT]) from L-tryptophan and project to vast areas of the CNS. They play a role in mood, aggression, and the induction of pon^iacid-ey^-movement (REM) sleep.

LocusCaeruleus

Cells in the locus caeruleus synthesize norepinephrine and send projections to most brain areas involved in the control of cortical activation (arousal). Decreased levels of norepinephrine are evident in REM (paradoxic) sleep.

PeriaqueductalGray

The periaqueductal (central) gray is a collection of nuclei surrounding the cerebral aqueduct in the midbrain. Opioid receptors are present on many periaqueductal gray cells, the projections from which descend to modulate pain at the level of the dorsal horn of the spinal cord.

Clinical Correlate

Neurons in both the raphe and locus coeruleus degenerate in Alzheimer's disease.

The Cerebellum

6

GENERAL FEATURES

The cerebellum is derived from the metencephalon and is located dorsal to the pons and the medulla. The fourth ventricle is found between the cerebellum and the dorsal aspect of the pons. The cerebeUimTjuxuli&BgiQjJie^lanning and fine-tvmiri^^f tifplftai mn<:r1p contractions. It performs these tasks by comparing an intended with an actual performance.

The cerebellum consists of a midline vermis and two lateral cerebellar hemispheres. The cerebellar cortex consists of multiple parallel folds that are referred to as folia. The cerebellar cortex contains several maps of the skeletal muscles in the body (Fig IV-6-1).

The topographic arrangement of these maps indicates that the vermis controls the axial and proximal musculature of the limbs, the intermediate part of the hemisphere controls distal musculature, and the lateral part of the hemisphere is involved in motor planning.

The flocculonodular lobe is involved in control of balance and eye movements.

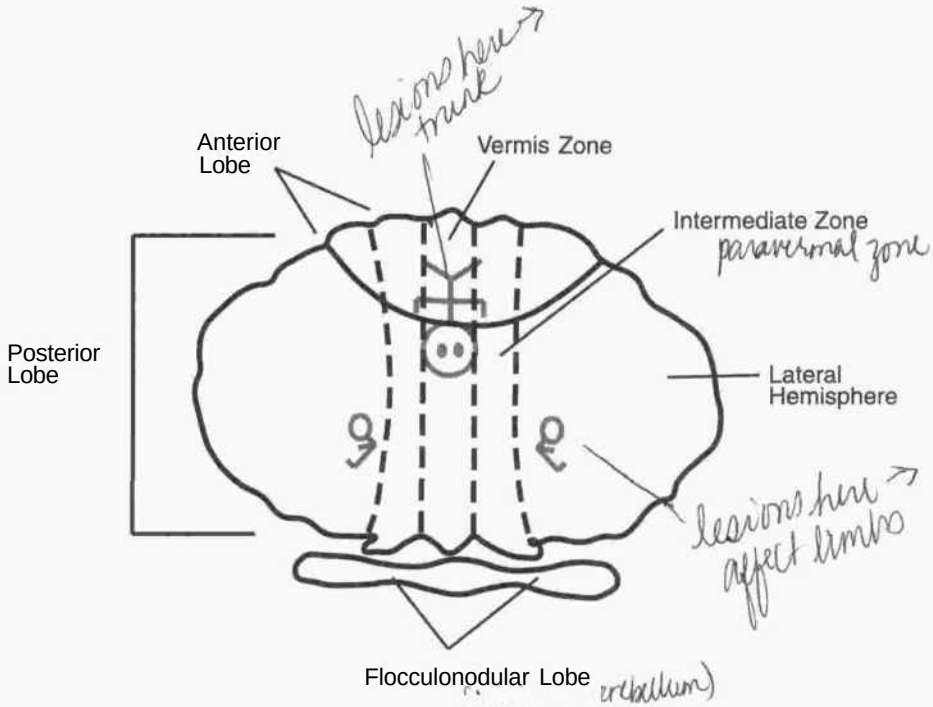


Figure IV-6-1. Cerebellum

Table IV-6-1. Cerebellum

Region	Function	Principle Input
Vermis and intermediate zones	Ongoing motor execution	Spinal cord
Hemisphere	Planning	Cerebral cortex
Flocculonodular lobe	Balance and eye movements	Vestibular nuclei (VIII)

Major input to the cerebellum travels in the inferior cerebellar peduncle (ICP) and middle cerebellar peduncle (MCP). Major outflow from the cerebellum travels in the superior cerebellar peduncle (SCP) (Table IV-6-1).

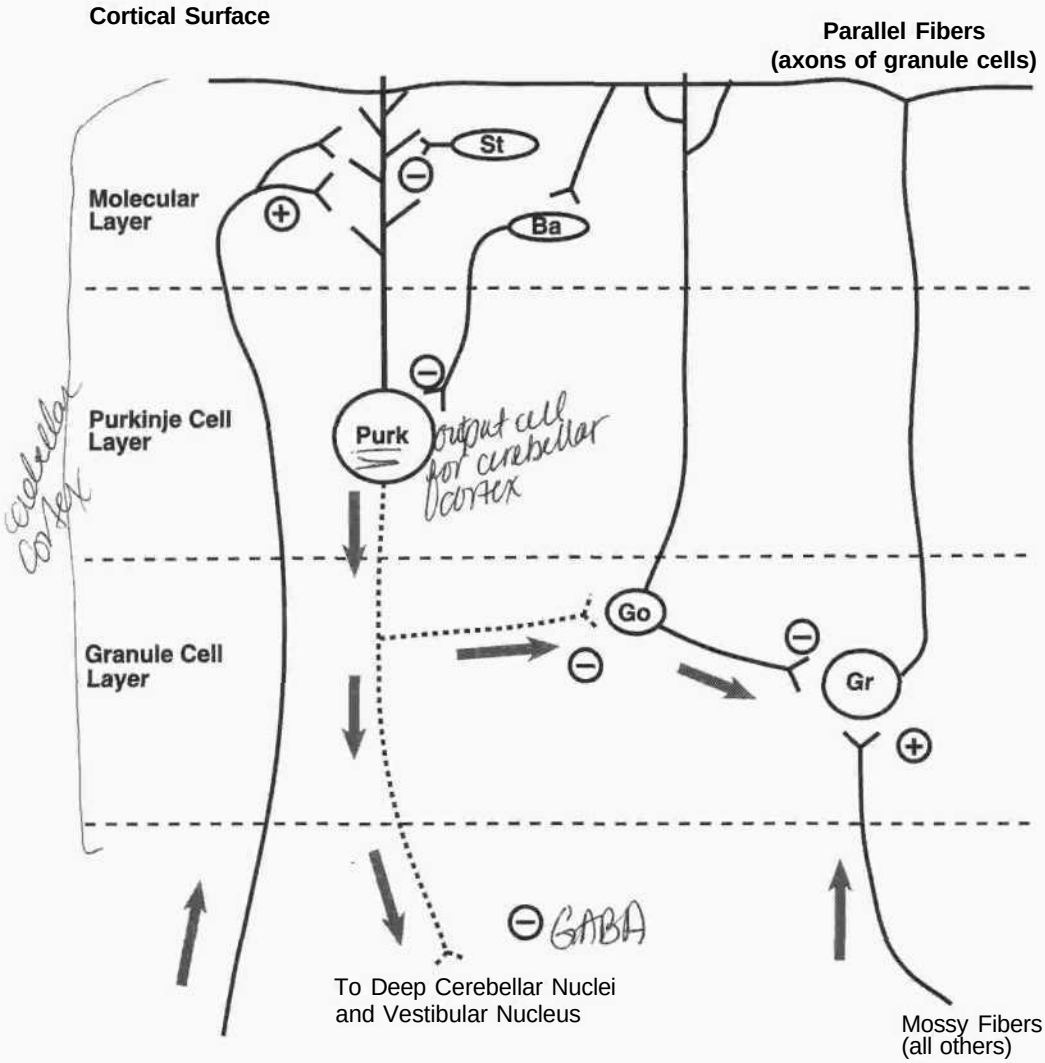
Table IV-6-2. Major Afferents to the Cerebellum

Name	Tract	Enter Cerebellum Via	Target and Function
Mossy fibers	Vestibulocerebellar Spinocerebellar (Cortico)pontocerebellar	ICP ICP and SCP MCP	Excitatory terminals **on** granule cells
Climbing fibers	Olivocerebellar	ICP	Excitatory terminals on Purkinje cells

ICP = inferior cerebellar peduncle; MCP = middle cerebellar peduncle; SCP = superior cerebellar peduncle

CEREBELLAR CYTOARCHITECTURE

All afferent and efferent projections of the cerebellum traverse the ICP, MCP, or SCP. Most afferent input enters the cerebellum in the ICP and MCP; most efferent outflow leaves in the SCP (Fig IV-6-2 and Table IV-6-2).



Purk = Purkinje cell
Gr = Granule
Go = Golgi cell
Ba = Basket cell
St = Stellate cell

** Of the neurons in the cerebellar cortex, the granule cells are the only excitatory neuron.

Figure IV-6-2. Cerebellar Cytoarchitecture

Internally, the cerebellum consists of an outer cortex and an inner medulla.

The three cell layers of the cortex are the molecular layer, the Purkinje layer, and the granule cell layer.

The **molecular layer** is the outer layer and is made up of basket and stellate cells as well as parallel fibers, which are the axons of the granule cells. The extensive dendritic tree of the Purkinje cell extends into the molecular layer.

The **Purkinje layer** is the middle and most important layer of the cerebellar cortex. All of the inputs to the cerebellum are directed toward influencing the firing of Purkinje cells, and only axons of Purkinje cells leave the cerebellar cortex. A single axon exits from each Purkinje cell and projects to one of the deep cerebellar nuclei or to vestibular nuclei of the brain stem.

The **granule cell layer** is the innermost layer of cerebellar cortex and contains Golgi cells, granule cells, and glomeruli. Each glomerulus is surrounded by a glial capsule and contains a granule cell and axons of Golgi cells, which synapse with granule cells. The granule cell is the only excitatory neuron within the cerebellar cortex. All other neurons in the cerebellar cortex, including Purkinje, Golgi, basket, and stellate cells, are inhibitory.

The **medulla** contains the deep cerebellar nuclei.

From medial to lateral, the deep cerebellar nuclei in the medulla are the fastigial nucleus, interposed nuclei, and the dentate nucleus.

Table IV-6-3. Cerebellum: Cell Types

Name	Target (Axon Termination)	Transmitter	Function
Purkinje cell	Deep cerebellar nuclei	GABA	Inhibitory **
Granule cell	Purkinje cell	Glutamate	Excitatory
Stellate cell	Purkinje cell	GABA	Inhibitory
Basket cell	Purkinje cell	GABA	Inhibitory
Golgi cell	Granule cell	GABA	Inhibitory

*,^Purkinje cells are the only outflow from the cerebellar cortex.

Two kinds of excitatory input enter the cerebellum in the form of climbing fibers and mossy fibers. Both types influence the firing of deep cerebellar nuclei by axon collaterals.

Climbing fibers originate exclusively from the inferior olivary complex of nuclei on the contralateral side of the medulla. Climbing fibers provide a direct powerful monosynaptic excitatory input to Purkinje cells.

Mossy fibers represent the axons from all other sources of cerebellar input. Mossy fibers provide an indirect, more diffuse excitatory input to Purkinje cells.

All mossy fibers exert an excitatory effect on granule **cells.** Each granule cell sends its axon into the molecular layer, where it gives off collaterals at a 90-degree angle that run parallel to the cortical surface (i.e., parallel fibers). These granule cell axons stimulate the apical dendrites of the Purkinje cells. Golgi cells receive excitatory input from mossy fibers and from the parallel fibers of the granule cells. The Golgi cell in turn inhibits the granule cell, which activated it in the first place.

The **basket** and **stellate cells,** which also receive excitatory input from parallel fibers of granule cells, inhibit Purkinje cells.

CIRCUITRY

The basic cerebellar circuits begin with Purkinje cells that receive excitatory input directly from climbing fibers and from parallel fibers of granule cells.

Purkinje cell axons project to and inhibit the deep cerebellar nuclei or the vestibular nuclei in an orderly fashion (Fig IV-6-3).

- Purkinje cells in the flocculonodular lobe project to the lateral vestibular nucleus.
- Purkinje cells' in the vermis project to the fastigial nuclei.
- Purkinje cells in the intermediate hemisphere primarily project to the interposed (globose and emboliform) nuclei.
- Purkinje cells in the lateral cerebellar hemisphere project to the dentate nucleus.

t. cerebellar affect A. muscles

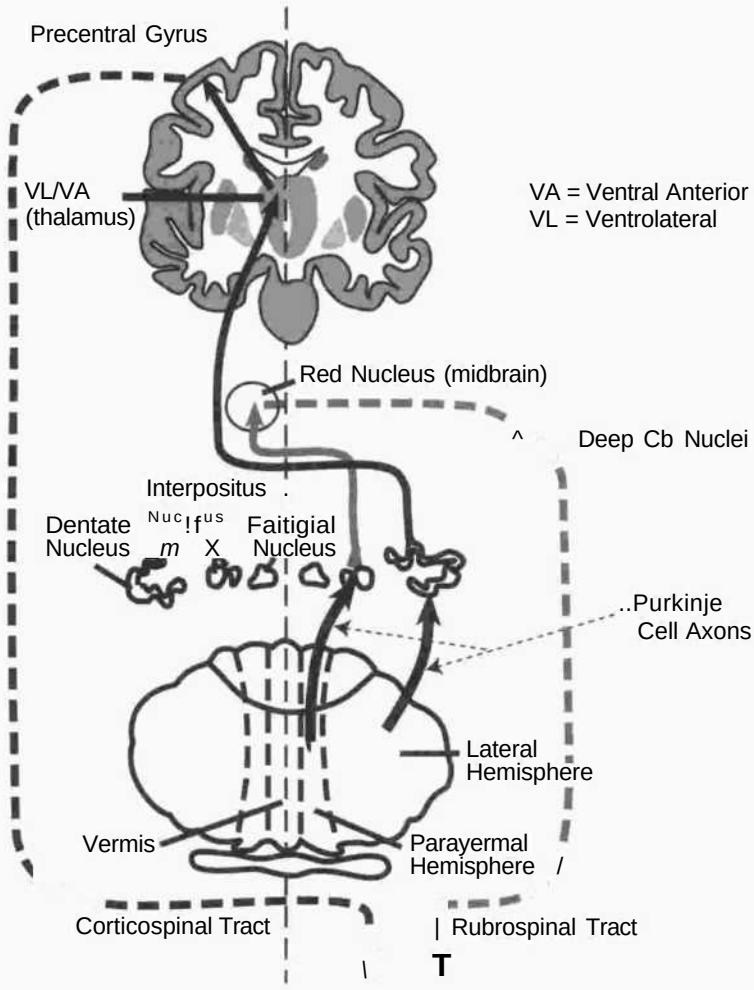


Figure IV-6-3. Cerebellar Efferents

Table IV-6-4. Major Efferents from the Cerebellum

Cerebellar Areas	Deep Cerebellar Nucleus	Efferents to:	Function
Vestibulocerebellum (Flocculo nodular lobe)	Fastigial nucleus	Vestibular nucleus	Elicit positional changes of eyes and trunk in response to movement of the head
Spinocerebellum (Intermediate hemisphere)	Interpositus nucleus	Red nucleus Reticular formation	Influence LMNs via the reticulospinal and rubrospinal tracts to adjust posture and effect movement
Pontocerebellum (Lateral hemispheres)	Dentate nucleus	Thalamus, then Cortex	Influence on LMNs via the corticospinal tract, which effect voluntary movements, especially sequence and precision

Efferents from the deep cerebellar nuclei leave mainly through the SCP and influence all upper motoneurons. In particular, axons from the dentate and interposed nuclei leave through the SCP, cross the midline, and terminate in the ventrolateral (VL) nucleus of the thalamus.

The VL nucleus of the thalamus projects to primary motor cortex and influences the firing of corticospinal and corticobulbar neurons.

Axons from other deep cerebellar nuclei influence upper motoneurons in the red nucleus and in the reticular formation and vestibular nuclei.

Cerebellar Lesions

The hallmark of cerebellar dysfunction is a tremor with intended movement without paralysis or paresis. Symptoms associated with cerebellar lesions are expressed ipsilaterally because the major outflow of the cerebellum projects to the contralateral motor cortex, and then the corticospinal fibers cross on their way to the spinal cord. Thus, unilateral lesions of the cerebellum will result in a patient falling toward the side of the lesion.

Lesions to the Vermal Region

Vermal lesions result in difficulty maintaining posture, gait, or balance (an ataxic gait). Patients with vermal damage may be differentiated from those with a lesion of the dorsal columns by the Romberg sign. In cerebellar lesions, patients will sway or lose their balance with their eyes open; in dorsal column lesions, patients sway with their eyes closed.

Lesions that Include the Hemisphere

Lesions that include the hemisphere produce a number of dysfunctions, mostly involving distal musculature.

An intention tremor is seen when voluntary movements are performed. For example, if a patient with a cerebellar lesion is asked to pick up a penny, a slight tremor of the fingers is evident and increases as the penny is approached. The tremor is barely noticeable or is absent at rest.

Dysmetria is the inability to stop a movement at the proper place. The patient has difficulty performing the finger to nose test.

Dysdiadochokinesia (adiadochokinesia) is the reduced ability to perform alternating movements, such as pronation and supination of the forearm, at a moderately quick pace.

Scanning dysarthria is caused by asynergy of the muscles responsible for speech. In scanning dysarthria, patients divide words into syllables, thereby disrupting the melody of speech.

Clinical Correlate

Anterior vermis lesions are usually the result of degeneration from alcohol abuse and are present with gait ataxia. Posterior vermis lesions result from medulloblastomas or ependymomas and present with truncal ataxia.

Gaze dysfunction occurs when the eyes try to fix on a point: They may pass it or stop too soon and then oscillate a few times before they settle on the target. A nystagmus may be present, particularly with acute cerebellar damage. The nystagmus is often coarse, with the fast component usually directed toward the involved cerebellar hemisphere.

Hypotonia usually occurs with an acute cerebellar insult that includes the deep cerebellar nuclei. The muscles feel flabby on palpation, and deep tendon reflexes are usually diminished.

Visual Pathways

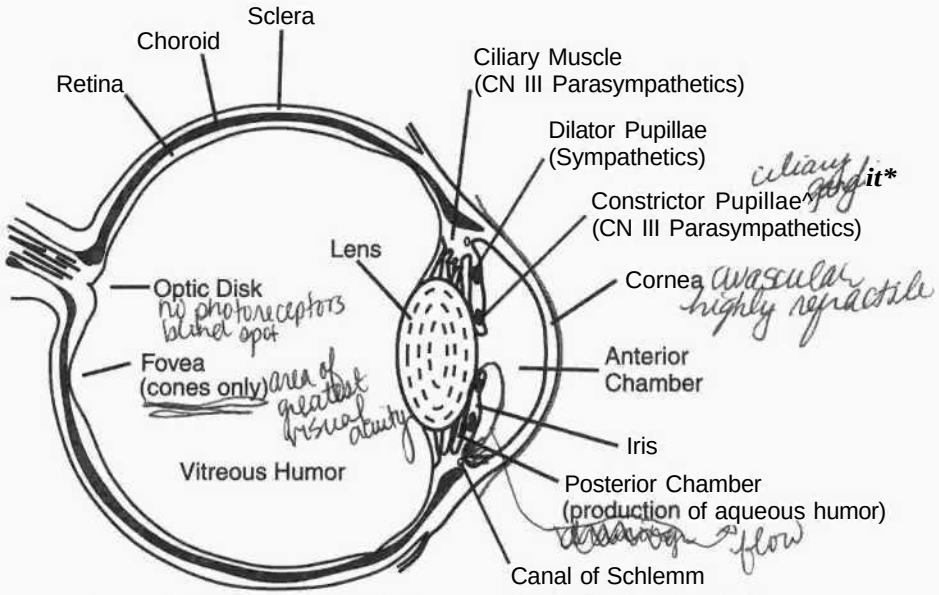
7

EYEBALL AND OPTIC NERVE

Light must pass through the cornea, aqueous humor, pupil, lens, and vitreous humor before reaching the retina (Fig IV-7-1). It must then pass through the layers of the retina to reach the photoreceptive layer of rods and cones. The outer segments of rods and cones transduce light energy from photons into membrane potentials. Photopigments in rods and cones absorb photons, and this causes a conformational change in the molecular structure of these pigments. This molecular alteration causes sodium channels to close, a hyperpolarization of the membranes of the rods and cones, and a reduction in the amount of neurotransmitter released. Thus, rods and cones release less neurotransmitter in the light and more neurotransmitter in the dark. Rods and cones have synaptic contacts on bipolar cells that project to ganglion cells (Fig IV-7-2). Axons from the ganglion cells converge at the optic disc to form the optic nerve, which enters the cranial cavity through the optic foramen. At the optic disc, these axons acquire a myelin sheath from the oligodendrocytes of the CNS.

Clinical Correlate

Vitamin A, necessary for retinal transduction, cannot be synthesized by humans. A dietary deficiency of vitamin A causes visual impairment resulting in night blindness.



Accommodation (near) Reflex

- Contraction of the ciliary muscle, which results in thickening of the lens
- Contraction of the pupillae muscle
- Convergence

Figure iV-7-1.The **Eyeball**

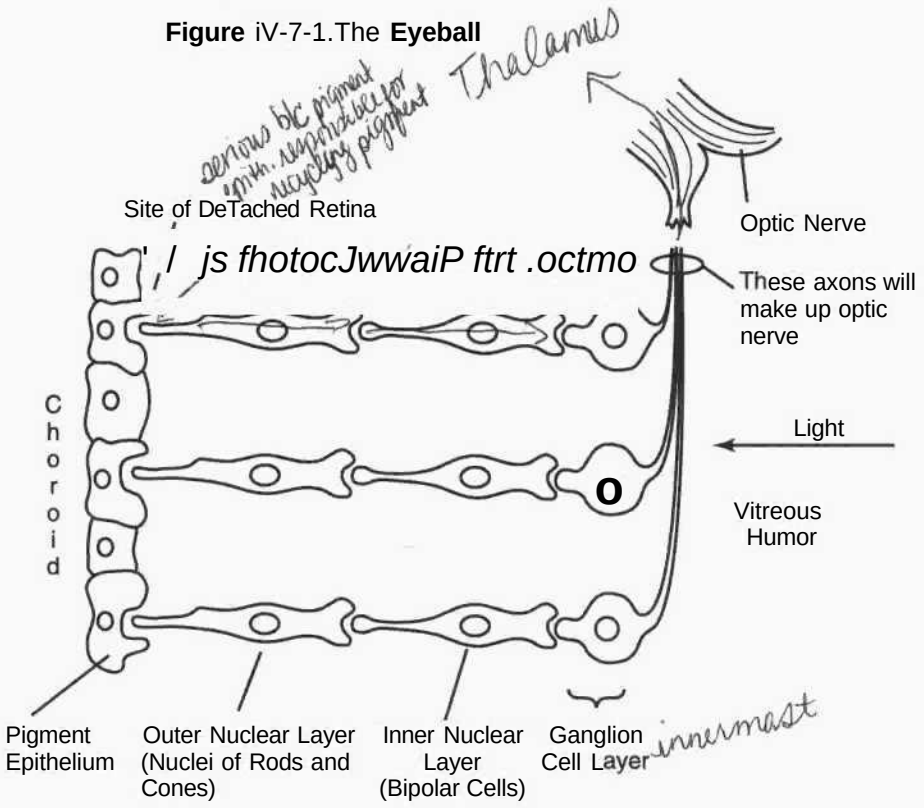


Figure IV-7-2. The Retina

At the optic chiasm, 60% of the optic nerve fibers from the nasal half of each retina cross and project into the contralateral optic tract (Fig IV-7-3). Fibers from the temporal retina do not cross at the chiasm and instead pass into the ipsilateral optic tract. The optic tract contains remixed optic nerve fibers from the temporal part of the ipsilateral retina and fibers from the nasal part of the contralateral retina. Because the eye inverts images like a camera, in reality each nasal retina receives information from a temporal hemifield, and each temporal retina receives information from a nasal hemifield. Most fibers in the optic tract project to the lateral geniculate nucleus. Optic tract fibers also project to the superior colliculi for reflex gaze, to the pretectal area for the light reflex, and to the suprachiasmatic nucleus of the hypothalamus for circadian rhythms.

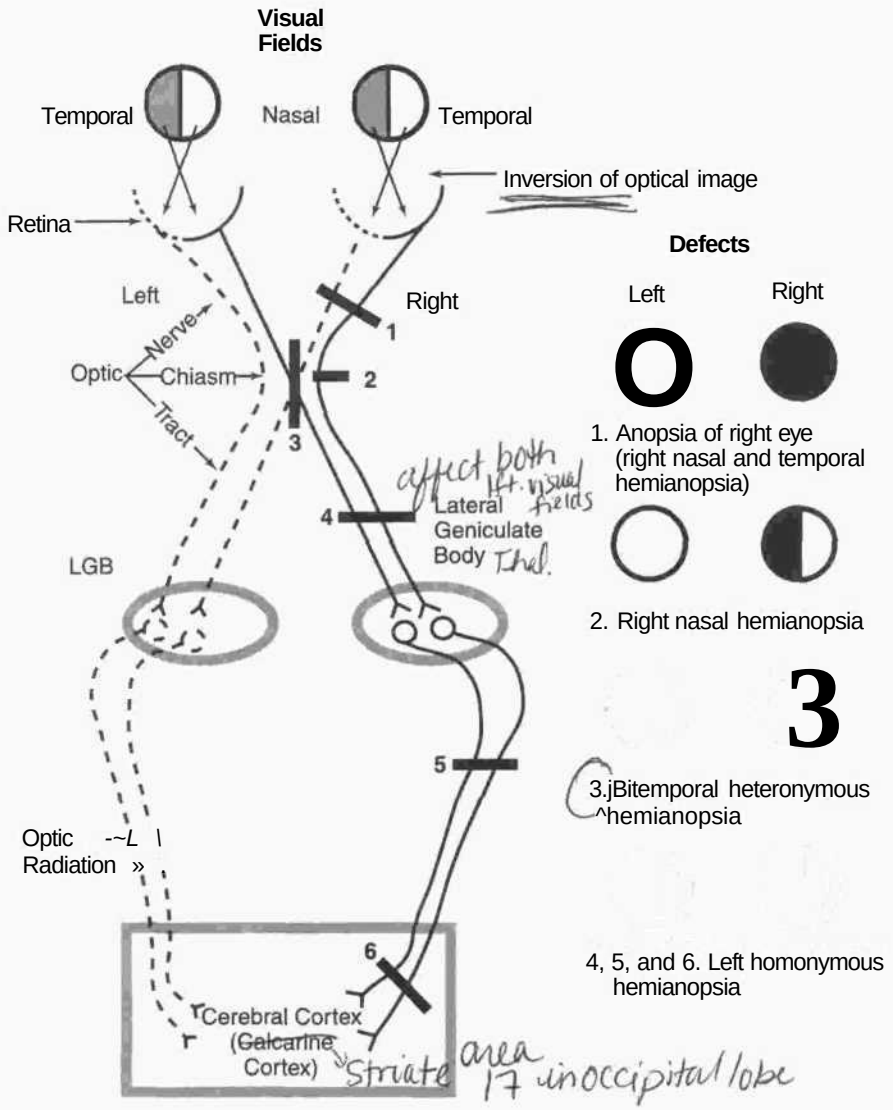


Figure IV-7-3. Visual System I

The lateral geniculate body (LGB) is a laminated structure that receives input from

Clinical Correlate

Some causes of lesions at #1-6:

1. Optic neuritis—in multiple sclerosis, occlusion of central artery of retina
2. Aneurysm of internal carotid **artery**
3. Craniopharyngioma, pituitary adenoma, aneurysm of anterior communicating artery
4. Vascular; lesion is rarely complete
5. 6. Vascular due to occlusion of branch of posterior cerebral artery

Note

Visual information from **lower** retina courses in **lateral** fibers forming Meyer's **loop,** which projects to the lingual gyrus.

Clinical Correlate

Some causes of lesions at #7-9:

7. Occlusion of branch of middle cerebral artery
8, 9. Occlusion of a branch of posterior cerebral artery. The macula is spared in #9 due to collateral blood supply from the middle cerebral artery.

the optic tract and gives rise to axons that terminate on cells in the primary visual cortex (striate cortex, Brodmann area 17) of the occipital lobe. The LGB laminae maintain a segregation of inputs from the ipsilateral and contralateral retina.

The axons from the LGB that project to the striate cortex are known as optic radiations, visual radiations, or the geniculocalcarine tract. The calcarine sulcus divides the striate cortex (primary visual cortex or Brodmann area 17) into the cuneus and the lingual gyri. The cuneus gyrus, which lies on the superior bank of the calcarine cortex, receives the medial fibers of the visual radiations. The lingual gyrus, which lies on the inferior bank of the calcarine cortex, receives the lateral fibers of the visual radiation. The medial fibers coursing in the visual radiations, which carry input from the upper retina (i.e., the lower contralateral visual field), pass from the LGB directly through the parietal lobe to reach the cuneus gyrus. Significantly, the lateral fibers coursing in the visual radiations, which carry input from the lower retina (i.e., the upper contralateral visual field), take a circuitous route from the LGB through Meyer's loop anteriorly into the temporal lobe. The fibers of Meyer's loop then turn posteriorly and course through the parietal lobe to reach the lingual gyrus in the striate cortex.

This figure shows the pathway for the right visual field only.

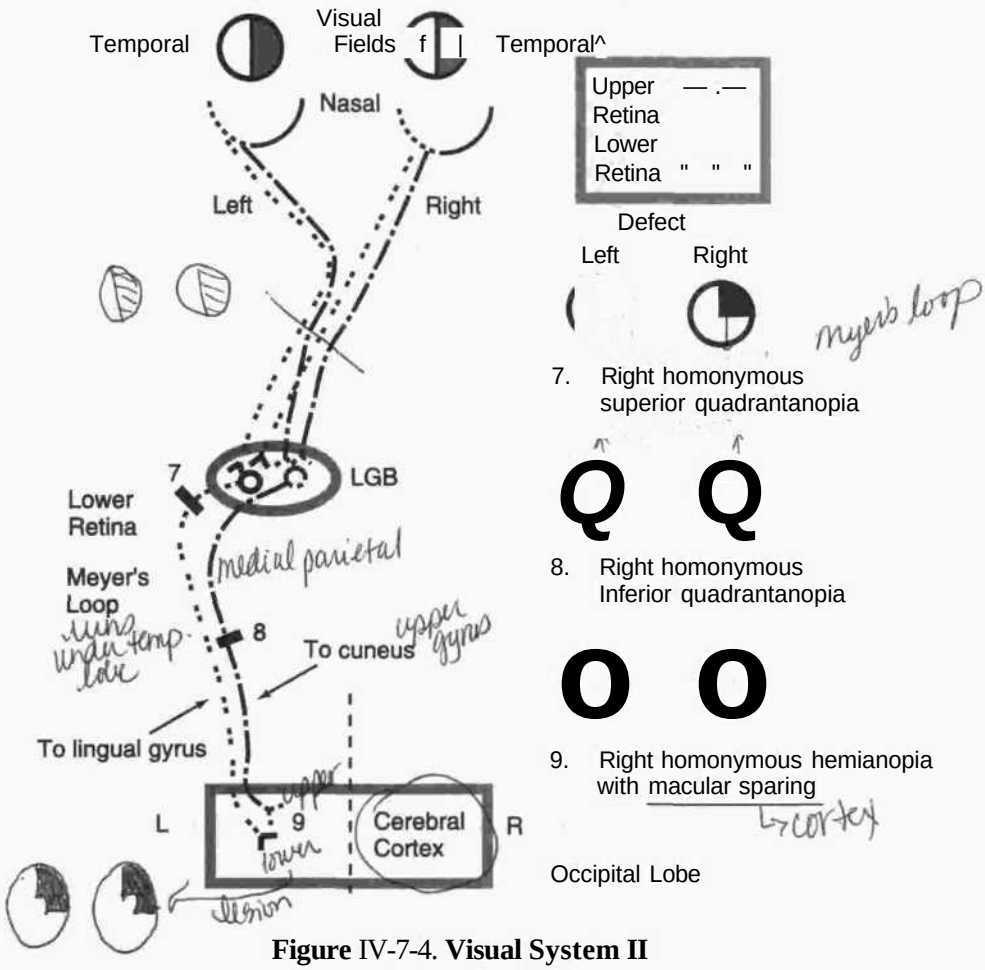


Figure IV-7-4. **Visual System II**

LESIONS OF THE VISUAL PATHWAYS

Lesions of the retina that include destruction of the macula produce a central scotoma. The macula is quite sensitive to intense light, trauma, aging, and neurotoxins.

Lesions of an optic nerve produce blindness (anopsia) in that eye and a loss of the sensory limb of the light reflex. The pupil of the affected eye constricts when light is shined into the opposite eye (consensual light reflex) but not when light is shined into the blinded eye (absence of direct light reflex).

Compression of the optic chiasm, often the result of a pituitary tumor or meningioma, results in a loss of peripheral vision in both temporal fields because the crossing fibers from each nasal retina are damaged. The resulting visual field defect is called a bitemporal heteronymous hemianopia.

All lesions past the chiasm produce contralateral defects. Lesions of the optic tract result in a loss of visual input from the contralateral visual field. For example, a lesion of the right optic tract results in a loss of input from the left visual field. This is called a homonymous hemianopia; in this example, a left homonymous hemianopia.

Lesions of the visual radiations are more common than lesions to the optic tract or lateral geniculate body and produce visual field defects (a contralateral homonymous hemianopia) similar to those of the optic tract if all fibers are involved.

Lesions restricted to the lateral fibers in Meyer's loop, usually in the temporal lobe, result in a loss of visual input from the contralateral upper quarter of the visual field. For example, a lesion of the temporal fibers in the **right** visual radiation results in loss of visual input from the upper left quarter of the field (a **left** superior quadrantanopia).

Lesions restricted to the medial fibers in the visual radiation in the parietal lobe result in a loss of visual input from the contralateral lower quarter of the field (an inferior quadrantanopia).

Lesions inside the primary visual cortex are equivalent to those of the visual radiations, resulting in a contralateral homonymous hemianopsia, except that macular (central) vision is spared.

Lesions of the cuneus gyrus are equivalent to lesions restricted to the parietal fibers of the visual radiation, with macular sparing.

Lesions of the lingula are similar to lesions of the Meyer's loop fibers except for the presence of macular sparing. The pupillary light reflex is spared in lesions of the radiations or inside visual cortex because fibers of the pupillary light reflex leave the optic tracts to terminate in the pretectal area. The combination of blindness with intact pupillary reflexes is termed cortical blindness.

Clinical Correlate

Unilateral optic nerve lesions are seen in multiple sclerosis where there is an immune-related inflammatory demyelination of the nerve. The lesion typically presents with a central scotoma due to involvement of the deep fibers in the nerve from the macula.

Note

Lesions to the visual radiations are more common than lesions to the optic tract.

VISUAL REFLEXES

Pupillary Light Reflex

When light is directed into an eye, it stimulates retinal photoreceptors and results in impulses carried in the optic nerve to the pretectal area. Cells in the pretectal area send axons to the Edinger-Westphal nuclei on both sides.

The Edinger-Westphal nucleus is the parasympathetic nucleus of the oculomotor nerve and gives rise to preganglionic parasympathetic fibers that pass in the third cranial nerve to the ciliary ganglion. Because cells in the pretectal area supply both Edinger-Westphal nuclei, shining light into one eye results in constriction of both the ipsilateral pupil (direct light reflex) and contralateral pupil (consensual light reflex).

Accommodation-Convergence Reaction

This reaction occurs when an individual attempts to focus on a nearby object after looking at a distant object. The oculomotor nerve carries the efferent fibers from the accommodation-convergence reaction, which consists of three components, accommodation, convergence, and pupillary constriction.

Accommodation refers to the reflex that increases the curvature of the lens needed for near vision. Preganglionic parasympathetic fibers arise in the Edinger-Westphal nucleus and pass via the oculomotor nerve to the ciliary ganglion. Postganglionic parasympathetic fibers from the ciliary ganglion supply the ciliary muscle. Contraction of this muscle relaxes the suspensory ligaments and allows the lens to increase its convexity (become more round). This increases the refractive index of the lens, permitting the image of a nearby object to focus on the retina.

Convergence results from contraction of both medial rectus muscles, which pull the eyes to look toward the nose. This allows the image of the near object to focus on the same part of the retina in each eye.

Pupillary constriction (miosis) results from contraction of the constrictor muscle of the iris. A smaller aperture gives the optic apparatus a greater depth of field. With Argyll Robertson pupils, both direct and consensual light reflexes are lost, but the accommodation-convergence reaction remains intact. This type of pupil is often seen in cases of neurosyphilis; however, it is sometimes seen in patients with multiple sclerosis or pineal tumors. The lesion site is believed to occur near the pretectal nuclei just rostral to the superior colliculi.

8 Diencephalon

The diencephalon can be divided into four parts: the thalamus, the hypothalamus, the epithalamus, and the subthalamus.

THALAMUS

The thalamus serves as the major sensory relay for the ascending tactile, visual, auditory, and gustatory information that ultimately reaches the neocortex. Motor control areas such as the basal ganglia and cerebellum also synapse in thalamic nuclei before they reach their cortical destinations. Other nuclei participate in the regulation of states of consciousness.

Major Thalamic Nuclei and Their Inputs and Outputs

Anterior Nuclear Group (part of the Papez circuit of limbic system)

Inrnitjsfrom the mammillary bodies via the mammillothalamic tract and from the cingulate gyrusf output is to the cingulate gyrus via the anterior limb of the internal capsule.

Medial Nuclear Group (part of limbic system)

Input is from the amygdala, prefrontal cortex, and temporal lobe; output is to the prefrontal cortex and cingulate gyrus. The most important nucleus is thejorso-medial nucleus.

↳damaged in ind. w/ Korsakoff's

Clinical Correlate

Thiamine deficiency in alcoholics results in degeneration of the dorsomedial nucleus of thalamus and the mammillary bodies, hippocampus, and vermis of the cerebellum (see chapter 10).

Clinical Correlate

Thalamic pain syndrome affects the ventral nuclear group. Patients present with burning, aching pain in contralateral limbs or body. Involvement of the DC/ML part of VPL increases the sensitivity to pain and presents as contralateral loss of vibratory sense and gait ataxia. Thalamic pain syndrome is resistent to analgesic medications.

Ventral Nuclear Group

Motor Nuclei

Ventral anterior nucleus (VA): Input to VA is from the globus pallidus, substantia nigra. Output is to the premotor and primary motor cortex.

Ventral lateral nucleus (VL): Input to VL is mainly from the globus pallidus and the dentate nucleus of the cerebellum. Output is to the primary motor cortex (Brodmann area 4).

Sensory Nuclei

Ventral posterolateral (VPL) nucleus: Input to VPL conveying somatosensory and nociceptive information ascends in the medial lemniscus and spinothalamic tract. Output is to primary somatosensory cortex (Brodmann areas 3, 1, and 2) of the parietal lobe.

Ventral posteromedial (VPM) nucleus: Input to VPM is from the ascending trigeminal pathways. Output is to primary somatosensory cortex (Brodmann areas 3, 1, and 2) of the parietal lobe.

Medial geniculate body (nucleus): Input is from auditory information that ascends from the inferior coOiculus. Output is to primary auditory cortex.

Lateral geniculate body (nucleus): Input is from the optic tract. Output is in the form of the geniculocalcarine or visual radiations that project to the primary visual (striate) cortex in the occipital lobe.

Midline **and** Intralaminar **Nuclei**

Midline and intralaminar nuclei receive input from the brain stem reticular formation, and from the spinothalamic tract. Intralaminar nuclei send pain information to the cingulate gyrus.

These nuclei appear to be important in mediating desynchronization of the electroencephalogram (EEG) during behavioral arousal.

HYPOTHALAMUS

The hypothalamus is composed of numerous nuclei that have afferent and efferent connections with widespread regions of the nervous system, including the pituitary gland, the autonomic system, and the limbic system (Fig IV-8-1).

Major Hypothalamic Regions or Zones, and Their Nuclei

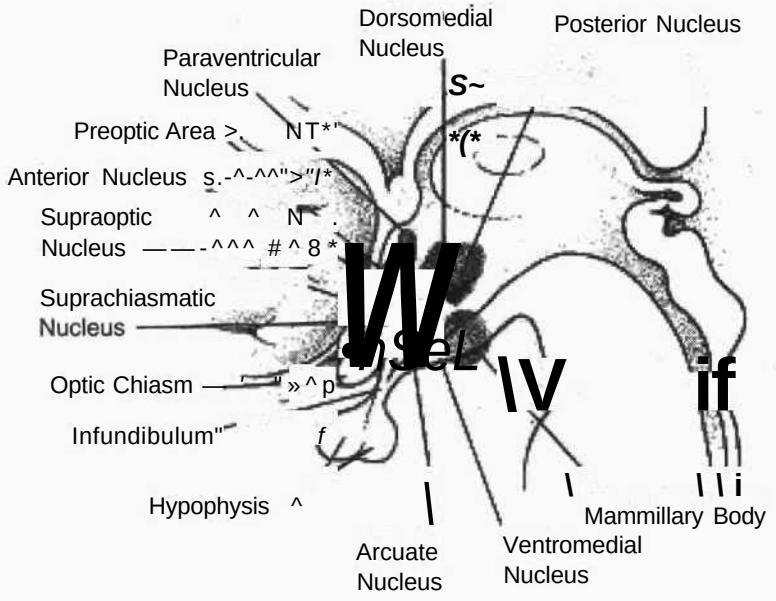


Figure IV-8-1.The Hypothalamic Nuclei

Anterior Region

Paraventricular and Supraoptic Nuclei

These nuclei synthesize the neuropeptides antidiuretic hormone (ADH) and oxytocin. Axons arisinglfbm these nuclei leave the hypothalamus and course nvBTe supraopticohypophysial tract, which carries neurosecretory granules to the posterior pituitary gland, where they are released into capillaries. Lesions of the supraoptic nuclei lead ta diabetes insipidus, which is characterized by polydipsia (excess water consumption) and polyuria (excess urination).

Suprachiasmatic Nucleus

Visual input from the retina by way of the optic tract terminates in the suprachiasmatic nucleus. This information helps set certain body rhythms to the 24-hour light-dark cycle (circadian rhythms).

TuberalRegion

Arcuate Nucleus

Cells in the arcuate nucleus rjroduce^releasing hormones and inhibitory factors, which enter capillaries in the tuberoinfundibular tract and pass through the hypophyseal-portal veins to reach the secondary capillary plexus in the anterior pituitary gland. Releasing hormones and inhibitory factors influence the secretory activity of the acidophils and basophils in the anterior pituitary. (See Histology section.)

Clinical Correlate

Dopaminergic projections from the arcuate nuclei inhibit prolactin secretion from the anterior pituitary. Lesions result in galactorrhea (milk discharge) and amenorrhea.

Ventromedial Nucleus

The ventromedial hypothalamus is a satiety *rpnt*<*r and regulates food intake. Lesions of the ventromedial hypothalamus result in obesity.

PosteriorRegion

Mammillary Bodies

The mammillary nuclei are located in the mammillary bodies and are part of the limbic system. The mammillothalamic tract originates in the mammillary nuclei and terminates in the anterior nuclear group of the thalamus.

Clinical Correlate

Korsakoffs Syndrome

Lesions of the mammillary bodies occur in Korsakoffs syndrome and are usually associated with thiamine deficiency associated witJLcJi£Qnic-alc.o-holism. Korsakoffs syndrome results in both anterograde and retrograde amnesia with confabulations.

AnteriorHypothalamicZone

The anterior hypothalamic zone senses an elevation of body temperature and mediates the response to dissigatelEeat. Lesions of the anterior hypothalamus lead to hyperthermia.

PosteriorHypothaiamicZone

The posterior hypothalamic zone senses a decrease of body ternperature and mediates^the conservation .ofjieat. Lesions of the posterior hypothalamus lead to poikilothermy (i.e., cold-blooded organisms). An individual with a lesion of the posterior hypothalamus has a body temperature that varies with the environmental temperature.

LateralHypothalamicZone

The lateral hypothalamic zone is a feeding center; lesions of the lateral hypothalamus produce severe aphagia.

PreopticArea

The preoptic area is sensitive to androgens and estrogens, whereas other areas influence the production of sex hormones through their regulation of the anterior pituitary. Before puberty, hypothalamic lesions here may arrest sexual development.

After puberty, hypothalamic lesions in this area may result in amenorrhea or impotence.

EPITHALAMUS

The epithalamus is the part of the diencephalon located in the region of the posterior commissure that consists of the pineal body and the habenular nuclei.

The pineal body is a small, highly vascularized structure situated above the posterior commissure and attached by a stalk to the roof of the third ventricle.

The pineal body contains pinealocytes and glial cells but no neurons.

- Pinealocytes synthesize melatonin, serotonin, and cholecystokinin.

The pineal gland plays a role in growth, development, and the regulation of circadian rhythms.

Environmental light regulates the activity of the pineal gland through a retinal-suprachiasmatic-pineal pathway.

The subthalamus is reviewed with the basal ganglia.

Clinical Correlate

Precocious Puberty

In young males, pineal lesions may cause precocious puberty.

Pineal Tumors

Pineal tumors may cause obstruction of CSF flow and increased intracranial pressure. Compression of the upper midbrain and pretectal area by a pineal tumor results in Parinaud's syndrome, in which there is impairment of conjugate vertical gaze and pupillary reflex abnormalities.

9 Basal Ganglia

GENERAL FEATURES

The basal ganglia initiate and provide gross control over skeletal muicle movements. The major components of the basal ganglia include:

- Striatum, which consists of the caudate nucleus and the putamen.
- External and internal segments of the globus pallidus.
- Substantia nigra.
- Subthalamic nucleus.

Together with the cerebral cortex and the VL nucleus of the thalamus, these structures are interconnected to form two parallel but antagonistic circuits known as the direct and indirect basal ganglia pathways (Figs IV-9-1 and IV-9-2). Both pathways are driven by extensive inputs from large areas of cerebral cortex, and both project back to the motor cortex after a relay in the VL nucleus of the thalamus. Both pathways use a process known as "disinhibition" to mediate their effects, whereby one population of inhibitory neurons inhibits a second population of inhibitory neurons.

Direct Basal Ganglia Pathway

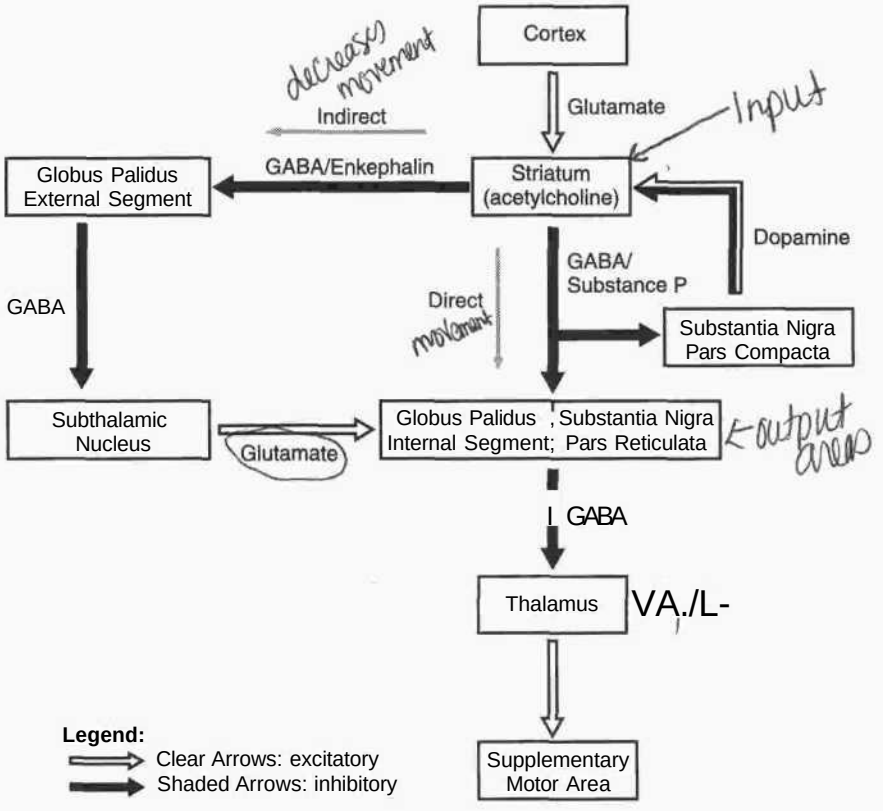
In the direct pathway, excitatory input from the cerebral cortex projects to striatal neurons in the caudate nucleus and putamen. Through disinhibition, activated inhibitory neurons in the striatum, which use 7-aminobutyric acid (GABA) as their neurotransmitter, project to and inhibit additional GABA neurons in the internal segment of the globus pallidus.

The GABA axons of the internal segment of the globus pallidus project to the thalamus (VL). Because their input to the thalamus is disinhibited, the thalamk input excites the motor cortex. The net effert_pXlliejiísuihibkiojiin^thedirert_pjthway results in an increased level of cortical excitation and the promotion of movement.

Indirect Basal Ganglia Pathway

In the indirect pathway, excitatory input from the cerebral cortex also projects to striatal neurons in the caudate nucleus and putamen. These inhibitory neurons in the striatum, which also use GABA as their neurotransmitter, project to and inhibit additional GABA neurons in the external segment of the globus pallidus.

The GABA axons of the external segment of the globus pallidus project to the subthalamic nucleus. Through disinhibition, the subthalamic nucleus excites inhibitory GABA neurons in the internal segment of the globus pallidus, which inhibits the thalamus. This decreases the level of cortical excitation, inhibiting movement. The net effect of the disinhibition in the indirect pathway results in a decreased level of cortical excitation.



Anatomy IV-9-1. Direct and Indirect Basal Ganglia Pathways

DopamineandCholinergicEffects

In addition to the GABA neurons, two other sources of chemically significant neurons enhance the effects of the direct or indirect pathways.

Dopaminergic neurons in the substantia nigra in the midbrain project to the striatum. The effect ofdopamineexcites or drives the_direct pathw_ay, increasing cortical excitation. Dopamine excites the dkect^atlway through D_1 receptors and inhibits the indirect pathway through D_2 receptors.

Cholinergic neurons found within the striatum have the opposite effect. Acetylcholine drives the indirect pathway, decreasing cortical excitation.

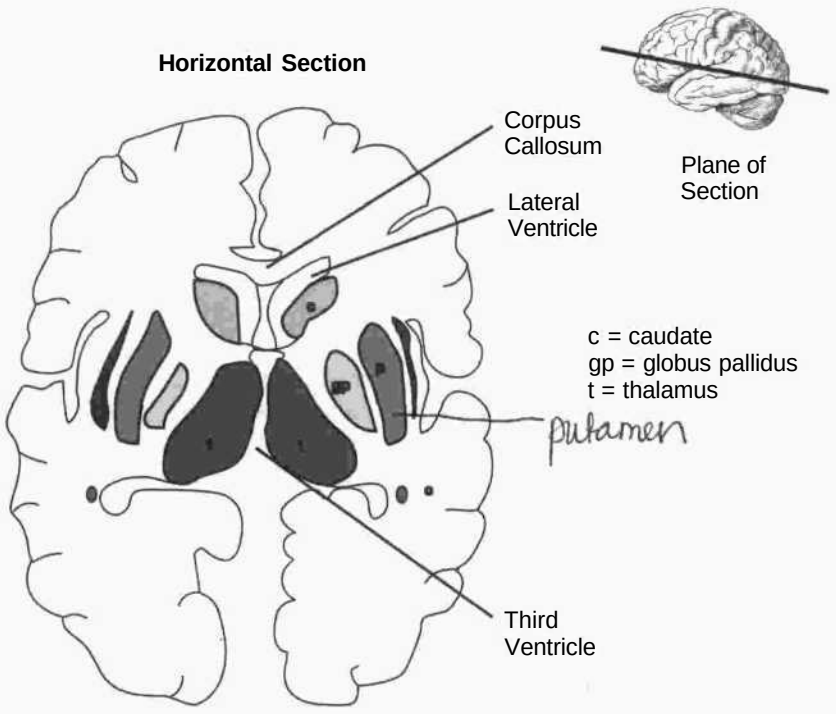


Figure IV-9-2.The Basal Ganglia

Table IV-9-1. Basal Ganglia—Clinicopathological **Correlations**

Movement Disorder	Lesion
Chorea: multiple quick, random movements, usually most prominent in the appendicular muscles	Atrophy of the **striatum.** Huntington's chorea.
Athetosis: low writhing movements, which are usually more severe in the appendicular muscles	Diffuse hypermyelinization of the **corpus striatum** and **thalamus** cerebral palsy.
Hemiballismus: wild flinging movements of half of the body	Hemorrhagic destruction of the **contralateral subthalamic nucleus.** Hypertensive patients.
Parkinsonism: pill-rolling tremor of the fingers at rest, lead-pipe rigidity, and akinesia	Degeneration of the **substantia nigra**

Lesions or Diseases of the Basal Ganglia

Lesions or diseases of the basal ganglia generally present with movement disorders, known as dyskinesias, and an involuntary tremor, or tremor at rest.

Most basal ganglia disorders seem to preferentially affect either the direct or the indirect pathways, altering the balance between the two.

Lesions of the Direct Pathway

Lesions of the direct pathway result in an underactive cortex and hypokinetic disturbances in which there is a slowing or absence of spontaneous movements. The best known disorder of the direct pathway is caused by the degeneration of dopaminergic neurons of the substantia nigra in Parkinson's disease. Because the cortex is underactive, Parkinson's patients have problems initiating movements, combined with a reduction in the velocity and amplitude of the movements. The tremor at rest is the classic pill rolling tremor seen in the fingers. Skeletal muscles in the upper limbs exhibit a cog wheel rigidity because of increased muscle tone. Patients also present with a stooped posture, an expressionless face, and a festinating or accelerating gait during which individuals seem to chase their center of gravity. One strategy for Parkinson patients is to give them L-dopa, a dopamine precursor that crosses the blood-brain barrier. Another strategy is to give anticholinergic drugs to inhibit the effects of acetylcholine on the indirect pathway.

Lesions of the Indirect Pathway

Other common disorders of the basal ganglia (chorea, athetosis, dystonia, tics) result from lesions to parts of the indirect pathway, which result in an overactive motor cortex. An overactive cortex produces hyperkinetic disturbances, expressed in numerous spontaneous movements. The involuntary tremors seen in these diseases range from being dancelike in chorea to ballistic with lesions to the subthalamic nucleus.

Chorea produces involuntary movements that are purposeless, quick jerks that may be superimposed on voluntary movements. Huntington's chorea exhibits autosomal dominant inheritance (chromosome 4) and is characterized by severe degeneration of GABA neurons in the striatum. In addition to chorea, these patients frequently suffer from athetoid movements, progressive dementia, and behavioral disorders. Sydenham's chorea is a transient complication in some children with rheumatic fever.

Athetosis refers to slow, wormlike, involuntary movements that are most noticeable in the fingers and hands but may involve any muscle group. It is present in Huntington's disease and may be observed in many diseases that involve the basal ganglia.

Dystonia refers to a slow, prolonged movement involving predominantly the truncal musculature. Dystonia often occurs with athetosis. Blepharospasm (contraction of the orbicularis oculi causing the eyelids to close), spasmodic torticollis (in which the head is pulled toward the shoulder), and writer's cramp (contraction of arm and hand muscles on attempting to write) are all examples of dystonic movements.

Lesions or Diseases of the Basal Ganglia *(continued)*

Hemiballismus results from a lesipji^fJh^^u^thjIanTicjaucleus usually seen in hypertensive patients. HemibailTsmusTefers to~a~violent projectile movement of a limb and is typically observed in the upper limb contralateral to the involved subthalamic nucleus.

Tourette's syndrome involves facial and vocal tics that progress to jerking movements of the limbs. It is frequently associated with explosive, vulgar speech.

Wilson's disease results from an abnormality of copper metabolism, causing the accumulation of copper in the liver and basal ganglia. Personality changes, tremor, dystonia, and athetoid movements develop. Untreated patients usually succumb because of hepatic cirrhosis. A thin brown ring around the outer cornea, the Kayser-Fleischer ring, may be present and aid in the diagnosis.

Cerebral Cortex

10

The surface of the cerebral cortex is highly convoluted with the bulges or eminences referred to as gyri and the spaces separating the gyri called sulci (Figs IV-10-1 and IV-10-2). Lobes of the cerebrum are divided according to prominent gyri and sulci that are fairly constant in humans. Two prominent sulci on the lateral surface are key to understanding the divisions of the hemispheres. The lateral fissure (of Sylvius) separates the frontal and temporal lobes rostrally; further posteriorly, it partially separates the parietal and the temporal lobes. The central sulcus (of Rolando) is situated roughly perpendicular to the lateral fissure. The central sulcus separates the frontal and the parietal lobes. The occipital lobe extends posteriorly from the temporal and parietal lobes, but its boundaries on the lateral aspect of the hemisphere are indistinct. On the medial aspect of the hemisphere, the frontal and parietal lobes are separated by a cingulate sulcus from the cingulate gyrus. The cingulate is part of an artificial limbic lobe. Posteriorly, the parieto-occipital sulcus separates the parietal lobe from the occipital lobe. The calcarine sulcus divides the occipital lobe horizontally into a superior cuneus and an inferior lingual gyrus.

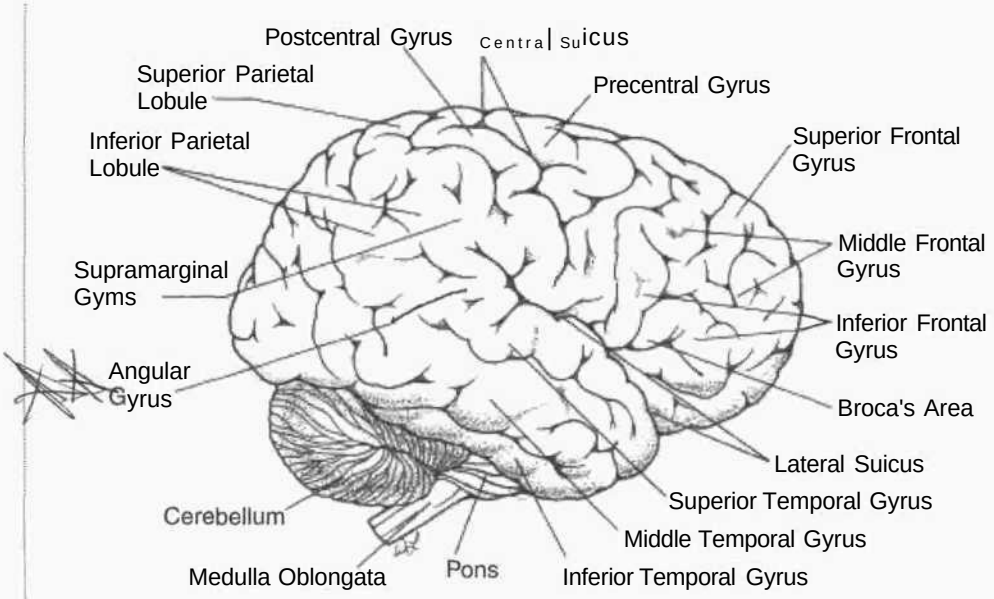


Figure IV-10-1. Lateral View of the Right Cerebral Hemisphere

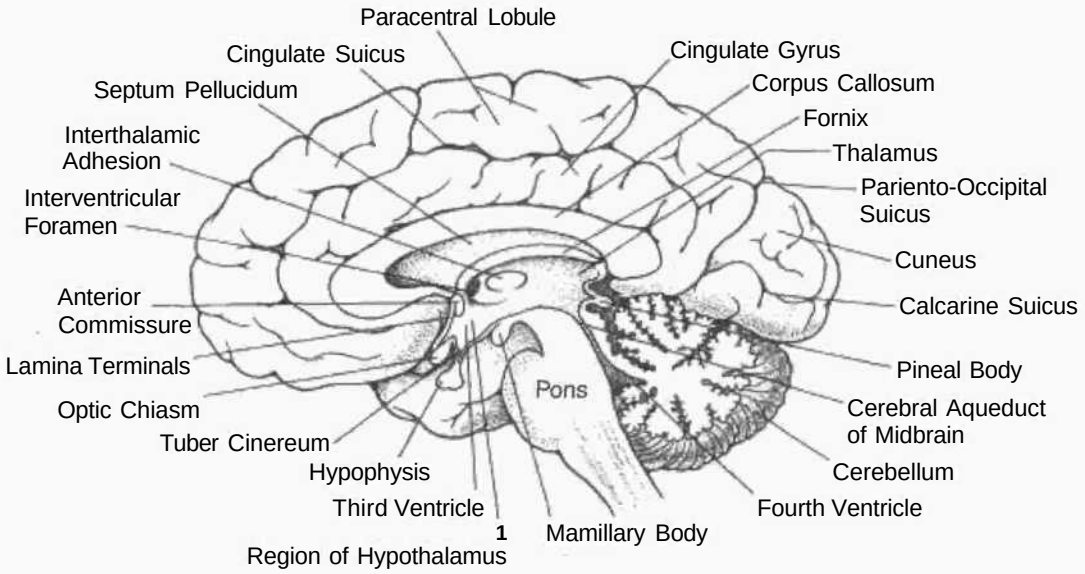


Figure IV-10-2. Medial View of the Cerebral Hemisphere

About 90% of the cortex is composed of six layers, which form the neocortex (Fig F/-10-3). The olfactory cortex and hippocampal formation are three-layered structures and together comprise the allocortex. All of the neocortex contains a six-layer cellular arrangement, but the actual structure varies considerably between different locations. On the basis of these variations in the cytoarchitecture, Brodmann divided the cortex into 47 areas, but only a few Brodmann numbers are used synonymously with functionally specific cortical areas.

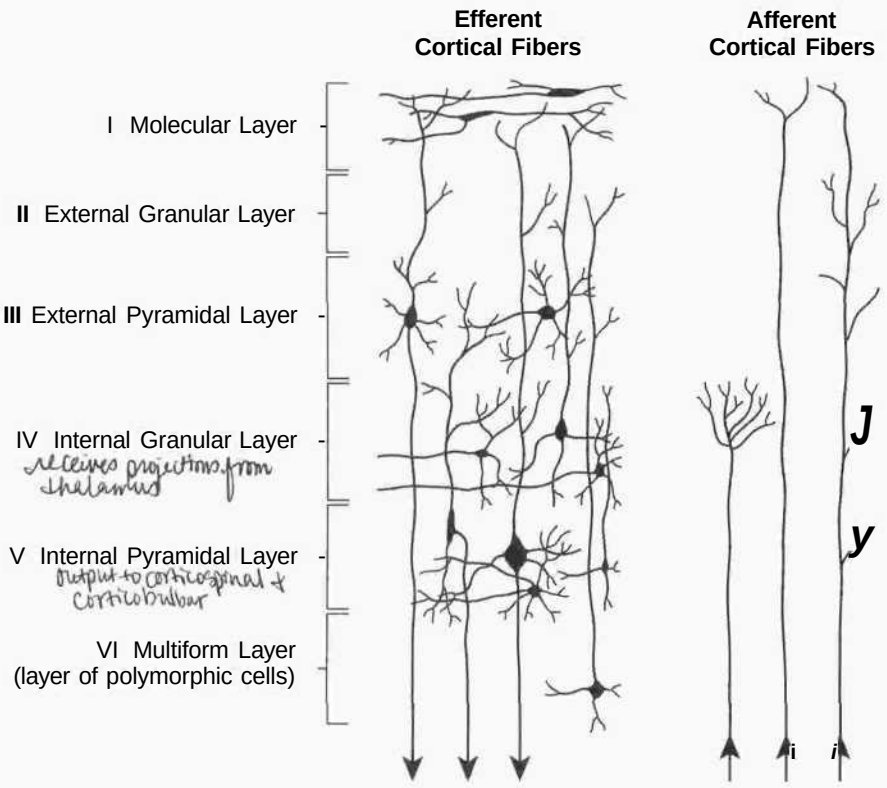


Figure IV-10-3.The Six-Layered Neocortex

LANGUAGE AND THE DOMINANT HEMISPHERE

Most people (about 80%) are right-handed, which implies that the left side of the brain has more highly developed hand-controlling circuits. In the vast majority of right-handed people, speech and language functions are also predominantly organized in the left hemisphere. Most left-handed people show language functions bilaterally, although a few, with strong left-handed preferences, show right-sided speech and language functions.

BLOOD SUPPLY

The cortex is supplied by the two internal carotid arteries and the two vertebral arteries (Figs IV-10-4 and FV-10-5). On the base (or inferior surface) of the brain, branches of the internal carotid arteries and the basilar artery anastomose to form the circle of Willis. The anterior part of the circle lies in front of the optic chiasm, whereas the posterior part is situated just below the mammillary bodies. The circle of Willis is formed by the terminal part of the internal carotid arteries; the proximal parts of the anterior and posterior cerebral arteries and the anterior and posterior communicating arteries. The middle, anterior, and posterior

Note

The internal granular layer is the site of termination of the thalamocortical projections. In primary visual cortex, these fibers form a distinct Line of Gennari. The internal pyramidal layer gives rise to axons that form the corticospinal and corticobulbar tracts.

A clot from carotid most likely ends up in middle cerebral a.

Clinical Correlate

Occlusion of the Middle Cerebral Artery

Occlusion of the middle cerebral artery results in spastic paresis of the contralateral lower face and upper limb and anesthesia of the contralateral face and upper limb.

An aphasia (e.g., Broca's, Wemicke's, or conduction) may result when branches of the left middle cerebral artery are affected, and left-sided neglect may be seen with a blockage of branches of the right middle cerebral artery to the right parietal lobe.

The middle cerebral artery also supplies the proximal parts of the visual radiations as they emerge from the lateral geniculate nucleus of the thalamus and course in Meyer's loop. These fibers course into the temporal lobe before looping posteriorly to rejoin the rest of the visual radiation fibers.

Occlusion of the branches that supply Meyer's loop fibers in the temporal lobe results in a contralateral superior quadrantanopsia.

cerebral arteries, which arise from the circle of Willis, supply all of the cerebral cortex, basal ganglia, and diencephalon.

The injexn_al carotid artery arises from the bifurcation of the common carotid and enters the skull through the carotid canal. It enters the subarachnoid space and terminates by dividing into the anterior and middle cereJmLarteries.

Just before splitting into the middle and anterior cerebral arteries, the internal carotid artery gives rise to the ophthalmic artery. The ophthalmic artery enters the orbit through the optic canal and supplies the eye, including the retina and optic nerve.

The middle cerebral artery is the larger terminal branch of the internal carotid artery. It supplies the bulk of the lateral surface of the hemisphere. Exceptions are the superior inch of the frontal and parietal lobes, which are supplied by the anterior cerebral artery, and the inferior part of the temporal lobe and the occipital pole, which are supplied by the posterior cerebral artery. The middle cerebral artery also supplies the genu and posterior limb of the internal capsule and the basal ganglia. leticulostriate arteries

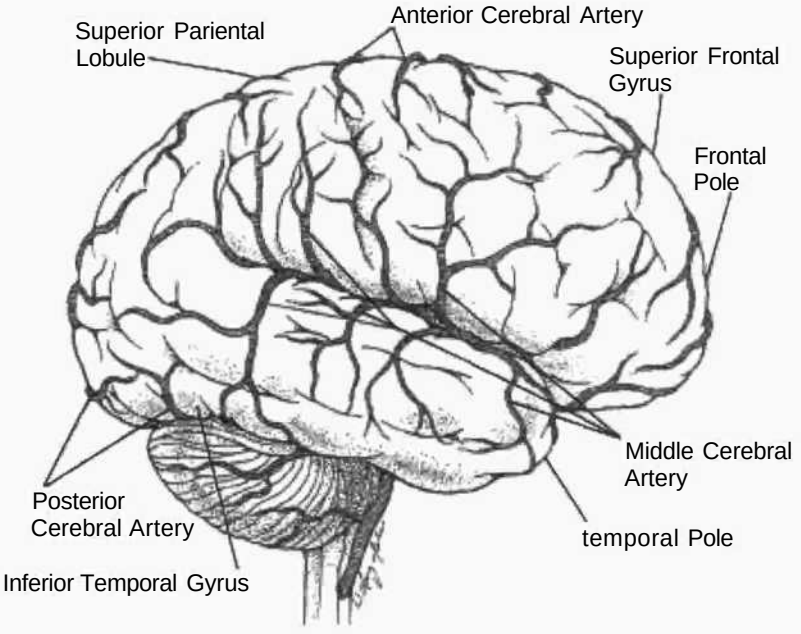


Figure IV-10-4.The Distributions of the Cerebral Arteries: I

The anterior cerebral artery is the smaller terminal branch of the internal carotid artery. It is connected to the opposite anterior cerebral artery by the anterior communicating artery, completing the anterior part of the circle of Willis. The anterior cerebral artery supplies the medial surface of the frontal and parietal lobes, which include motor and sensory cortical areas for the pelvis and lower limbs. The anterior cerebral artery also supplies the anterior four fifths of the corpus callosum and approximately 1 inch of the frontal and parietal cortex on the superior aspect of the lateral aspect of the hemisphere.

Occlusion of the anterior cerebral artery results in spastic paresis of the contralateral lower limb and anesthesia of the contralateral lower limb. Urinary incontinence may be present, but this usually occurs only with bilateral damage. A transcortical apraxia of the left limbs may result from involvement of the anterior portion of the corpus callosum. A transcodic.aljipraxiajx:curs because the left hemisphere (language dominant) hjsbe£n_disconnected from the motor cortex of the right hemisphere. The anterior cerebral artery also supplies the anterior limb of the internal capsule.

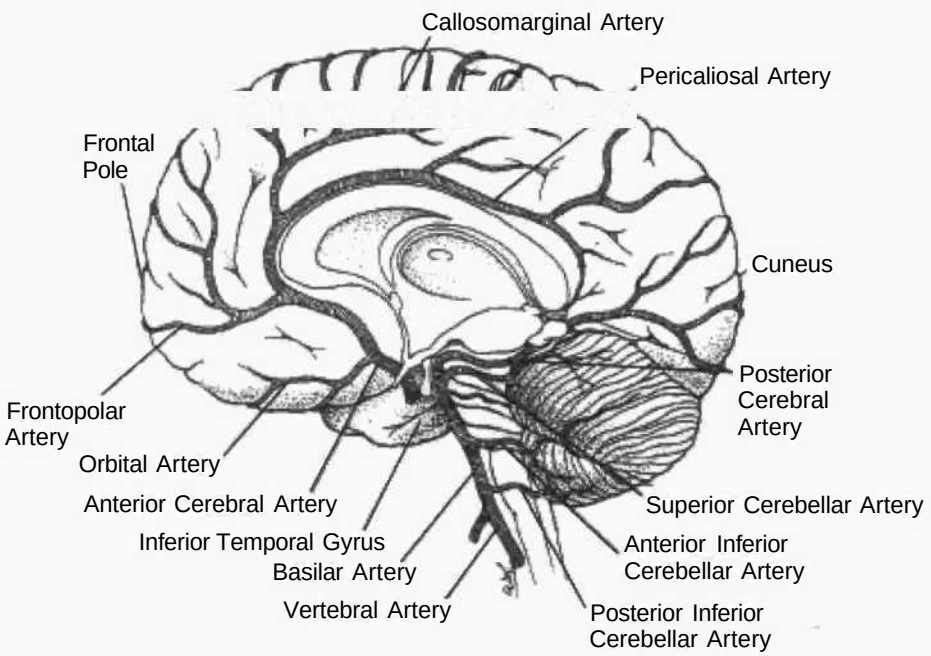
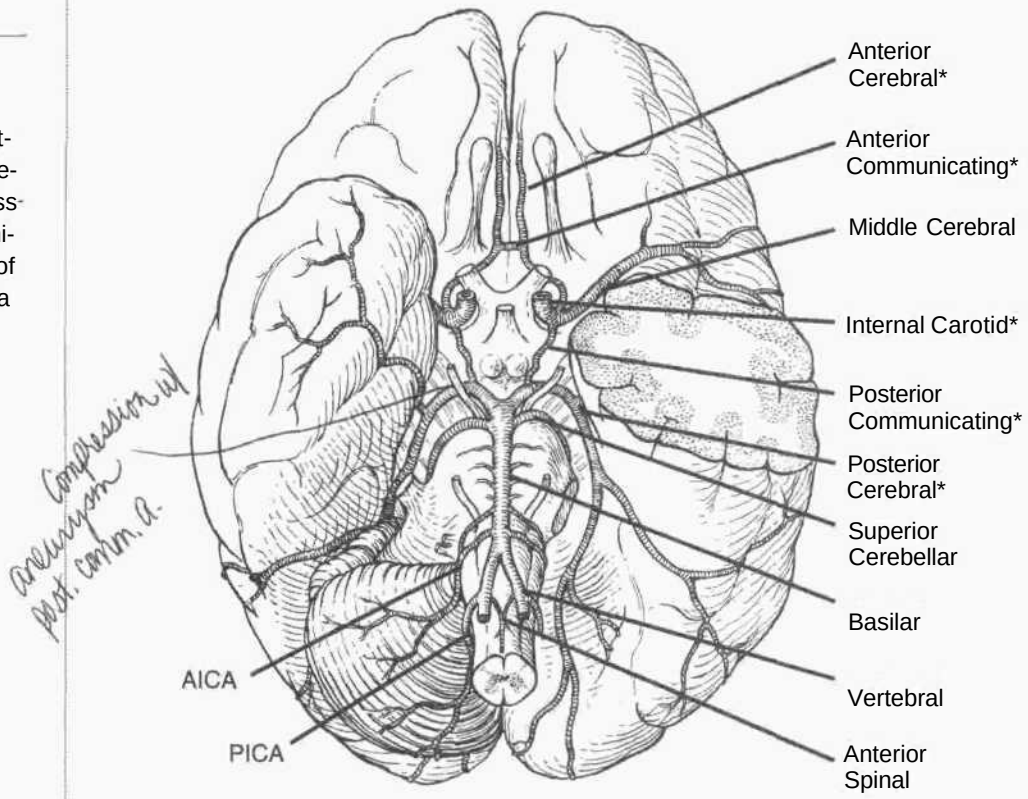


Figure IV-10-5. The Distributions of the Cerebral Arteries: II

Clinical Correlate

The most common aneurysm site in the circle of Willis is where the anterior communicating artery joins an anterior cerebral artery. The aneurysm presses on the fibers in the optic chiasm from the upper quadrant of each temporal field producing a bitemporal inferior quadrant anopsia.



* These arteries form the circle of Willis.

Figure IV-10-6. Arterial Supply of the Brain

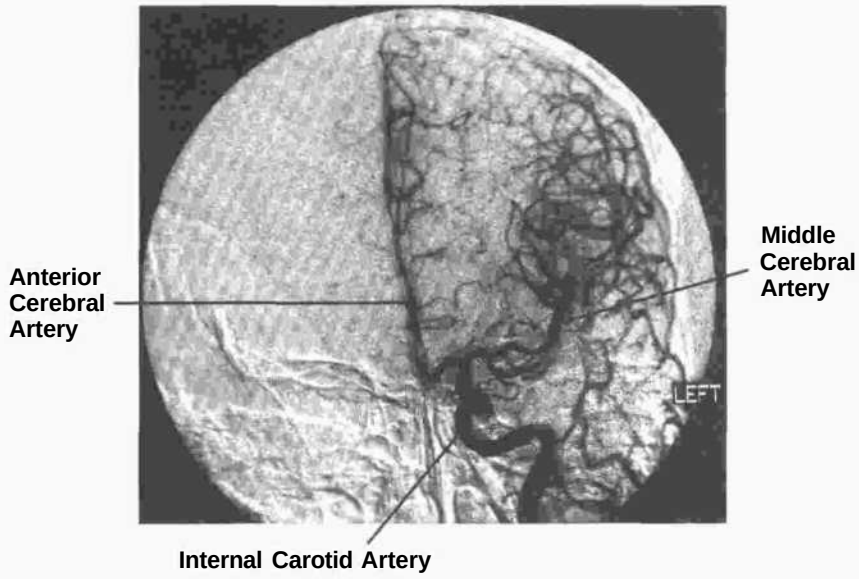


Figure IV-10-7. Anteroposterior View of Left Internal Carotid

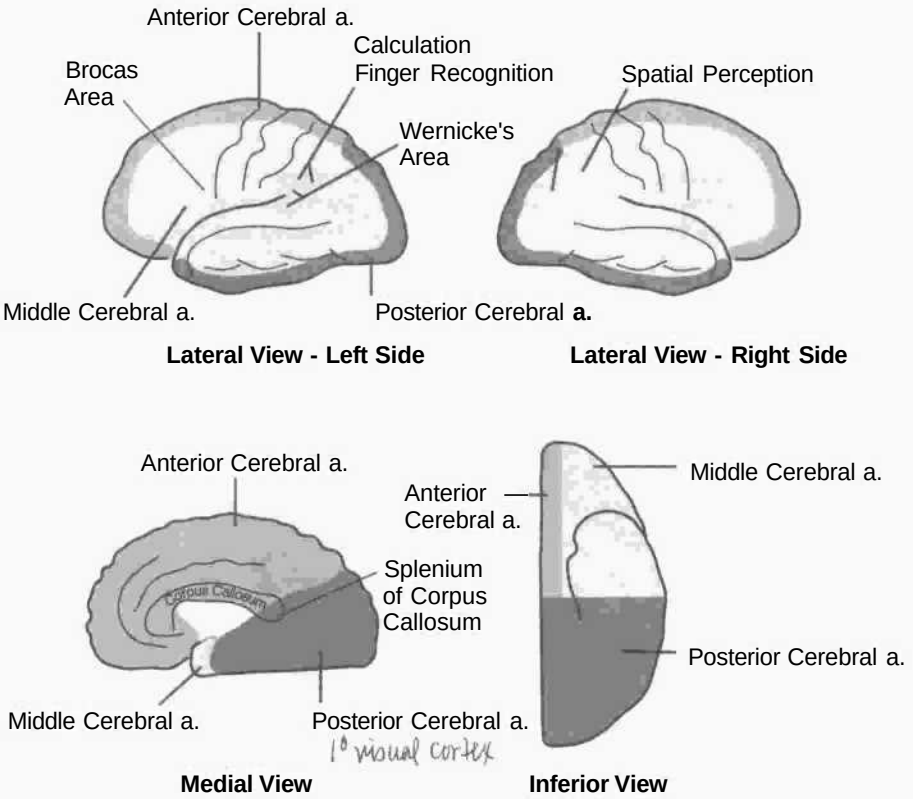


Figure IV-10-8. Territories Supplied by the Cerebral Arteries

The posterior cerebral artery is formed by the terminal bifurcation of the basilar artery. The posterior communicating artery arises near the termination of the internal carotid artery and passes posteriorly to join the posterior cerebral artery. The posterior communicating arteries complete the circle of Willis by joining the vertebrobasilar and carotid circulations. The posterior cerebral artery supplies the occipital and temporal cortex on the inferior and lateral surfaces of the hemisphere, the occipital lobe and posterior two thirds of the temporal lobe on the medial surface of the hemisphere, and the thalamus and subthalamic nucleus.

Occlusion^of the posterior cerebral artery results in a homonyrnous hemianopia of the contralateral visual held with macular sparing.

FUNCTIONAL FEATURES AND CLINICAL ASPECTS OF INDIVIDUAL LOBES

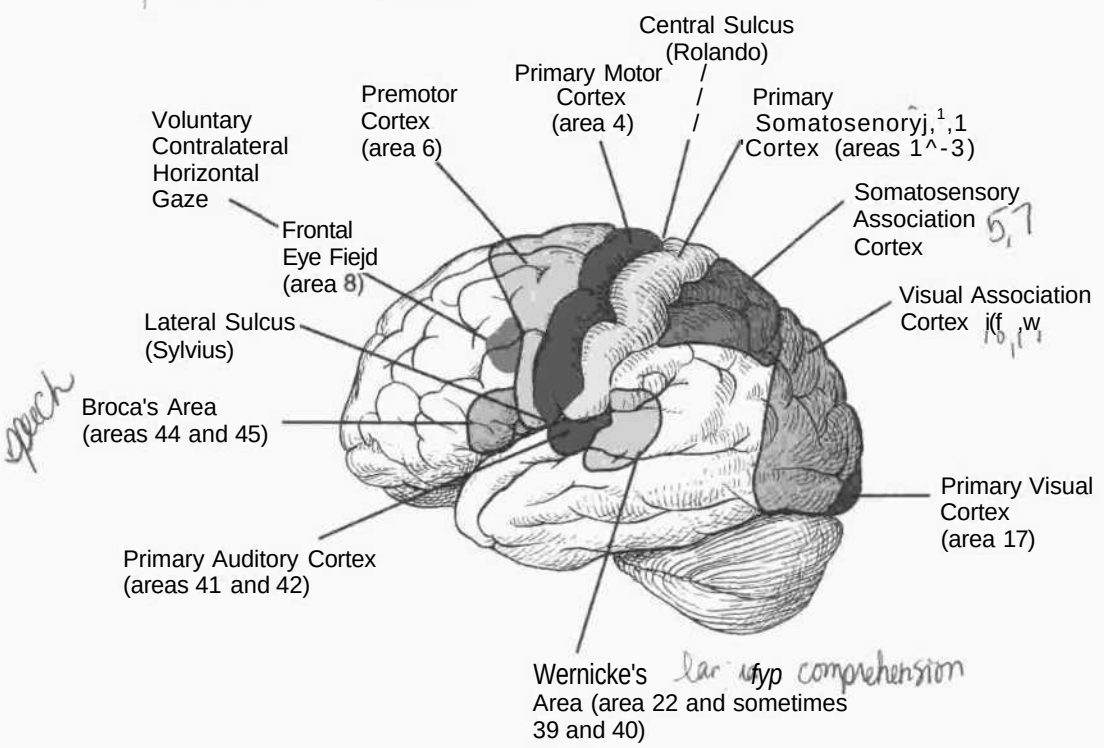


Figure IV-10-9. **Cerebral Cortex: Functional Areas**

Frontal Lobe

A large part of the frontal cortex rostral to the central sulcus is related to the control of movements, primarily on the opposite side of the body. These areas include primary motor cortex (Brodmann area 4), premotor cortex (area 6), the frontal eye field (area 8), and the motor speech areas of Broca (area 44 and 45). Traditionally, area 4 is considered the primary motor cortex. It is in the precentral gyrus, immediately anterior to the central sulcus, and contains an orderly skeletal motor map of the contralateral side of the body (Fig IV-10-10).

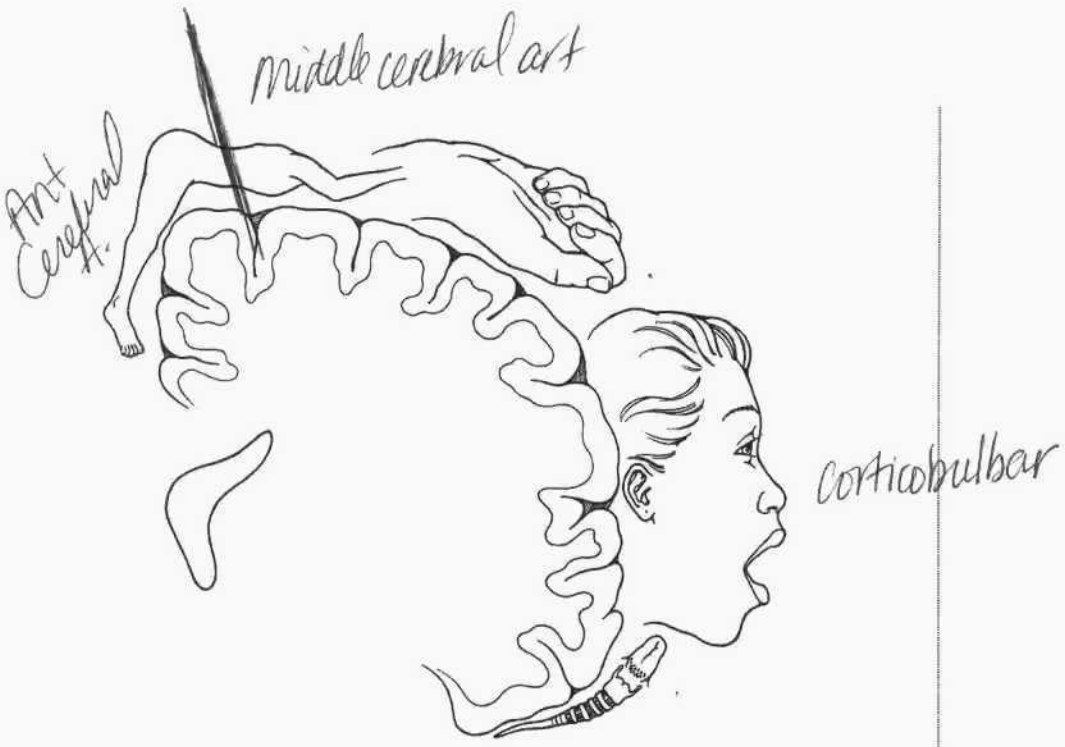


Figure IV-10-10. The **Motor Homunculus in Precentral** Gyrus **(Area 4) Frontal Lobe**

The muscles of the head are represented most ventrally closest to the lateral fissure, then, proceeding dorsally, are the regions for the neck, upper limb, and trunk on the lateral aspect of the hemisphere. On the medial aspect of the hemisphere is the motor representation for the pelvis and lower limb.

*Premotor Cortex {jUkJOuaJicTi? (JAJL^^*

Just anterior to area 4 is the premotor cortex (area 6). Neurons here are particularly active prior to the activation of area 4 neurons, so it is thought that the premotor cortex is involved in the planning of motor activities. Damage here results in an apraxja^a disrugtion of the patterning and execution of learned motor movejfieats. Individual movements are intact, and there is no weakness, but the patient is unable to perform movements in the correct sequence.

Prefrontal Cortex ersonalit ^

The prefrontal cortex is located in front of the premotor area and represents about a quarter of the entire cerebral cortex in the human brain. This area is involved in organizing and planning the intellectual and emotional aspects of behavior, much as the adjacent premotor cortex is involved in planning its motor aspects.

Clinical Correlate

Lesion of the Frontal Eye Reid

The frontal eye field lies in front of the motor cortex in Brodmann area 8. This cortical area is the center for contralateral horizontal gaze. A lesion here results in an inability to make voluntary eye movements toward the contralateral side. Because the activity of the intact frontal eye field in the opposite cortex would also be unopposed after such a lesion, the result is conjugate slow deviation of the eyes toward the side of the lesion. If motor cortex is involved in the lesion, the patient may have a contralateral spastic paresis. The intact frontal eye field in the opposite hemisphere deviates the eyes **away** from the paralysed limbs.

Clinical Correlate

Lesions In the Prefrontal Area

Lesions in the prefrontal area produce what is called the frontal lobe syndrome. The patient cannot concentrate and is easily distracted; there is a general lack of initiative, foresight, and perspective. Another common aspect is apathy (i.e., severe emotional indifference). Apathy is usually associated with abulia, a slowing of intellectual faculties, slow speech, and decreased participation in social interactions. Prefrontal lesions also result in the emergence of infantile suckling or grasp reflexes that are suppressed in adults. In the suckling reflex, touching the cheek causes the head to turn toward the side of the stimulus as the mouth searches for a nipple to suckle. In the grasp reflex, touching the palm of the hand results in a reflex closing of the fingers, which allows an infant to grasp anything that touches the hand.

Clinical Correlate

Expressive Aphasia

Broca's area is just anterior to the motor cortex region that provides upper motoneuron innervation of cranial nerve motor nuclei. This area in the left or dominant hemisphere is the center for motor speech and corresponds to Brodmann areas 44 and 45. Damage to Broca's area produces a motor, nonfluent, or expressive aphasia that reflects a difficulty in piecing together words to produce Expressive speech. Patients with this lesion can understand written and spoken langual^buTnormally say almost nothing. When pressed on a question such as "what did you do today?" they might reply "went town." The ability to write is usually also affected in a similar way (agraphia) in all aphasias, although the hand used for writing can be used normally in all other tasks. Patients are keenly aware and frustrated by an expressive aphasia, because of their lack of the ability to verbalize their thoughts orally or in writing.

Broca's area damage often extends posteriorly into the primary motor cortex and might be combined with a contralateral paralysis of the muscles of the lower face, resulting in a drooping of the corner of the mouth. If the lesion is larger, the patient might have a spastic hemiparesis of the contralateral upper limb.

Parietal Lobe

Primary Somatosensory Cortex

The parietal lobe begins just posterior to the central sulcus with the postcentral gyrus. The postcentral gyrus corresponds to Brodmann areas 3,1, and 2 and contains primary somatosensory cortex. Like primary motor cortex, there is a similar somatotopic representation of the body here, with head, neck, upper limb, and trunk represented on the lateral aspect of the hemisphere, and pelvis and lower limb represented medially (Fig IV-10-11). These areas are concerned with discriminative touch, vibration, position sense, pain, and temperature. Lesions in

somatosensory cortex result in impairment of all somatic sensations on the opposite side of the body, including the face and scalp.

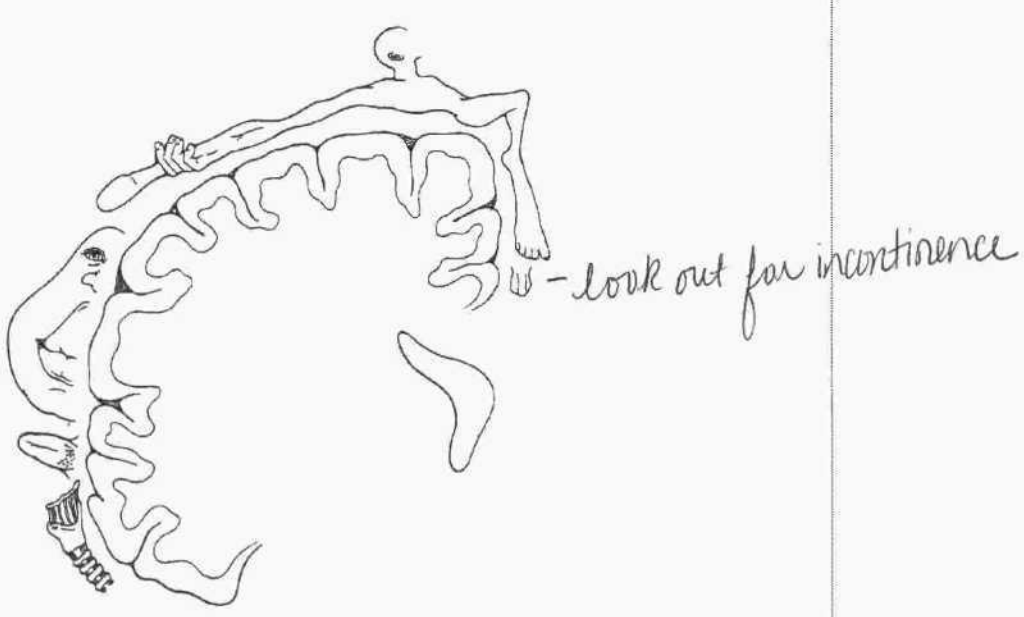


Figure IV-10-11. The Sensory Homunculus in Postcentral Gyrus (Areas 3,1,2) Parietal Lobe

Posterior Parietal Association Cortex

Just posterior and ventral to the somatosensory areas is the posterior parietal association cortex, including Brodmann areas 5 and 7.

Clinical Correlate

Lesions, usually in the dominant hemisphere and which include areas 5 and 7 of the posterior parietal association areas, often result in apraxia (also seen with lesions to the premotor cortex). Apraxia is a disruption of the patterning and execution of learned motor movements. This deficit seems to reflect a lack of understanding how to organize the performance of a pattern of movements (i.e., what should be done first, then next, etc.). The patient may be unable, for example, to draw a simple diagram (constructional apraxia) or describe how to get from his home to work.

Another deficit, with lesions of areas 5 and 7 is astereognosia (inability to recognize objects by touch). There is no loss of tactile or proprioceptive sensation; rather, it is the integration of visual and somatosensory information that is impaired. Both apraxia and astereognosia are more common after left hemisphere damage than in right hemisphere damage. The astereognosia is usually confined to the contralateral side of the body; in contrast, apraxia is usually bilateral. Apraxia is probably a result of the loss of input to the premotor cortex (area 6), which is involved in the actual organization of motor movements into a goal-directed pattern.

Note

Any blockage of the left middle cerebral artery that results in an aphasia (Broca's Wernicke's, conduction) or Gerstmann's syndrome will also result in agraphia.

Wernicke's Area

The inferior part of the parietal lobe and adjacent part of the temporal lobe in the dominant (left) hemisphere, known as Wernicke's area, are cortical regions that function in language comprehension. At a minimum, Wernicke's area consists of area 22 in the temporal lobe but may also include areas 39 and 40 in the parietal lobe. Areas 39 (the angular gyms) and 40 (the supramarginal gyrus) are regions of convergence of visual, auditory, and somatosensory information.

Clinical Correlate

Receptive Aphasia

Lesions in area 22 in the temporal lobe and 39 or 40 in the parietal lobe produce a nonfluent, receptive, or Wernicke's aphasia. The patient with Wernicke's aphasia cannot comprehend spoken language.and may or may not be able to read (alexia) depending on the extent of the lesion. The deficit is characterized by fluent verbaNzatioji but lacks meaning. Patients are paraphasic, often misusing words as if speaking using a "word salad."

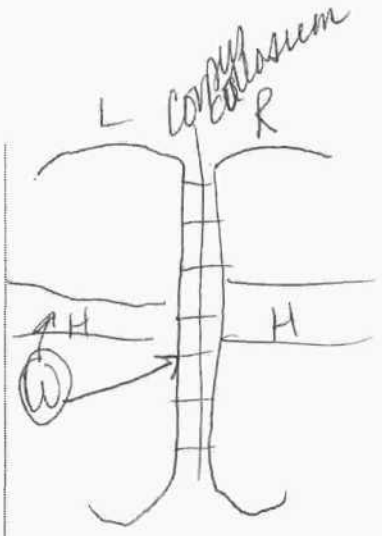
Patients with Wernicke's aphasia are generally unaware of their deficit and show no distress as a resuTf~of their condition.

Gerstmann's Syndrome

If the lesion is confined to just the angular gyrus (area 39), the result is a loss of ability to comprehend just wjitten language (alexia) and to writeitjagraphia), but spoken language may be understood. Alexia with agraphia in pure angular gyrus lesions is often seen with three other unique symptoms: acalculia (loss of the ability to perform simple arithmetic problems), finger agnosia (inability to recognize one's fingers), and right-left disoriejitation. This constellation of deficits constitutes Gerstmann's syndrome and underscores the role of this cortical area in the integration of how children begin to count, add, and subtract using their fingers.

Conduction Aphasia

There is a large fiber bundle connecting aieas_22*_39J_and_40 with Broca's area in the frontal lobe, known as the superior longitudinal fasciculus (or the arcuate fasciculus). A lesion affecting this fiber bundle results in a conduction apRasia. inTRIs'patient, verbal output is fluent, but there are many paraphrases and word-finding pauses. Both verbal and visual language comprehension "are also normal, but if asked to, the patient cannot repeat words or execute verbal commands by an examiner (such as count backwards beginning at 100) and also demonstrates poor object naming. This is an example of a **disconnect** syndrome in which the deficit represents an inability to send information from one cortical area to another. Like an expressive aphasia, the patient is aware of the deficit and is frusirate4-toLtheir inability to execute aj/erbaj command that they fully understand.



Clinical Correlate *(continued)*

Transcortical Apraxia

Lesions to the corpus callosum caused by an infarct of the anterior cerebral artery may result in another type of disconnect syndrome known as a transcortical apraxia. As in other cases of apraxia, there is no motor weakness, but the patient cannot execute a command to move their left arm. They understand the command, which is perceived in Wernicke's area of the left hemisphere, but the callosal lesion disconnects Wernicke's area from the right primary motor cortex so that the command cannot be executed. The patient is still able to execute a command to move the right arm because Wernicke's area in the left hemisphere is able to communicate with the left primary motor cortex without using the corpus callosum.

Asomatognosia

The integration of visual and somatosensory information is important for the formation of the "body image" and awareness of the body and its position in space. Widespread lesions in areas 7, 39, and 40 in the nondominant right parietal lobe may result in unawareness or neglect of the contralateral half of the body known as asomatognosia. Although somatic sensation is intact, the patients ignore half of their body and may fail to dress, undress, or wash the affected (left) side. Patients will have no visual field deficits, so they can see, but deny the existence of things in the left visual field. Asking them to bisect a horizontal line produces a point well to the right of true center. If asked to draw a clock face from memory, they will draw only numbers on the right side, ignoring those on the left. The patients may deny that the left arm or leg belongs to them when the affected limb is passively brought into their field of vision. Patients may also deny their deficit, an anosognosia.

Occipital Lobe

The occipital lobe is essential for the reception and recognition of visual stimuli and contains primary visual and visual association cortex.

Visual Cortex

The visual cortex is divided into striate (area 17) and extrastriate (areas 18 and 19). Area 17, also referred to as the primary visaaLcortex, lies on the medial portion of the occipital lobe on either side of the calcarine sulcus. Its major thalamic input is from the lateral geniculate nucleus. Some input fibers are gathered in a thick bundle that can be visible on the cut surface of the gross brain, called the line of Gennari. The retinal surface (and therefore the visual field) is represented in an orderly manner on the surface of area 17, such that damage to a discrete part of area 17 will produce a scotoma (i.e., a blind spot) in the corresponding portion of the visual field. A unilateral lesion inside area 17 results in a contralateral homonymous hemianopsia with macular sparing, usually caused by an

infarct of a branch of the posterior cerebral artery. The area of the macula of the retina containing the fovea is spared because of a dual blood supply from both the posterior and middle cerebral arteries. The actual cortical area serving the macula is represented in the most posterior part of the occipital lobe. Blows to the back of the head or a blockage in occipital branches of the middle cerebral artery that supply this area may produce loss of macular representation of the visual fields. Bjla^erajjasuaLcorlexIesions result injajrtical blindness; the patient cannot see, but pupillary reflexes are intact.

Visual Association Cortex

Anterior to the primary visual or striate cortex are extensive areas of visual association cortex. Visual association cortex is distributed throughout the entire occipital lobe and in the posterior parts of the parietal and temporal lobes. These regions receive fibers from the striate cortex and integrate complex visual input from both hemispheres. From the retina to the visual association cortex, information about form and color, versus motion, depth and spatial information are processed separately. Form and color information is processed by the parvocellular-blob system. This "cone stream" originates mainly in the central part of the retina, relays through separate layers of the lateral geniculate, and projects to blob zones of primary visual cortex. Blob zones project to the inferior part of the temporal lobe in areas 20 and 21. Unilateral lesions here resulHnachromatopsia, a complete lossof color vision in the contralateral hemifields. Patients !e2~everything in jhades of %ray. Additionally, these patients may also present with prosopagnosia, an inabiluyJxiiecognize faces.

Motion and depth are processed by the magnocellular system. This "rod stream" originates in the peripheral part of the retina, relays through separate layers of the lateral geniculate, and projects to thick stripe zones of primary visual cortex. Striped areas project through the middle temporal lobe to the parietal lobe in areas 18 and 19. Lesions here result in a deficit in perceiving visual motion; visual fields, color vision, and reading are unaffected (Fig IV-10-8).

Clinical Correlate

Visual Agnosia

Damage to parts of the temporal lobes involving the cone stream produces **a** visual agnosia. Visual agnosia is the inability to recognize visual patterns (including objects) in the absence of a visual field deficit. For example, you might show a patient with an object agnosia a pair of glasses, and the patient would describe them as two circles and a bar. Lesions in areas 20 and 21 of the temporal lobe that also include some destruction of adjacent occipital lobe in either hemisphere result in prosopagnosia, a specific inability to recognize faces. The patient can usually read and name objects. The deficiency is an inability to form associations between faces and identities. On hearing the voice of the same person, the patient can immediately identify the person.

Alexia Without Agraphia

A principal "higher-order" deficit associated with occipital lobe damage is alexia without agraphia (or pure word blindness). The patients are unable to read at all and, curiously, often have a color anomia (inability to name colors). However, they are able to write. This is another example of a disconnect syndrome in which information from the occipital lobe is not available to the parietal or frontal lobes to either understand or express what has been seen.
(Recall that alexia with agraphia—inability to read or write—occurs with lesions encompassing the angular gyrus in the dominant parietal lobe.) The cause of the syndrome is usually an infarction of the left posterior cerebral artery that affects not only the anterior part of the occipital lobe but the splenium of the corpus callosum. Involvement of the left occipital cortex results in a right homonymous hemianopsia with macular sparing. Involvement of the splenium of the corpus callosum prevents visual information from the intact right occipital cortex from reaching language comprehension centers in the left hemisphere. Patients can see words in the left visual field but do not understand what the word's" mean.

Temporal Lobe

Primary Auditory Cortex

On its superior and lateral aspect, the temporal lobe contains the primary auditory cortex. Auditory cortex (areas 41 and 42) is located on the two transverse gyri of HeschI, which cross the superior temporal lobe deep within the lateral sulcus. Much of the remaining superior temporal gyrus is occupied by area 22 (auditory association cortex), which receives a considerable projection from both areas 41 and 42 and projects widely to both parietal and occipital cortices.

Patients with unilateral damage to the primary auditory cortex show little loss of auditory sensitivity but have some difficulty in localizing sounds in the contralateral sound field. Area 22 is a component of Wernicke's area in the dominant hemisphere, and lesions here produce a Wernicke's aphasia.

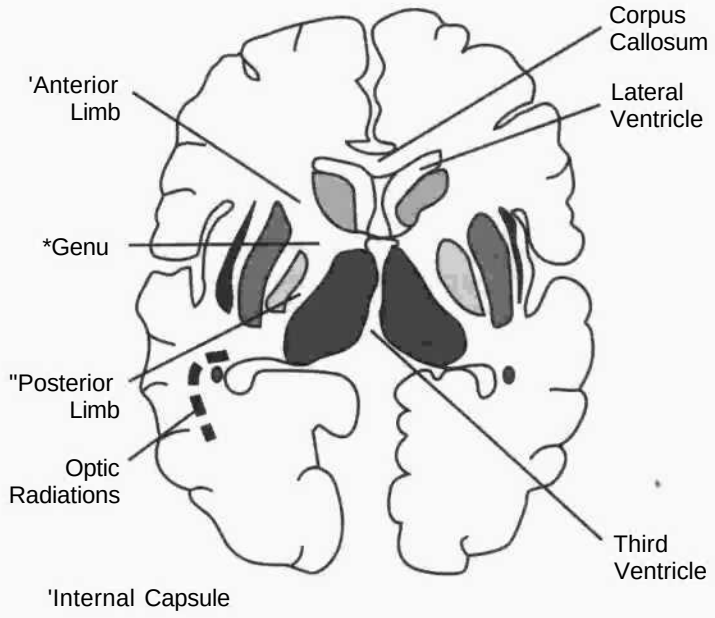


Figure IV-10-12. Internal Capsule: Arterial Supply

Table IV-10-1. Internal Capsule: Arterial Supply

Internal Capsule	Arterial Supply	Tracts
Anterior limb	Anterior cerebral artery	Thalamocortical
Genu	Middle cerebral artery	Corticobulbar
Posterior limb	Middle cerebral artery	Corticospinal, all somatosensory thalamocortical projections

Note: The posterior cerebral artery also supplies the optic radiations

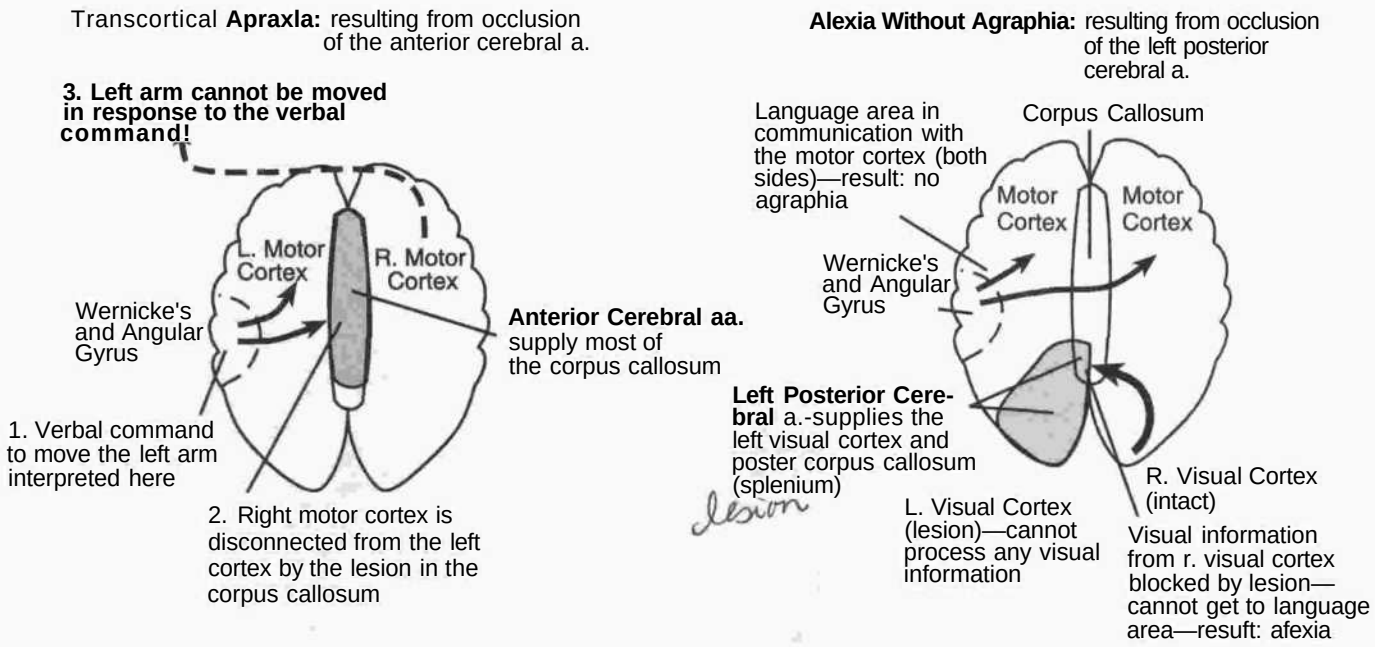
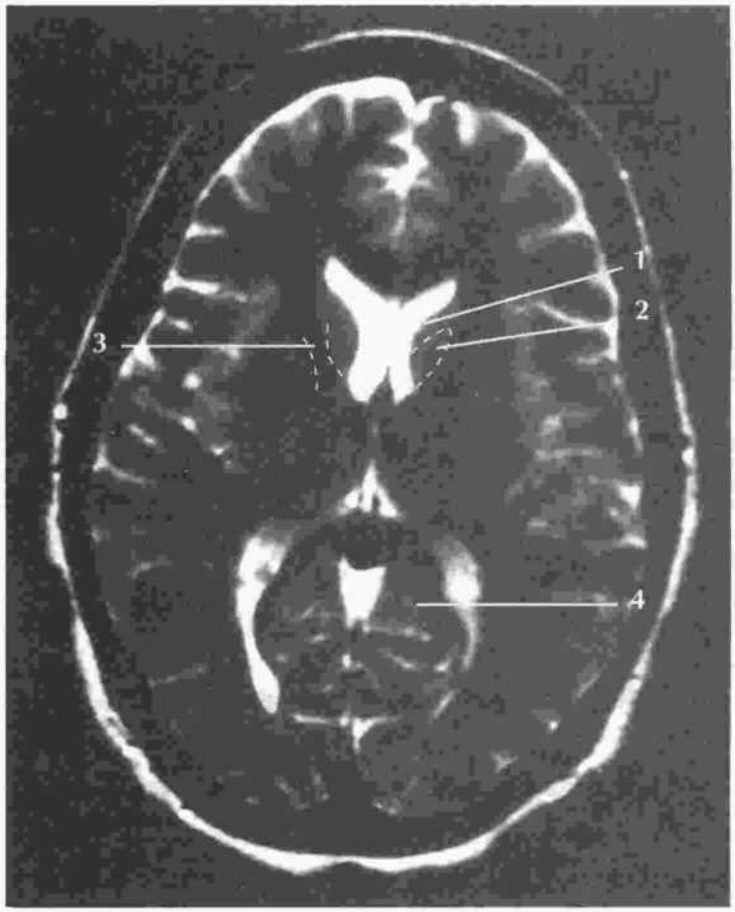


Figure IV-10-13. Symptoms Following Occlusion of the Cerebral Arteries

Table FV-10-2. Symptoms Following Occlusion of the Cerebral Arteries

Anterior Cerebral	**Middle Cerebral**		**Posterior Cerebral**
Contralateral spastic paralaysis and anesthesia of the lower limbs	Contralateral spastic paralysis and anesthesia of the body excluding the lower limbs (mainly arms and face)		Contralateral homonomous hemianopsia (usually with macular sparing)
Urinary incontinence	LEFTSIDE	RIGHT SIDE	LEFT SIDE: Alexia without agraphia (see above)—cannot read, but can write
Transcortical apraxia—cannot move left arm in response to a command	Aphasias: Broca's, Wernicke's, or Global	Parietal lobe: 1. Inattention and neglect of the contralateral side of the body 2. Spatial perception defects	
	Gerstmann's Syndrome (parietal lobe-angular gyrus): 1. R-L disorientation 2. Finger agnosia 3. Acalcula 4. Agraphia		



1. Lateral Ventricle
2. Caudate nucleus
3. Internal Capsule
4. Cerebellum

Figure IV-10-14. Horizontal Section

11 The Limbic System

GENERAL FEATURES

The limbic system is involved in emotion, memory, attention, feeding, and mating behaviors. It consists of a core of cortical and diencephalic structures found on the medial aspect of the hemisphere. A prominent structure in the limbic system is the hippocampal formation on the medial aspect of the temporal lobe. The hippocampal formation extends along the floor of the inferior horn of the lateral ventricle in the temporal lobe and includes the hippocampus, the dentate gyrus, the subiculum, and adjacent entorhinal cortex. The hippocampus is characterized by a three-layered cerebral cortex. Other limbic-related structures include the amygdala, which is located deep in the medial part of the anterior temporal lobe rostral to the hippocampus, and the septal nuclei, located medially between the anterior horns of the lateral ventricle. The limbic system is interconnected with thalamic and hypothalamic structures, including the anterior and dorsomedial nuclei of the thalamus and the mammillary bodies of the hypothalamus. The cingulate gyrus is the main limbic cortical area. The cingulate gyrus is located on the medial surface of each hemisphere above the corpus callosum. Limbic-related structures also project to wide areas of the prefrontal cortex.

OLFACTORY SYSTEM

Central projections of olfactory structures reach parts of the temporal lobe and the amygdala. The olfactory nerve consists of numerous fascicles of the central processes of bipolar neurons, which reach the anterior cranial fossa from the nasal cavity through openings in the cribriform plate of the ethmoid bone. These primary olfactory neurons differ from other primary sensory neurons in two

Clinical Correlate

Alzheimer's disease results from neurons, beginning in the hippocampus, that exhibit neurofibrillary tangles and amyloid plaques. Other nuclei affected are the cholinergic neurons in the nucleus basalis of Meynert, noradrenergic neurons in the locus coeruleus, and serotonergic neurons in the raphe nuclei. Patients with Down syndrome commonly present with Alzheimer's in middle age because chromosome 21 is one site of a defective gene.

ways. First, the cell bodies of these neurons, which lie scattered in the olfactory mucosa, are not collected together in a sensory ganglion, and second, primary olfactory neurons are continuously replaced. The life span of these cells ranges from 30 to 120 days in mammals.

Within the mucosa of the nasal cavity, the peripheral process of the primary olfactory neuron ramifies to reach the surface of the mucous membrane. The central processes of primary olfactory neurons terminate by synapsing with neurons found in the olfactory bulb. The bulb is a six-layered outgrowth of the brain that rests on the cribriform plate. Olfactory information entering the olfactory bulb undergoes a great deal of convergence before the olfactory tract carries axons from the bulb to parts of the temporal lobe and amygdala.

Clinical Correlate

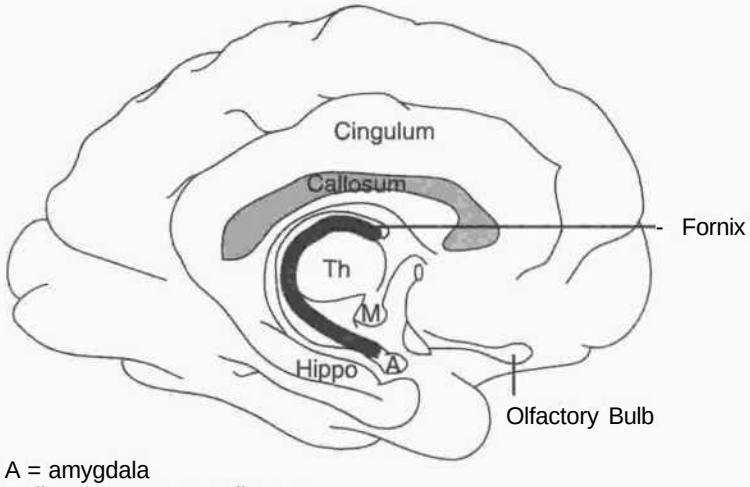
Olfactory Deficits

Olfactory deficits may be incomplete (hyposmia), distorted (dysosmia), or complete (anosmia). Olfactory deficits are caused by transport problems or by damage to the primary olfactory neurons or to neurons in the olfactory pathway to the CNS. Head injuries that fracture the cribriform plate can tear the central processes of olfactory nerve fibers as they pass through the plate to terminate in the olfactory bulb, or they may injure the bulb itself. Because the olfactory bulb is an outgrowth of the CNS covered by meninges, separation of the **bulb** from the plate may tear the meninges, resulting in CSF leaking through the cribriform plate into the nasal cavity.

THE PAPEZ CIRCUIT

A summary of the simplified connections of the limbic system is expressed by the Papez circuit (Fig IV-11-1). The Papez circuit oversimplifies the role of the limbic system in modulating feelings, such as fear, anxiety, sadness, happiness, sexual pleasure, and familiarity; yet, it provides a useful starting point for understanding the system. Arbitrarily, the Papez circuit begins and ends in the hippocampus. Axons of hippocampal pyramidal cells converge to form the fimbria and, finally, the fornix The fornix projects mainly to the mammillary bodies in the hypothalamus. The mammillary bodies, in turn, project to the anterior nucleus of the thalamus by way of the mammillothalamic tract. The anterior nuclei project to the cingulate gyrus through the anterior limb of the internal capsule, and the cingulate gyrus communicates with the hippocampus through the cingulum and entorhinal cortex.

The amygdala functions to attach an emotional significance to a stimulus and helps imprint the emotional response in memory.



A = amygdala
Callosum = corpus callosum
M = mammillary body
Th = thalamus
Hippo = hippocampus

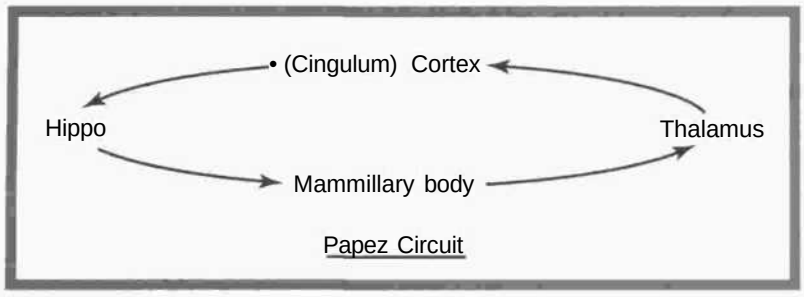


Figure IV-11-1.The Limbic System

Clinical Correlate

Alzheimer's Disease and Anterograde Amnesia

Alzheimer's patients lose episodic memory (events in time) earliest and most severly. Also impaired may be working memory (short-term retention) and semantic memory (objects or facts). Procedural memory (how to use tools) is affected late.

Korsakoff's patients have both anterograde and retrograde amnesia but it is limited to episodic memory.

Clinical Correlate

Thiamine treatment improves signs of Wernicke's encephalopathy. but it does not reverse amnesia in Korsakoff's syndrome.

Clinical Correlate

Anterograde Amnesia

Bilateral damage to the medial temporal lobes including the hippocampus results in a profound loss of the ability to acquire new information, known as anterograde amnesia.

Korsakoff's Syndrome

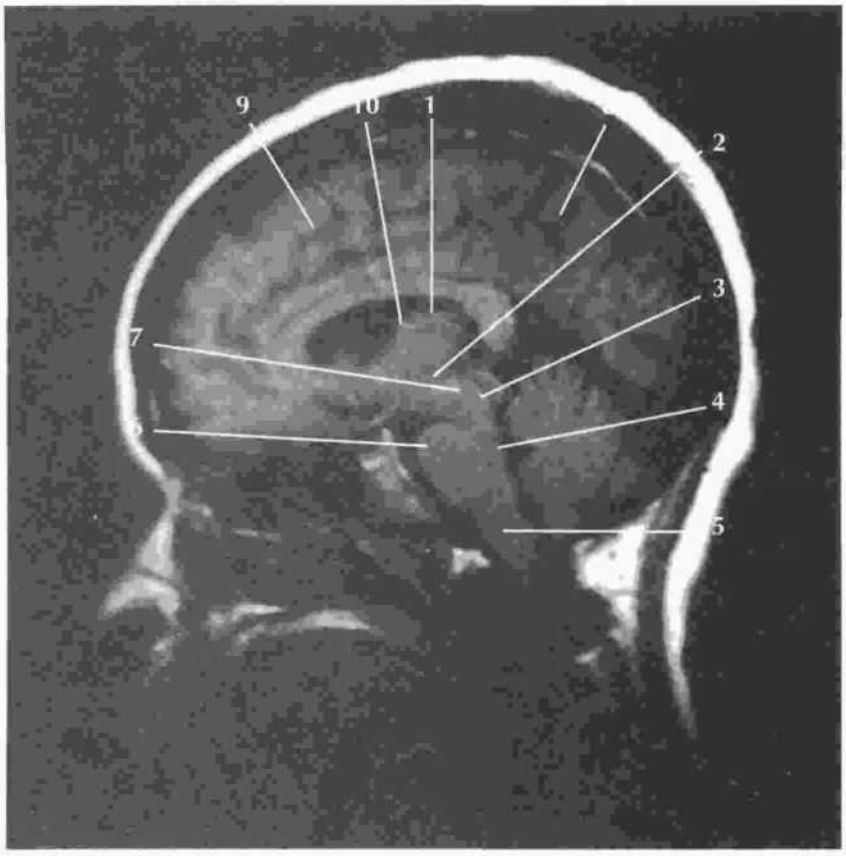
Anterograde amnesia is also observed in patients with Korsakoffs syndrome. Korsakoff's syndrome is seen mainly in alcoholics who have a thiamine deficiency and often follows an acute presentation of Wernicke's encephalopathy. Wernicke's encephalopathy presents with ocular palsies, confusion, and gait ataxia and is also related to a thiamine deficiency. In Wemicke-Korsakoff syndrome, lesions are always found in the mammillary bodies and the dorsomedial nuclei of the thalamus.

In addition to exhibiting an anterograde amnesia, Korsakoff's patients also present with retrograde amnesia. These patients confabulate, making up stories to replace past memories they can no longer retrieve.

Klüver-Bucy Syndrome

Klüver-Bucy syndrome results from bilateral lesions of the amygdala and hippocampus. These lesions result in:

- Placidity—there is marked decrease in aggressive behavior; the subjects become passive, exhibiting little emotional reaction to external stimuli.
- Psychic blindness—objects in the visual field are treated inappropriately. For example, monkeys may approach a snake or a human with inappropriate docility.
- Hypermetamorphosis—visual stimuli (even old ones) are repeatedly approached as though they were completely new.
- Increased oral exploratory behavior—monkeys put everything in their mouths, eating only appropriate objects.
- Hypersexuality and loss of sexual preference
- Anterograde amnesia



1. Corpus Cailosum
2. Thalamus
3. Tectum (superior and inferior colliculi)
4. Fourth Ventricle
5. Medulla
6. Pons
7. Cerebral Aqueduct
8. Superior Sagittal Sinus
9. Subarachnoid Space
10. Lateral Ventricle

Figure IV-11-2. Sagital View of the Brain

USMLE Step 1 Physiology

Lecture Notes

KAPLAN' medical

SECTION I

General Topics

Membrane Transport

1

MEMBRANE STRUCTURE

General Features

Biological membranes are bilayers that are assembled from a mixture of lipids and proteins. The general structure of a membrane is shown in Figure I-1-1.

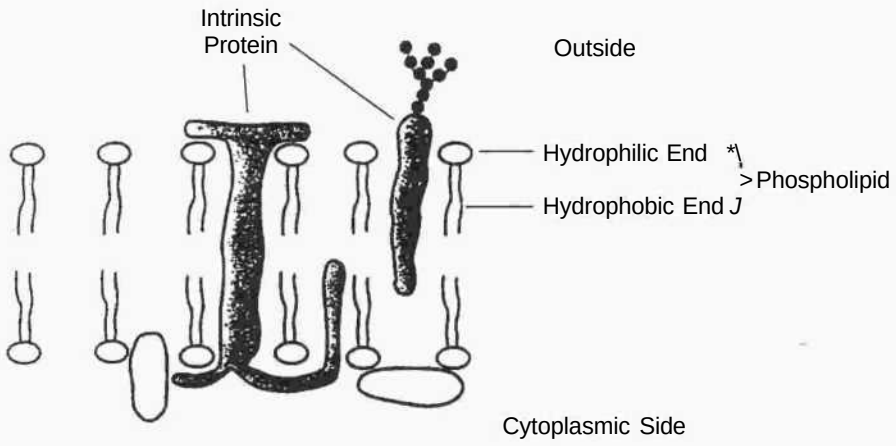


Figure 1-1-1. The Structure of Biological Membranes

What the USMLE Requires You to Know

- Factors affecting the rate of diffusion
- General characteristics of protein-mediated transport
- The differences among the various membrane transport mechanisms

Lipids

The lipid component is composed primarily of a bilayer of phospholipids, with the hydrophilic (water-soluble) ends facing the aqueous environment and the hydrophobic (water-insoluble) ends facing the interior of the membrane. Other major components include unesterified cholesterol and glycolipids.

Proteins

The proteins are responsible for the dynamic aspects of membrane function. There are two main types of membrane proteins.

Integral membrane proteins: They are embedded in the lipid bilayer and cannot be removed without disrupting the bilayer. They include channels, pumps, carriers, and receptors.

Peripheral proteins: They bind to the hydrophilic polar heads of the lipids or to the integral proteins. Peripheral proteins contribute to the cytoskeleton and the glycocalyx (glycolipid and glycoprotein that cover the cell membrane).

MEMBRANE TRANSPORT

Diffusion

Factors that affect the rate of diffusion (D) of a substance between two compartments separated by a membrane are given in the following formula:

$$\text{Doc} \frac{\text{AP} \times SA \times SOL}{TX \sqrt{MW}}$$

AP = concentration gradient across the membrane. The greater the concentration gradient, the greater the rate of diffusion.

SA = surface area of the membrane. The greater the surface area, the greater the rate of diffusion. (For example, exercise opens additional pulmonary capillaries, increasing the surface area for exchange. Emphysema decreases the surface area for exchange.)

SOL = solubility in the membrane or permeability. The more soluble the substance, the faster it will diffuse. Generally CO_2 diffuses faster across membranes than O_2 because CO_2 exhibits greater solubility.

T = thickness of the membrane. The thicker the membrane, the slower the rate of diffusion, (e.g., lung fibrosis).

MW = molecular weight. This factor is not important clinically.

The molecules of each species diffuse independently. There is no direct interaction among molecules during diffusion. If the inspired nitrogen in room air is replaced by helium, the rate of oxygen and carbon dioxide diffusion will be unaffected.

Osmosis

low osmolarity → high osmolarity

Osmosis is the diffusion of water across a semipermeable or selectively permeable membrane. Water will diffuse from a region of higher water concentration to a region of lower water concentration. The water concentration of a solution is determined by the concentration of solute. The greater the solute concentration, the lower the water concentration. The basic principles are demonstrated in Figure 1-1-2.

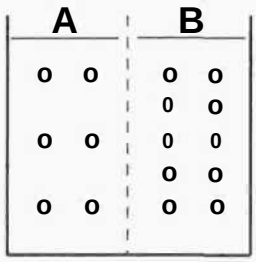


Figure 1-1-2

This figure shows two compartments separated by a membrane that is permeable to water but not to solute. Side B has the greater concentration of solute (circles) and thus a lower water concentration than side A. As a result, water will diffuse from A to B, and the height of column B will rise, and that of A will fall.

mOsm (milliosmolar) = an index of the concentration of particles per liter of solution

mM (millimolar) = an index of the concentration of molecules dissolved per liter of solution

isotonic solutions = 300 mOsm = 150 mM NaCl (one NaCl molecule yields two particles in solution) ~~~~~~~~~~

300 mOsm = 300 mM glucose

The 300 mOsm is rounded off from the true value of 285 to 290 mOsm.

PROTEIN (CARRIER)-MEDIATED TRANSPORT

Protein carriers transport substances that cannot readily diffuse across a membrane. There are no transporters for gases and other lipid-soluble substances because these substances readily penetrate cell membranes.

Characteristics Common to All Protein-Mediated Transport

Rate of transport: A substance is transported more rapidly than it would be by diffusion, because the membrane is not usually permeable to any substance for which there is a transport protein.

Saturation kinetics: As the concentration of the substance initially increases on o"5e~side of the membrane, the transport rate will increase. Once the transporters become saturated, transport rate is maximal (T_M = transport maximum). T_M is the transport rate when the carriers are saturated. It is directly proportional to the number of functioning transporters-

Chemical specificity: To be transported, the substance must have a certain chemical structure. Generally, only the natural isomer will be transported. (e.g., D-glucose but not L-glucose).

Competition for carrier: Substances of similar chemical structure may compete for the same transporter. For example, glucose and galactose will generally compete for the same transport protein.

Types of Protein Transport

Facilitated Transport (Passive Process) indirect ATPase

Net movement is always down a concentration gradient. It is the concentration gradient that drives both facilitated transport and simple diffusion.

Active Transport (Active Process) djsWC{jr\£ -=> high CMC.

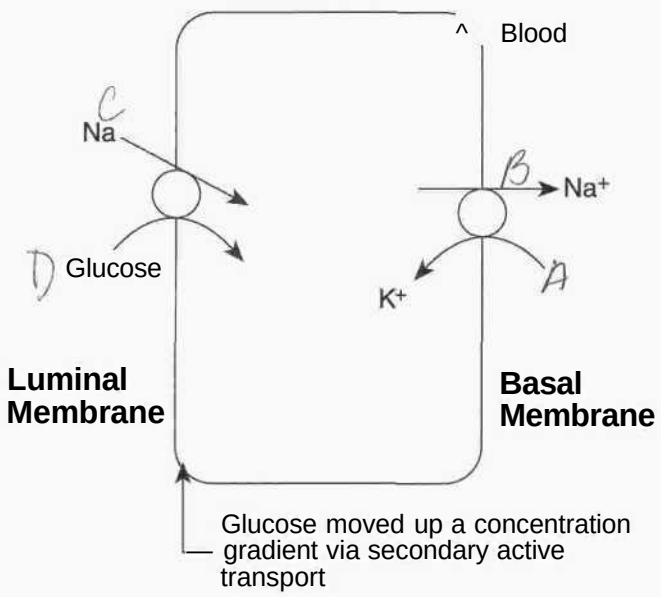
Net movement is against a concentration gradient

Requires chemical energy (ATP)

Primary and Secondary Transport

In primary active transport, ATP is consumed djrgctly by the transporting protein, (e.g., the Na/K-ATPase pump,"oTThe calcium pump of the sarcolemma).

Secondary active transport depends indirectly on ATP as a source of energy, as in the **cotransport** (molecules move in the same direction) of Na^+ and glucose in the renal tubules and gut. This process is depends on ATP utilized by the Na/K-ATPase pump.



which one uses passive transport?
A, B, C, (D) b/c being dragged by Na into cell.

Figure 1-1-3. Renal Tubule or Small Intestine

Figure 1-1-3 represents a renal proximal tubular cell or a cell lining the small intestine. In this figure, the Na/K-ATPase pump maintains a low intracellular sodium concentration, which creates a large gradient across the cell membrane. It is this sodium gradient across the luminal membrane that drives secondary active transport of glucose.

In summary, the secondary active transport of glucose

Depends upon luminal sodium

Is stimulated by luminal sodium (via increased sodium gradient)

Is linked to the uptake of sodium

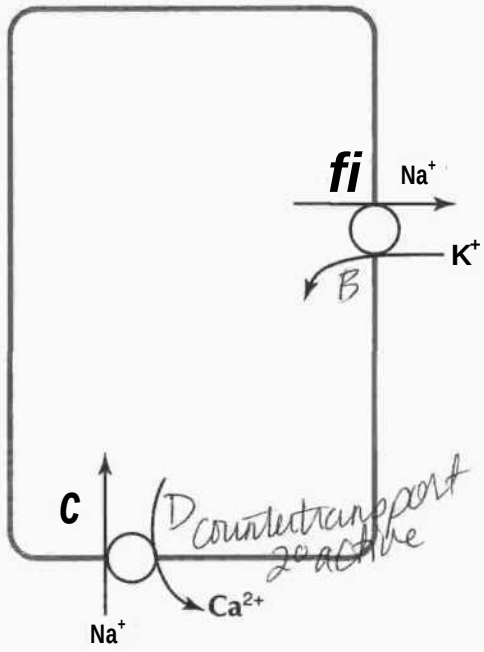


Figure 1-1-4. Heart Muscle Cell

Another example of secondary active transport, the **countertransport** (molecules move in the opposite direction) of Na^+ and Ca^{2+} in heart muscle, is shown in Figure 1-1-4. In this case, as in the cotransport of sodium and glucose, transport is dependent on the ATP utilized by the Na/K-ATPase pump.

VESICULAR TRAFFIC AND THE PLASMA MEMBRANE

Endocytosis

Endocytosis is the movement of macromolecules from outside the cell to the inside of the cell by the active imagination of the plasma membrane.

Categories Based on State (Solid or in Solution) of the Substance Taken Up

Phagocytosis: The process by which solid bits of material, (e.g., bacteria, dead tissue) are engulfed by cells.

Fluid-phase endocytosis or pinocytosis: The uptake of molecules in solution.

Categories Based Upon Uptake Mechanisms

Constitutive endocytosis: A noninduced process whereby vesicles are continuously fusing withlhe cell membrane.

Receptor-mediated endocytosis: The molecule being internalked (the ligand) binds to a receptor on the surface of the cell. These receptor-ligand complexes concentrate at clathrin-coated pits on the plasma membrane. The pit then pinches off, forming a vesicle. In some cases the receptors recycle back to the membrane. This process is more rapid and more specific than constitutive endocytosis.

Exocytosis

Exocytosis is the process by which macromolecules are packaged in secretory vesicles and then extruded from the cell. This process requires both calcium and energy.

Constitutive secretion: The vesicles are not coated with clathrin and are continuously fusing with the cell membrane.

Regulated exocytosis: The vesicles are coated with clathrin, and a signal is required before the vesicle will fuse with the membrane, (e.g., the release of vesicular-bound water-soluble hormones).

Graphical Representation of Transport Processes

One method of testing your understanding of physiological process is by presenting a graph to interpret. Figure 1-1-5 and the accompanying questions test your understanding of membrane transport. The graph simply represents extracellular concentration versus rate of transport across the cell membrane.

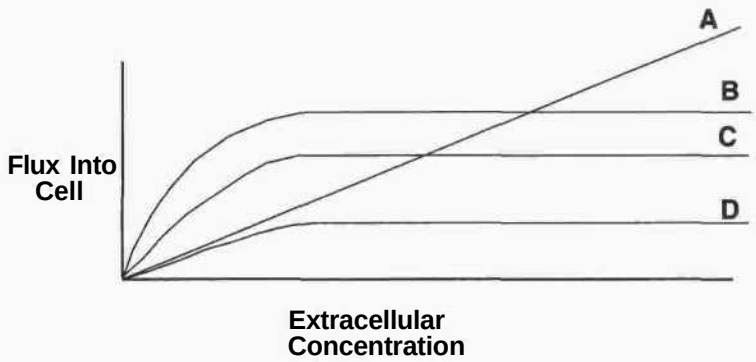


Figure 1-1-5

QUESTIONS

The following questions refer to Figure 1-1-5:
(answers with explanations on the next page)

1. Which curves could represent simple diffusion? If the surface area for diffusion increased, what would happen to the slope of the diffusion curve?
2. Which curves could represent protein-mediated transport? Could you separate active transport versus facilitated transport curves?
3. Which curves demonstrate a T_M? Which curve has the lowest T_M, and which curve has the greatest T_M?
4. If "C" represents the movement of glucose into skeletal muscle under control conditions, which curve would represent glucose transport after adding additional insulin? What does insulin do to the number of functioning transporters in the system?

ANSWERS

1. A. It is a straight-line relationship: the greater the concentration gradient, the greater the rate of diffusion. If the surface area for diffusion increased, the slope would increase. This means that at a given concentration gradient the rate of diffusion would be greater.
2. B, C, D. These three curves demonstrate saturation kinetics (plateau), which is a characteristic of all protein-mediated transport. You cannot determine which curves would represent facilitated transport versus active transport. Facilitated transport is always down a concentration gradient, whereas active transport can be against a concentration gradient. This information is not presented in the graph.
3. B, C, D. Again, this is a characteristic of all protein-mediated transport. T_M is the rate of transport of the plateau (measured on the y axis). D has the lowest T_M and B the greatest.
4. B. Insulin simply places more transporters in the membrane system, which would increase T_M.

Chapter Summary

A cell membrane is a lipid bilayer composed mainly of phospholipid. Dynamic properties are due to the protein component, which includes pumps, channels, receptors, and carriers.

Simple diffusion and facilitated transport are both passive processes (not energy dependent) driven by concentration gradients.

The rate of protein-mediated transport will increase with increased substrate delivery until the carriers are saturated. The maximum rate with carrier saturation is called T_M, and this rate is directly proportional to the number of functioning carriers present in the system.

Secondary active transport is driven by the sodium gradient across the cell membrane, which is maintained by the Na/K-ATPase pump.

Endocytosis and exocytosis represent uptake and extrusion of macromoiecules via vesicular transport.

2 Body Compartments

TBW = ICF + ECF < ISF 2/3, VF (plasma) 1/3
2/3 1/3

DISTRIBUTION OF FLUIDS WITHIN THE BODY

Total Body Water

Intracellular fluid (ICF): approximateIy 2/3 of total of body water

Extracellular fluid (ECF): approximately J73 of total body water

Interstitial fluid (ISF): approximately 2/3 of the extracellular fluid

Vascular fluid (VF): approximately 1/3 of the extracellular fluid (plasma plus red blood cells). A normal vascular volume is close to 5 L (blood volume).

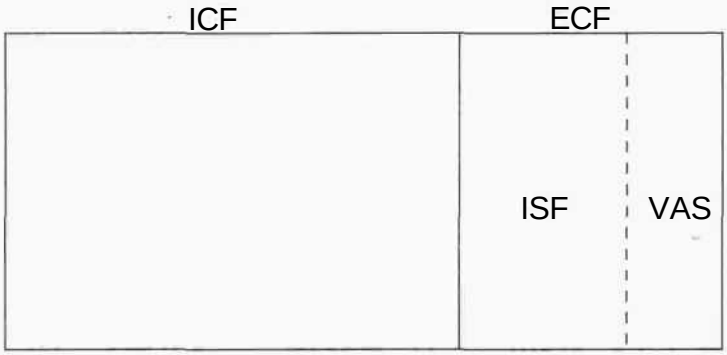


Figure 1-2-1

The solid line division represents the cell membrane, and the dashed line capillary membranes.

What the USMLE Requires You to Know

- What determines the effective osmotic pressure between two compartments
- The changes in body osmolarity and intracellular and extracellular volumes in clinically relevant situations
- The principles involved in measuring the volume of a body compartment

Intracellular Fluid (ICF) versus Extracellular Fluid (ECF)

These two compartments are separated by cell membranes which generally have the following important characteristics:

Freely Permeable to Water

In a steady state, intracellular and extracellular osmolarity will be the same. Normally, this is close to 300 mOsrn.

Impermeable to Sodium (Chloride)

The difference in the concentration of impermeable particles determines the osmotic movement of water across membranes. The concentration of these particles is often referred to as the effective osmolarity of a particular compartment. Because sodium chloride represents most of the nonpermeant particles of the extracellular fluid, the concentration of sodium chloride represents most of the effective osmolarity of this compartment. Twice the extracellular sodium concentration is usually a good index of body osmolarity.

If ECF effective osmolarity increases, cells shrink (ICF II).

If ECF effective osmolarity decreases, cells swell (ICF ft).

Interstitial versus Vascular (Plasma) Fluid

Movement of fluid between these compartments occurs across capillary membranes. Capillary membranes are freely permeable to all natural substances dissolved in the plasma, except proteins. Thus, it is the concentration of plasma proteins that determines the effective osmolarity between these two compartments. (Capillary exchange is discussed in the peripheral circulation unit.)

isotonic - same amt. of fluid as
hypertonic - fluid more Na than plasma

(H[1]

A pt. was brought into ER after drinks a bottle of distilled
H_2O. distilled-salt

Diuretics unsupp

Hemorrhage → isotonic
Sweating → hypotonic
Chronic diarrhea hyper

Graphical Representation of Volume versus Solute Concentration in the ICF and ECF

It is important to understand how body osmolarity and the intracellular and extracellular volumes change in clinically relevant situations. Figure 1-2-2 is one way of presenting this information. The y axis is solute concentration or osmolarity. The x axis is the volume of intracellular (2/3) and extracellular (1/3) fluid. If the solid line represents the control state, the dashed lines show a decrease in osmolarity and extracellular volume but an increase in intracellular volume.

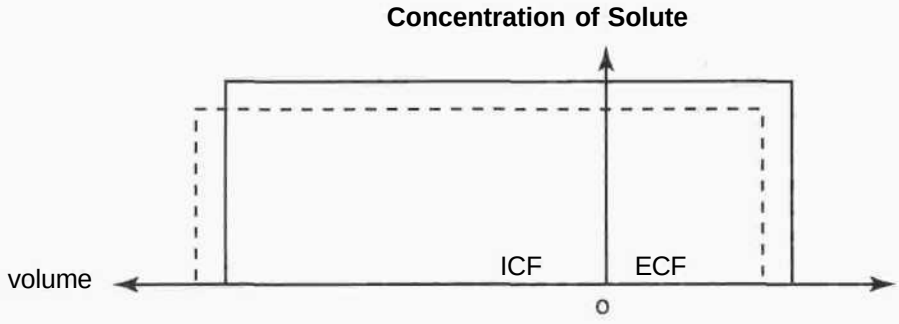


Figure 1-2-2. Darrow-Yannet Diagram

1- When a person gains or loses fluid, if yes, then coming from ECF.
The ICF only changes when ECF changes

2. What tonicity of fluid is involved

3. ICF only changes when the ECF osmolarity changes

Addison's dis. any changes
no aldosterone → no salt
hypertonic
H2O moves from ECF → ICF

Someone injected w/ Img HCTP.
What happens to him?
Urine is concentrated
hypertonic

Extracellular Volume

When there is a net gain of fluid by the body, this compartment always enlarges. A net loss of body fluid decreases extracellular volume.

Concentration of Solute Particles

This is equivalent to body osmolarity and in most cases is approximated as twice the sodium concentration (mM) of the extracellular fluid. Remember, at equilibrium the intracellular and extracellular osmolarity will be the same.

Intracellular Volume

This varies with the effective osmolarity of the extracellular compartment, that is, the concentration of particles that do not penetrate the cell membrane. An increase in osmolarity decreases intracellular volume, and the opposite occurs with a decrease in body osmolarity.

QUESTIONS

(Answers below)

Using the graph presented in Figure 1-2-2, determine the volume and concentration changes associated with the following states of hydration. If you need help, see Table 1-2-1.

1. Loss of isotonic fluid
   Examples: hemorrhage (neglect loss of intracellular fluid as RBC volume), the formation of isotonic urine, and the immediate consequences of diarrhea or vomiting

2. Loss of hypotonic fluid
   Examples: sweating (dehydration), hypotonic urine formation such as occurs in diabetes insipidus and alcoholism

3. Ingestion of salt tablets

4. Person who drinks 1 L of tap (or distilled) water. (This is equivalent to water intoxication.)

5. Infusion of hypotonic saline (1/2 normal saline)

6. Infusion of isotonic saline

7. Infusion of hypertonic saline (or hypertonic mannitol)

8. Primary adrenal insufficiency (volume and salt depletion, volume replacement exceeds salt replacement)

Changes in Volume and Concentration

1. Loss of isotonic fluid that might be due to hemorrhage (neglect loss of intracellular fluid as RBC volume), isotonic urine, or the immediate consequences of diarrhea or vomiting:

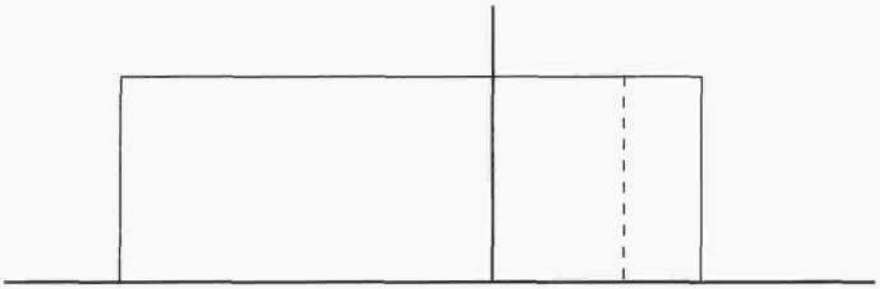


Figure 1-2-3

There will be a loss of volume but no change in extracellular effective osmolarity. The fact that extracellular osmolarity is unchanged means no change in intracellular volume.

2. Loss of hypotonic fluid that might be due to sweating (dehydration), hypotonic urine, or diabetes insipidus:

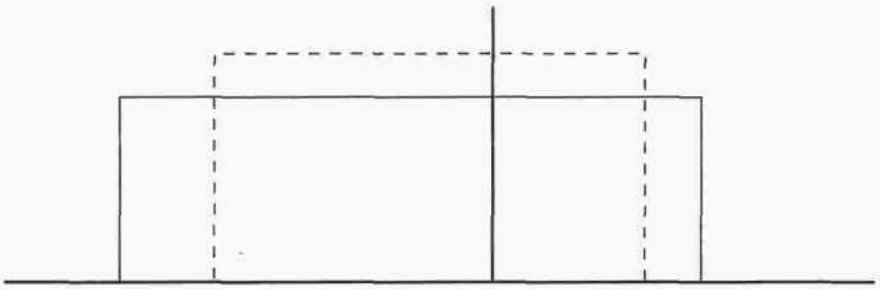


Figure 1-2-4

Losing hypotonic fluid from the extracellular space would increase extracellular effective osmolarity (sodium concentration would increase). Fluid would move from the intracellular to the extracellular compartment until osmolarity was again equal in the two compartments. The fluid entering the extracellular space would partially but not completely compensate for the originate insult.

3. Ingestion of salt tablets:

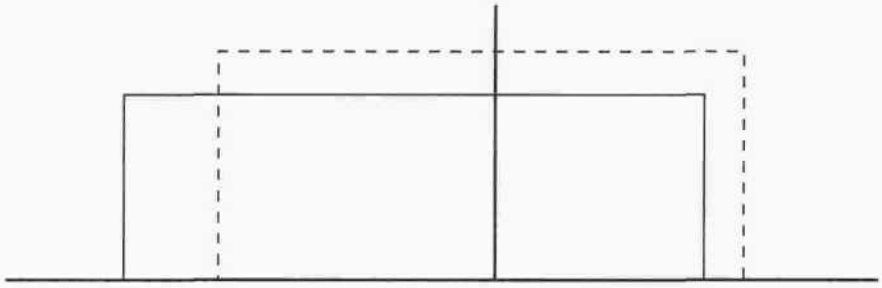


Figure I-2-5

The salt tablets would increase the effective osmolarity of the extracellular fluid. The result would be a fluid shift from the intracellular to the extracellular compartment

4. Person who drinks 1 liter of tap (or distilled) water:

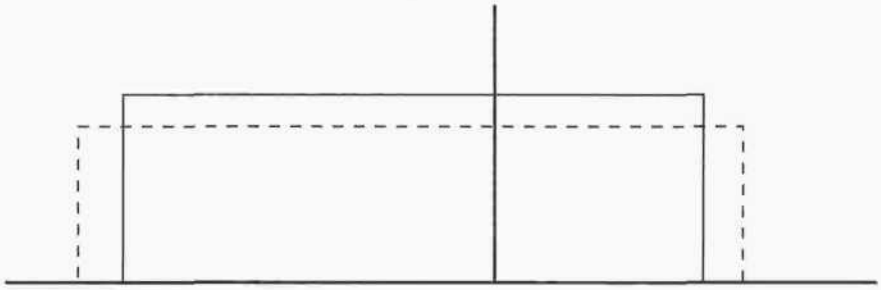


Figure 1-2-6

The tap water entering the extracellular space would increase its volume and decrease its osmolarity. Because of the decrease in osmolarity, some of the ingested water would diffuse into the intracellular space.

5. Infusion of hypotonic saline (half-normal saline):

The answer is the same as answer 4.

6. Infusion of isotonic saline:

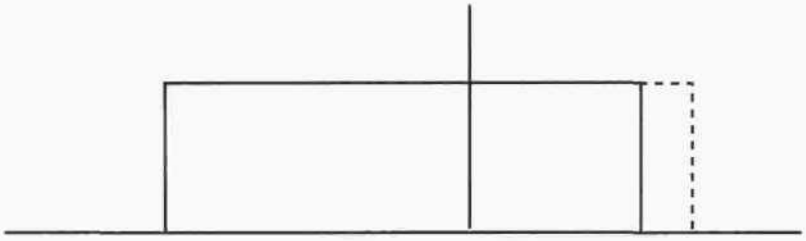


Figure 1-2-7

The infusion of isotonic saline would increase the volume but not the effective osmolarity of the extracellular space. Because there was no change in osmolarity, the intracellular volume is unchanged. An additional point is that most of the saline would enter the interstitial space. A much smaller volume would remain in the intravascular compartment. If plasma, which does contain protein, was infused, however, almost all of the fluid would remain in the vascular space because the proteins do not easily cross capillary membranes.

7. Infusion of hypertonic saline (or hypertonic mannitol):

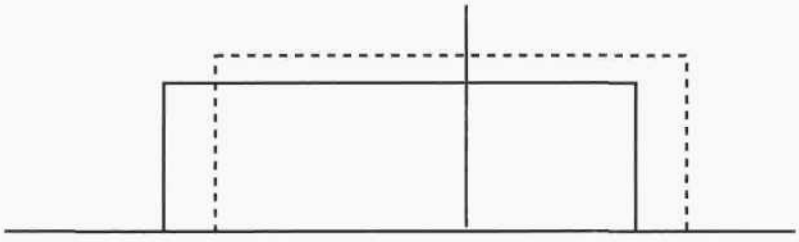


Figure 1-2-8

The hypertonic saline would increase both the volume and effective osmolarity of the extracellular compartment. The increased osmolarity would cause a fluid shift from the intracellular to the extracellular space, reducing intracellular volume and further increasing extracellular volume.

8. Primary adrenal insufficiency:

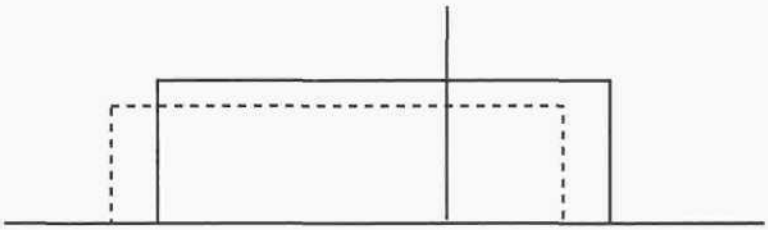
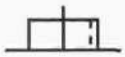
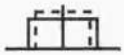
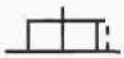
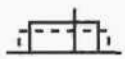
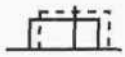


Figure I-2-9

This individual will lose both fluid and salt. There will be partial dietary replacement, and extracellular sodium will generally be below normal. The loss of effective extracellular osmolarity will expand the intracellular volume.

Table 1-2-1.
Summary of Volume Changes and Body Osmolarity Following Changes in Body Hydration

	ECF Volume	Body Osmolarity	ICF Volume	D-Y Diagram
Loss of isotonic fluid Hemorrhage Diarrhea Vomiting	⇓	no change	no change	
Loss of hypotonic fluid Dehydration Diabetes insipidus Alcoholism	⇓	⇑	⇓	
Gain of isotonic fluid Isotonic saline	⇑	no change	no change	
Gain of hypotonic fluid Hypotonic saline Water intoxication	⇑	⇓	⇑	
Gain of hypertonic fluid Hypertonic saline Hypertonic mannitol	⇑	⇑	⇓	

ECF = extracellular fluid; ICF = intracellular fluid.

SUPPLEMENTAL TOPICS

Volume Measurement in the Major Fluid Compartments

Principle

To measure the volume of a body compartment, a tracer substance must be evenly distributed within that compartment. In this situation, the volume of the compartment can usually be calculated by using the following relationship:

V X C = A

V = Volume of the compartment to be measured

C = Concentration of the tracer in the compartment to be measured

A = Amount of the tracer

Sample problem: 300 mg of a dye was injected intravenously. At equilibrium, the concentration in the blood was 0.05 mg/mL. Determine the volume of the compartment which contained the dye.

Answer: 6000 mL

Required Properties of the Tracer

Tracers are generally introduced into the vascular compartment, and they will distribute through body water until they reach a barrier they cannot penetrate. The two major barriers encountered are capillary membranes and cell membranes.

Required criteria of tracers to measure the following compartments:

Total body water: permeable to capillary and cell membranes, e.g., tritiated water, urea

ECF: permeable to capillary membranes but not cell membranes, e.g., inulin, mannitol, sodium, sucrose

Plasma: not permeable to capillary membranes, e.g., albumin

Blood Volume versus Plasma Volume

Definition of Blood Volume

Blood volume represents the plasma volume plus the volume of red blood cells (RBCs), which is usually expressed as hematocrit (fractional concentration of red blood cells).

Calculation of Blood Volume

Formula

The fn11r>wjpg fnrmn|aj-an be utilized to convert plasma volume to blood volume:

$$\text{Blood volume} = \frac{\text{plasma volume}}{1 - \text{Hct}}$$

Hct = hematocrit

Example:

Hct = **50%** (0.50)

Plasma volume = 3 L

$$\text{Blood volume} = \frac{3\text{L}}{1\text{-}0.5} = 6\text{L}$$

Note that if the hematocrit is 0.5 (or 50%), the blood is half RBCs and half plasma. Therefore, blood volume will be double the plasma volume.

Changes in Red Blood Cell Volume

Principle

1. Na can't cross membrane freely
2. Urea can cross membrane
3. Glycerol has bipolar in beginning no crossing end crosses

Changes in red blood cell volume in an *injntro* solution are be due to the movement of water (osmosis) across the cell membrane. This is determined by the effective osmolarity (concentration of impermeable solutes) of the external fluid. Just remember, water will diffuse from ajggion gfhigher water^oncentration to a region of lower water concentration.

Effect of Isotonic Saline

If a normal red blood cell is placed in isotonic saline (300 mOsm NaCl), no change in red cell volume will occur. This is because the effective osmolarity of the solution equals the effective osmolarity inside the red blood cell. As long as the concentration of nonpenetrating particles of the external solution is 300 mOsm, there will be no significant change in the volume of the red blood cell.

Problems Involving a Nonpenetrating Solute

Predict the changes in cell volume (increase, decrease, no change) when a normal red blood cell previously equilibrated in isotonic saline is placed in the following solutions. Assume the fluid volume of the external solution is large, and thus, as water moves in or out of the cell, there is no significant change in the concentration of beaker solutes (answers below). *300 mO ^TY^>*

1. 200mOsm NaCl(hypotonic) water will move from RBC. swell
2. 400 mOsm NaCl hypertonic shrink
3. 150 mM NaCl - *(.SQirrusC ^A* thing will happen
4. 300 mM NaCl Jypertonic shrink

→ 1mM = f Na+ / Cl = 2 mOsm

Effect of Substances That Rapidly Penetrate Cell Membranes

The presence of a substance, such as urea, that penetrates the cell membrane quickly does not affect the osmotic movement of water. If the total concentration of nonpenetrating solutes is <300 mOsm, the RBC will swell; if it is >300 mOsm, the RBC will shrink.'

Problems Involving a Rapidly Penetrating Solute

Predict the changes in cell volume (increase, decrease, no change) when a normal red blood cell previously equilibrated in isotonic saline is placed in the following solutions:

5. 200 mOsm NaCl and 200 mOsm urea *&uKM*
6. 300 mOsm urea only *JLU. O%rr)t£tS O %eM* swells
7. 500 mOsm urea only *jjt o ^ m ^ Q ^* cell swells

Urea does not have any osmotic effect

Effect of Substances That Slowly Penetrate Cell Membranes

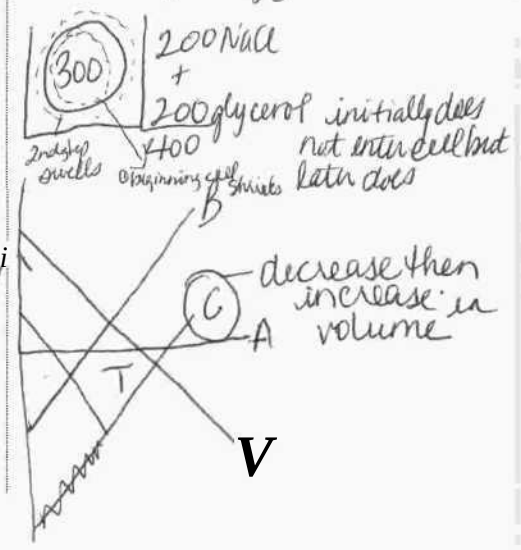
Some substances penetrate cell membranes but do so slowly. Thus, they initially have an osmotic effect like sodium chloride but no osmotic effect at equilibrium.

Problem Involving a Slowly Penetrating Solute

Predict the changes in cell volume (increase, decrease, no change) when a normal red blood cell previously equilibrated in isotonic saline is then placed in the following solution. Determine the initial effect versus the long-term effect.

8. 200 mOsm NaCl and 200 mOsm glycerol (a slowly penetrating substance) .i

Put RBC in a 200 mOsm NaCl and 200 mOsm glycerol



ANSWERS

1. 200 mOsm NaCl: Because the effective osmolarity of the solution is <300 mOsm, the RBC will swell. Cells in hypotonic saline swell.
2. 400 mOsm NaCl: Because the effective osmolarity of the solution is >300 mOsm, the RBC will shrink. Cells in hypertonic saline shrink.
3. 150 mM NaCl: This is equivalent to 300 mOsm NaCl or isotonic saline. There is no change in RBC volume.
4. 300 mM NaCl: This is equivalent to 600 mOsm NaCl or hypertonic saline. Cells in hypertonic saline shrink.
5. 200 mOsm NaCl and 200 mOsm urea: The effective osmolarity of the solution is determined only by the nonpenetrating solutes. A penetrating substance, such as urea, will diffuse across the membrane and equalize its concentration in the two compartments. Therefore, it will not contribute to effective osmolarity. If the effective osmolarity is less than 300, the cell swells. Here the effective osmolarity is 200; therefore, the cell swells.
6. 300 mOsm urea only: The effective osmolarity of the solution is zero, which is the same as pure water; therefore, the cell swells.
7. 500 mOsm urea only: Again, the effective osmolarity is zero; therefore, the cell swells.
8. 200 mOsm NaCl and 200 mOsm glycerol (a slowly penetrating substance): Timing is important in this question. Initially, the glycerol will not penetrate; therefore, it contributes to the initial effective osmolarity of the solution. Because the initial effective osmolarity is 400, the cell will shrink. With time, the glycerol will penetrate the membrane and equalize its concentration in the two compan ments. The long-term effective osmolarity will be due to only the NaCl, 200 mOsm. Therefore, over the long term it will swell.

Chapter Summary

Extracellular volume increases with a net gain of fluid and decreases with a net loss of body fluid.

Extracellular effective osmolarity is generally determined by twice the sodium concentration (mM).

Intiacellular volume increases with a decrease in ECF osmolarity and decreases with an increase in ECF osmolarity.

A comprehensive summary is given in Table 1-2-1.

MEMBRANE TRANSPORT/BODY COMPARTMENTS

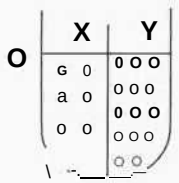
Review Questions

Directions: Select the ONE best answer.

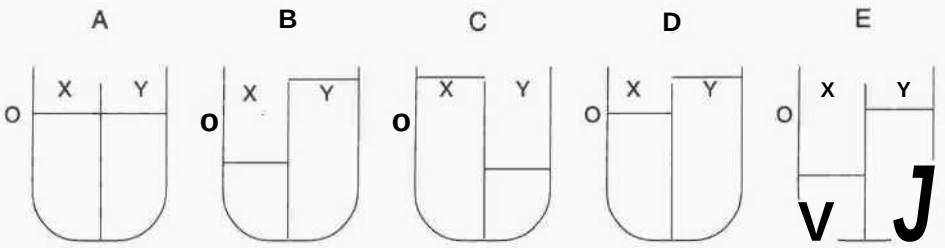
1. Red blood cells are suspended in a solution containing 250 mOsm/L of sodium chloride in water. Ignoring transient changes, intracellular red cell volume will:

   A. increase
   B. decrease
   C. remain unchanged

2. Two compartments (X and Y) of water are separated by a semipermeable membrane. The concentrations of impermeant solute at time zero are shown in the following drawing:



   Which of the drawings below represents the volumes of X and Y when the system reaches equilibrium?



3. Identify the fluid compartment that contains approximately two-thirds of the total body water.

   A. transcellular
   B. plasma
   C. interstitial
   D. intracellular
   E. extracellular

4. Facilitated diffusion can be distinguished from simple diffusion by which of the following statements?

   A. facilitated diffusion is saturable, simple diffusion is not
   B. facilitated diffusion requires ATP, simple diffusion does not
   C. facilitated diffusion is not chemically specific, simple diffusion is
   D. facilitated diffusion is dependent on concentration gradient, simple diffusion is not

Questions 5 and 6

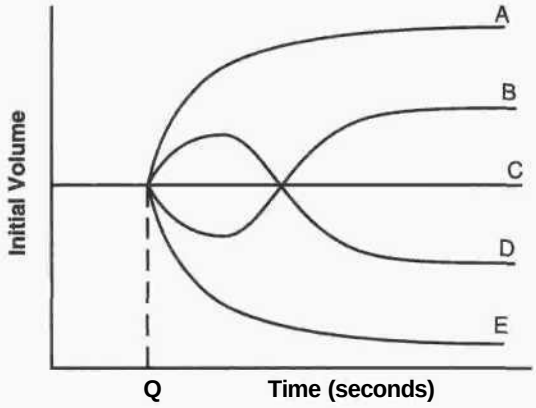
Red blood cells are placed in a beaker containing one of the following solutions. Ignoring transient (initial) changes, predict the effect of the solution on red blood cell volume.

A. increase in cell volume
B. decrease in cell volume
C. no change in cell volume

5. 200 mOsm sodium chloride

6. 400 mOsm glycerol

Questions 7 and 8



The diagram above illustrates possible changes in red blood cell volume resulting from a change in extracellular fluid composition for a cell equilibrated in 150 mM/L NaCl solution at time 0.

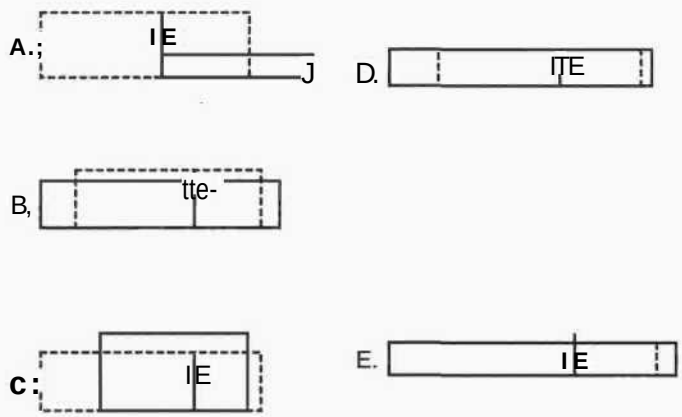
300 mOsm

7. Which curve best illustrates the volume caused by immersion of the cell into an aqueous solution of 300 mOsm $CaCl_2$?

8. Which curve best illustrates the volume change caused by immersion of the cell into an aqueous solution of 200 mOsm/L NaCl and 200 mOsm/L of glycerol?

2, p_O → 400
Shrink

Questions 9 and 10



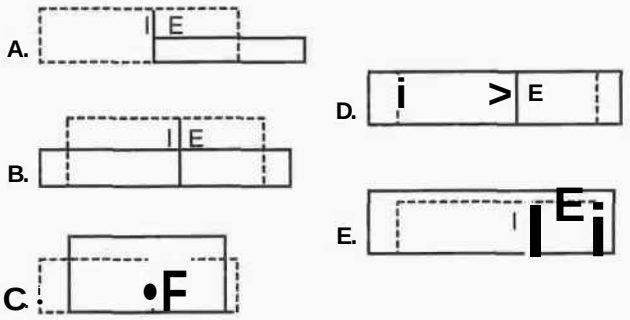
ECFV ↓
m osm ↑
ICF → ECF

In the above Dannett-Yarrow diagrams, the dashed boxes represent original conditions of intracellular space (I) and extracellular space (E). The x axis is volume and the y axis represents osmolarity.

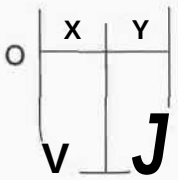
9. Which of the diagrams best illustrates the changes in fluid compartments resulting from loss of pure water from the body?

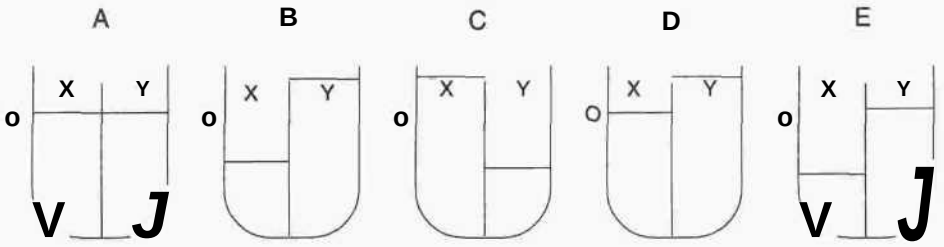
10. Which of the diagrams best illustrates the changes in fluid compartments resulting from infusion of 300 mOsm/L NaCl solution?

11. Select the Dannett-Yarrow diagram (below) which best illustrates the before (dashed) and after (solid) status of a person who received 1 L of a hypertonic saline solution intravenously.



12. In the diagram below, two water-filled chambers are separated by a semipermeable membrane. Choose the diagram which best illustrates the volumes of the two chambers at equilibrium after 100 mOsm/L of a permeating solute is added to chamber X.

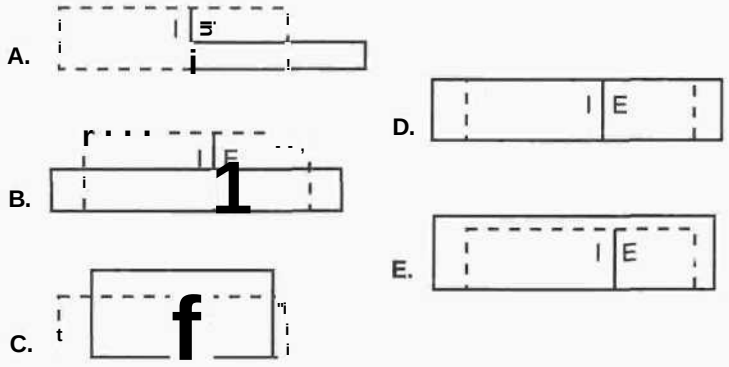




13. The most rapid form of transport over a distance greater than 1 cm is:

A. simple diffusion
B. facilitated diffusion
C. primary active transport
D. secondary active transport
E. bulk flow (flow due to pressure differences)

14. Which of the following diagrams best illustrates the fluid shifts resulting from infusion of 1 L of distilled water into the bloodstream (dashed lines represent original conditions and solid lines the final steady-state situation)?



15. Which of the following characteristics is not associated with facilitated diffusion:

A. stereospecificity for substrate
B. competitive inhibition by structurally similar substrates
C. saturation kinetics
D. direct dependence on ATP concentration

16. Check each of the following statements concerning intracellular fluid that is true:

1. it contains more than 50% of the body water
2. it has a higher osmotic pressure than extracellular fluid
3. is has a higher concentration of organic anions than extracellular fluid

Which one of the following best summarizes your conclusions?

A. statement 1 is true
B. statement 2 is true
C. statements 1 and 2 are true
D. statements 1 and 3 are true
E. statements 1,2, and 3 are true

17. Check each of the following statements concerning the diffusion of water that is true:

    1. the net flux of water is from an area of low solute concentration to an area of high solute concentration
    2. requires a semipermeable membrane
    3. is an energy-requiring process

    Which one of the following best summarizes your conclusions?

    A. statement 1 is true
    B. statement 2 is true
    C. statements 3 is true
    D. statements 2 and 3 are true
    E. statements 1,2, and 3 are true

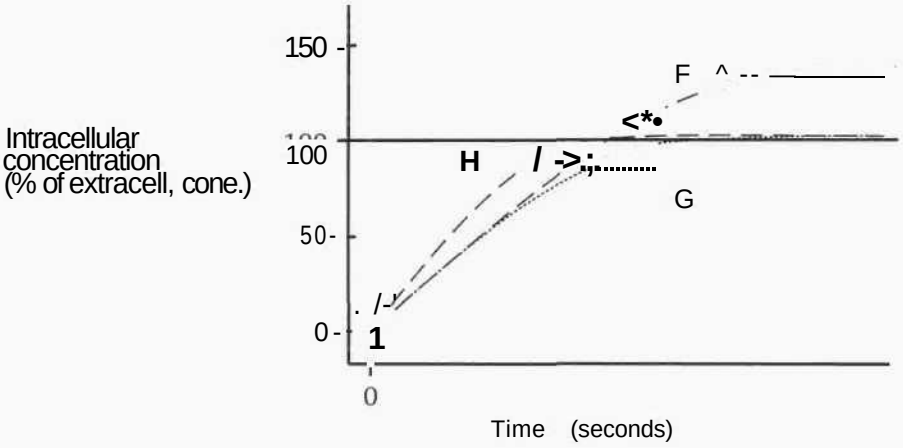
18. One liter of isotonic saline was injected intravenously into a 7O-kg woman. Assume the injection had no significant effect on capillary hydrostatic pressure. After 15-30 minutes the (check each correct answer)

    1. extracellular water would increase by more than 900 ml
    2. interstitial water would increase by more than 900 ml
    3. intracellular water would increase by more than 900 ml
    4. plasma water would increase by more than 900 ml
    5. total body water would increase by more than 900 ml

19. If 1 month later, 1 liter of plasma was given intravenously to the woman in question 18, and once again the capillary hydrostatic pressure stayed constant, what would be the effect on fluid volume 15-30 minutes after the injection (choose one or more correct answers from possibilities 1 through 5 in question 18)?

20. If two months later, 1 liter of an isosmolar solution of urea was injected intravenously into the woman in question 18, and once again the capillary hydrostatic pressure stayed constant, what would be the effect on fluid volume 15-30 minutes after the injection (choose one or more correct answers from possibilities 1 through 5 in question 18)?

21. The following diagram shows the rate of entry of various molecules into a cell:



Choose the correct statement.

A. If curves F and G represent molecules that enter only by diffusion through pores, then curve F represents the diffusion of a larger molecule than curve G.

B. If curves G and H represent molecules that enter only through the lipid portion of the cell membrane, then curve H represents a less lipid-soluble molecule than curve G.

C. If curve F represents an ion being moved by facilitated diffusion, then curve G represents the movement of the same ion after ATPase inhibition by ouabain.

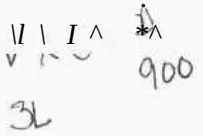
D. If curve H represents a molecule being moved by facilitated diffusion, then curve G represents the movement of the same molecule after the addition of a molecule of similar chemical structure.

22. A 60-kg patient has a hematocrit reading of 40 and a plasma volume of 3 liters. What is his total blood volume?

A. 4.0 liters
B. 5.0 liters
C. 6.0 liters
D. 7.0 liters
E. greater than 7.5 liters

23. Nine hundred millimicrocuries of albumin labeled with radioactive iodine are injected intravenously into a lean, 70-kg man. If there is complete mixing in the plasma and no excretion of the albumin, what approximate plasma concentration of the labeled albumin do you expect to find 10 minutes after injection (assume normal plasma volume of about 3L)?

A. < 29 millimicrocuries/liter
B. 60 millimicrocuries/liter
C. 130 millimicrocuries/liter
D. 300 millimicrocuries/liter
E. 500 minimicrocuries/liter



24. Which set of the following best illustrates the consequences of the infusion of plasma:

	Intracellular Volume	Extracellular Volume	Extracellular Osmolarity	Extracellular Sodium Cone.	Hematocrit
A.	no change	increase	no change	no change	decrease
B.	increase	increase	increase	increase	no change
C.	no change	increase	no change	no change	no change
D.	increase	increase	decrease	decrease	no change
E.	no change	no change	no change	increase	decrease

25. An excessive intake of tap water over a short period of time would be expected to produce which of the following:

	Extracellular Volume	Intracellular Volume	Extracellular Sodium Cone.	Intracellular Osmolarity
A.	increase	decrease	decrease	increase
B.	increase	decrease	decrease	increase
C.	increase	increase	decrease	decrease
D.	increase	increase	increase	decrease
E.	increase	increase	decrease	increase

26. Exposure to the sun in a hot desert environment for a prolonged period of time without adequate fluid intake would produce:

	Intracellular Volume	Intracellular Osmolarity	Extracellular Sodium Cone.	Extracellular Osmolarity	Urine Osmolarity
A.	decrease	decrease	increase	increase	increase
B.	decrease	increase	increase	increase	increase
C.	increase	increase	increase	increase	decrease
D.	decrease	increase	decrease	increase	increase
E.	decrease	decrease	decrease	decrease	decrease

Answers

1. Ans A — A 250 mOsm/L (or stated as just mOsm) solution of sodium chloride is a hypotonic solution, thus it has a higher water concentration than the red blood cell interior. Water will thus diffuse into the red blood cell, and the cell's volume will increase.

2. Ans B — The "X" side has the lower solute concentration and thus the higher water concentration. Water diffuses from X to Y, thus the level of side X decreases and the level of side Y increases.

3. Ans D — Body water is approximately distributed as 2/3 intracellular fluid and 1/3 extracellular fluid.

4. Ans A — Facilitated diffusion and simple diffusion are both passive processes driven by concentration gradients; however, facilitated diffusion has characteristics that apply to protein-mediated transport, e.g., exhibits saturation kinetics and chemical specificity.

5. Ans A — A 200 mOsm sodium chloride solution is hypotonic and thus has a greater water concentration than the red blood cell. Thus water diffuses into the cell and its volume increases.

6. Ans A — A 400 mOsm glycerol solution represents a solution with a lower water concentration than in the red blood cell. The glycerol, however, will penetrate the red blood cell but does so slowly. Thus, initially water will leave the red blood cell and the cell will shrink. However, the question says to ignore this initial effect and only consider the long-term changes. The glycerol will enter the cell until the concentration of glycerol in the red blood cell will equal the concentration of glycerol in the beaker. The problem is that there is no nonpenetrating solute like NaCl in the beaker to balance the 300 mOsm of nonpenetrating solutes inside the red blood cell, thus the cell will swell.

7. Ans C — The red blood cell was equilibrated in 150 mM NaCl which equals 300 mOsm and thus is an isotonic saline solution. A 300 mOsm $CaCl_2$ solution is also an isotonic solution of a nonpenetrating solute, thus, there will be no change in red blood cell volume.

8. Ans B — 200 mOsm NaCl is nonpenetrating but the 200 mOsm glycerol penetrates slowly. Initially the effective osmolarity of the solution is 400 mOsm, thus the cell shrinks. With time the glycerol penetrates and the final effective osmolarity of the solution is only 200 mOsm due to the NaCl. Thus as the glycerol penetrates, water moves into the red blood cell and the final volume will be greater

than at time zero. Curve B, which shows an initial shrinkage then overall swelling, is the best answer.

9. **Ans** C Loss of pure water from the extracellular fluid would increase body osmolarity and decrease extracellular volume. The increased extracellular osmolarity will cause some water to diffuse out of cells, decreasing intracellular volume.

10. **Ans** E 300 mOsm NaCl is isotonic saline, thus, there is no change in body osmolarity. The fluid will enter the extracellular compartment and the volume of this space will increase. Since no change occurred in osmolarity, there will be no net movement of water across the cell membrane. This means no change in intracellular volume.

11. **Ans** A Infusing hypertonic saline will increase body osmolarity. Since fluid is given, the volume of the extracellular compartment will increase. The increased osmolarity of the extracellular fluid will cause water to diffuse out of cells, decreasing intracellular volume.

12. **Ans** A If a permeating solute is added to chamber X, the solute will diffuse across the membrane until its concentration is equal in X and Y. Since the solute concentration is equal in X and Y, there will not be a water concentration difference and thus no net diffusion of water. The fluid levels in X and Y will be equal.

13. **Ans** E Simple diffusion and membrane transport are rapid over short distances. When distances reach 1 cm or greater a significant movement can occur only with pressure differences, which is also referred to as bulk flow.

14. **Ans** B Infusion of distilled water would decrease body osmolarity and increase the volume of the extracellular fluid. The decreased extracellular osmolarity would cause water to diffuse into cells and raise intracellular volume.

15. **Ans** D Answers A, B, and C are characteristics of all protein-mediated transport. Facilitated diffusion is a passive process driven by a concentration gradient, thus is independent of ATP.

16. **Ans** D Intracellular fluid contains 2/3 of body water. Under steady-state conditions the intracellular osmolarity and extracellular osmolarity are equal. If there was a difference, water would diffuse until they were equal. The intracellular compartment does have a higher concentration of organic anions, mainly proteins, than the extracellular fluid.

17. **AnsA** Low solute concentration means high water concentration and water diffuses from a higher water concentration. Even if no membrane was present the water would still diffuse down its concentration gradient. Diffusion depends upon a concentration gradient and is not an energy demanding (ATP) process.

18. **Ans 1,5** If 1 liter of isotonic saline is injected it will disperse in the extracellular compartment which will increase in volume by 1 liter. Since it is isotonic, there will be no change in osmolarity and thus no change in intracellular volume. NaCl can cross capillary membranes and at least 3/4 of the 1 liter (750 ml) will enter the interstitial space. Less than 250 ml will remain in the vascular compartment. This will be in part due to the dilution of plasma proteins.

19. **Ans 1,4,5** If plasma is infused it will remain almost entirely in the vascular space. This is due to the fact that the plasma proteins cannot diffuse readily across the capillary membrane. Retention of the proteins in the vascular compartment will prevent the loss of water to the interstitium.

20. **Ans** 5 Urea can penetrate capillary membranes and almost all cell membranes in the body. Thus, the infused water and urea will distribute within the total body water, 2/3 inside cells and 1/3 outside cells.

21. **Ans** D The y axis is the intracellular concentration as a percentage of the extracellular concentration. At the origin there is nothing inside the cells. Moving up the y axis, intracellular concentration is increasing and when the 100 point is reached, the intracellular and extracellular concentrations are equal. Above the 100 point, the intracellular concentration is greater than the extracellular concentration. Substance H moves into the cell down its concentration gradient, but once the concentration gradient is eliminated (100 point), net transport stops. This indicates that H is transported by a passive process. Movement of G into the cell is also dependent upon a concentration gradient but it moves more slowly than H. F initially moves into the cell down its concentration gradient but continues to be transported into the cell after the concentration gradient is eliminated. This indicates active transport is involved.

22. **Ans** B Blood volume $= \frac{\text{plasma volume}}{1\text{-Hct}}$

$$= \frac{3L}{1 - 0.40} = 5L$$

23. Ans D Volume (V) X concentration (C) = amount of tracer (A)

$$C = \frac{A}{V} = \frac{900 \text{ millicuries}}{3 \text{ liters}}$$

$$= 300 \text{ millicuries/liter}$$

24. Ans A The infusion of plasma will add significant volume only to the vascular compartment, which is part of the extracellular fluid. The protein present in the plasma prevents fluid from crossing the capillary membrane into the interstitial compartment. However, because of a slight increase in capillary pressure a very small amount of fluid would be filtered to the interstitium, but this would be a minor effect (see cardiovascular). The infused plasma will have the same osmolarity and sodium concentration as the extracellular fluid, thus no change would occur in these variables. Since extracellular osmolarity will not change, intracellular osmolarity will not change. Plasma does not contain red blood cells. Thus, infusing plasma will dilute the red blood cells and decrease hematocrit.

25. Ans C Ingesting excessive amounts of tap water will increase the volume of the extracellular fluid. Since tap water contains few if any electrolytes, it will dilute the extracellular sodium and reduce extracellular osmolarity. The decreased extracellular osmolarity will cause a diffusion of water into cells, increasing intracellular volume but reducing intracellular osmolarity.

26. Ans B Loss of hypotonic fluid from the skin (sweat) in this environment would cause a decrease in volume but an increase in extracellular fluid osmolarity. Since extracellular osmolarity is determined to a large part by sodium, sodium concentration should also rise. The increased extracellular osmolarity will cause a diffusion of water out of cells, decreasing intracellular volume, but causing a rise in intracellular osmolarity. The dehydrated individual will form a small volume of highly concentrated urine.

SECTION II

Excitable Tissue

Ionic Equilibrium and Resting Membrane Potential

1

ELECTROCHEMICAL POTENTIAL

Membrane Conductance

Definition

Membrane conductance refers to the number of channels that are open in a membrane. For example, Na^+ conductance is proportional to the number of open channels that will allow the Na^+ to pass through the membrane. It does not indicate if there will be a net diffusion of ions through the channels.

GeneralProperties

If conductance is **increasing,** channels are **opening,** and if conductance is **decreasing,** channels are closing.

The rate at which ions move across a membrane depends on the number of open channels and the net force.

When ions flow through channels, the cell's membrane potential changes. However, under physiological conditions, too few ions flow to produce a significant effect on the ion's extracellular concentration or the concentration gradient across the membrane.

Channels are classified into three main groups:

- Ungated channels: Because these channels have no gates, they are always open. For example, all cells possess ungated potassium channels. This

What the USMLE Requires You to Know

- That the three general channel groupings are known as ungated, voltage-gated, and ligand-gated
- The direction and magnitude of an ion's net force in a simple model of concentration and electrical forces
- The information gained from a calculation using the Nernst equation
- The conclusions drawn about the dynamic behavior of an ion when the membrane potential (Em) of the cell is known and the equilibrium potential for a particular ion x (Ex) has been calculated from the Nernst equation
- The dynamics of the potassium ions and sodium ions across the membrane of a typical resting excitable cell *in vivo*

means there will be a net flux of potassium ions through these channels unless potassium is at equilibrium.

- Voltage-gated channels: In these channels, the gates open and/or close in response to a membrane voltage change. For example, many excitable cells possess voltage-gated sodium channels. The channels are closed under resting conditions, but membrane depolarization causes them to quickly open and then quickly close.
- Ligand-gated channels: The channel complex includes a receptor to a specific substance (ligand). It is the interaction of the ligand with the receptor that regulates the opening and closing of the channel. For example, post-junctional membranes of chemical synapses possess ligand-gated channels, and transmission depends on the interaction of the transmitter and the ligand-gated channel.

Net Force

The net force acting on an ion across a membrane is the sum of two independent forces.

Concentration Force

Determined by the concentration difference across the membrane.

The greater the concentration difference, the greater the concentration force.

Electrical Force

The size of this force is determined by the electrical difference across the membrane (usually measured in millivolts [mV]). The *in vivo* magnitude is determined by the membrane potential (Em), which is a value that must be measured or given.

The direction of the force is based on the fact that like charges repel and opposite charges attract. For example, if the membrane potential is -70 mV, this represents a force of 70 mV that attracts all positive ions and repels all negative ions.

The two forces (concentration and electrical) can be represented by separate vectors.

If the two_yectors_act in the same direction, the net force is the sum of the individual forces.

If the twnvpr|nr«; aft in opposite directions, the net force is the difference between the two forces and is directedalong the axis of the largerjorce.

If the two forces are eg^iaLbut-appasite, there is no_net force and the ion is in a state of equilibrium.

At equilibrium, the two forces are_ajways equal but oppositein direction.

A simple model demonstrating concentration and electrical forces is illustrated in Figure II-1-1.

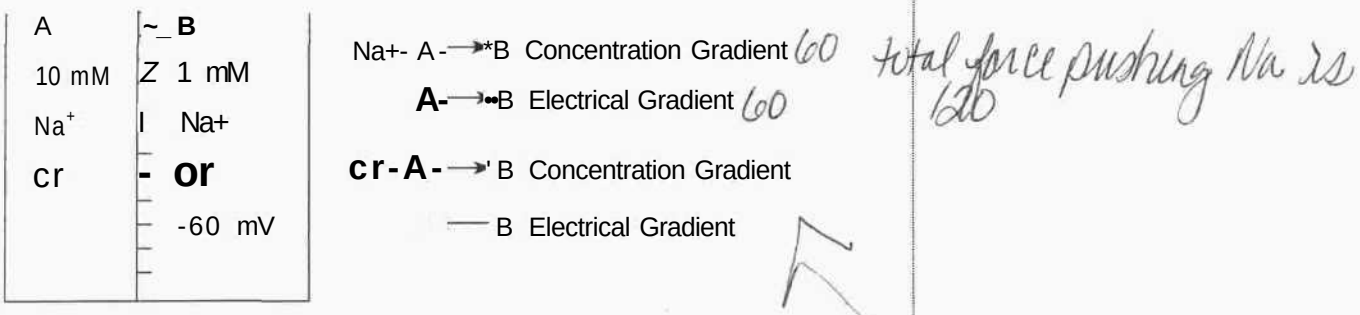


Figure 11-1-1

The concentration force for both sodium ions and chloride ions is directed from A to B. Because they have the same concentration gradient, they have the same concentration force.

The electrical force on sodium ion is directed toward B. The negative membrane potential (-60 mV) attracts the positive sodium ion with a force of 60 mV.

With open membrane sodium channels, positive sodium ion charges flow from A to B, driven by the concentration force and the electrical force.

The electrical force on the chloride ion is also 60 mV, but because like charges repel, this force is directed from B to A. Because the forces on the chloride ion are opposite in direction, the greater force determines the direction of the net force.

The Nernst Equation

In order to compare the concentration and electrical forces, they must be expressed in the same units. This can be achieved by using the Nernst equation.

$$E_X = \frac{-60\ \text{mV}}{z} \log_{10} \frac{[X]_A}{[X]_B} \qquad \log_{10} T = 1$$

Z= charge (Na = 1, Cl = -1)

Unknowns in the Nernst equation are the ion's concentration on the two sides of the membrane (= concentration force). The Equation will express this concentration force in mV. **Notice that if there is a concentration difference across a membrane, the concentration force has a magnitude of 60 mV.**

Thus the concentration force on the chloride ion is a force with the same magnitude as 60 mV. The chloride ion has equal and opposite forces and is in a state of equilibrium.

The concentration force on sodium is 60 mV. Since both forces are directed toward B, the total force on sodium is 120 mV.

The main function of the Nernst equation is to calculate the ion's equilibrium potential at a given concentration gradient. The equilibrium potential is the theoretical intracellular electrical potential that would be equal in magnitude but opposite in direction to the concentration force.

REVIEW QUESTIONS

Question Group A

Answer the following questions concerning the model presented below. Assume an initial membrane conductance of zero for both ions.

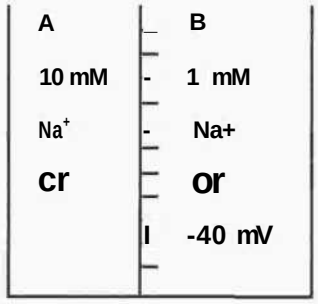


Figure 11-1-2

1. What are the direction and the magnitude of the sodium ion concentration gradient (in mV)?
2. What are the direction and the magnitude of the sodium ion electrical gradient (in raV)?
3. What is the net force on the sodium ions (in mV)?
4. If the membrane conductance to sodium ion increases (sodium channels are opened), what will be the directional change in the electrical potential in B? That is, will it move in a positive or negative direction?
5. What will the electrical potential in compartment B become if sodium ion reaches equilibrium?
6. What is the sodium ion equilibrium potential for the initial state presented in the model?
7. What are the direction and the magnitude of the chloride ion concentration gradient (in mV)?
8. What are the direction and the magnitude of the chloride ion electrical gradient (in mV)?
9. What is the net force on the chloride ions (in mV)?
10. If the membrane conductance to chloride ion increases (chloride channels are opened), what will be the directional change in the electrical potential in B? That is, will it move in a positive or negative direction?

11 What will the electrical potential in compartment B become if the chloride ions reach equilibrium?

12. What is the chloride ion equilibrium potential for the initial state presented in the model?

Question Group B

The following is a common model to test the basic theory presented on the previous pages. The figure represents two solutions separated by a membrane.

X	Y
100 mM KC1	10 mM KC1
10 mM NaCl	100 mM NaCl
	-60 mV

Between compartments X and Y, for each ion, determine the magnitude (in mV) and direction of the:

Electrical force

Concentration force

Net force

Determine also the equilibrium potential for each ion.

Question Group C

In the following graph, Em represents the measured initial membrane potential for a hypothetical cell *in vivo.* In relation to this membrane potential, the equilibrium potentials of three ions (X, Y, Z) are represented. Pick the path most likely taken by the membrane potential when the membrane conductance is increased with respect to each of the following ions:

X-

Y"

Z+

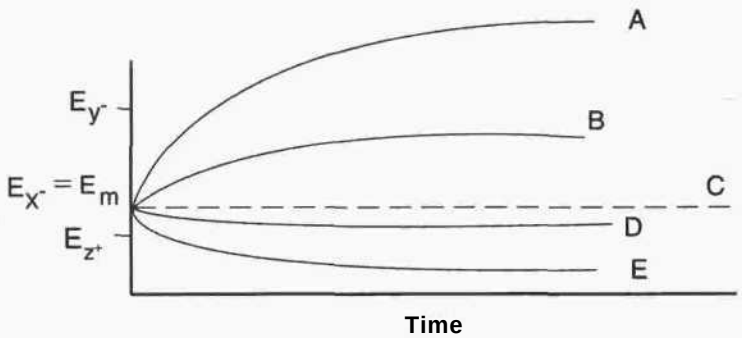


Figure 11-1-3

ANSWERS

Group A

1. The concentration gradient is from A to B. There is a tenfold difference in concentration, which is equivalent to 60 mV.
2. The electrical gradient is from A to B (unlike charges attract), and the magnitude is 40 mV.
3. The concentration and electrical forces are in the same direction; therefore, the net force is 60 mV (concentration force) plus 40 mV (electrical force), a total of 100 mV A to B.
4. Because the net force is A to B, opening sodium channels will cause positive sodium ions to diffuse from A to B. The potential in B (-40 mV) will become more positive.
5. As the sodium ions move from A to B, there will not be a significant change in the concentration gradient; therefore, the concentration force will not change. It is the electrical force that will change. As sodium ions diffuse into B, the original -40 mV will become more positive. It will continue to change until the electrical force becomes equal and opposite to the concentration force. When the potential in B is +60 mV, the electrical force will be equal but opposite in direction to the concentration force.
6. The sodium ion equilibrium potential for the model would be +60 mV. If this potential existed in compartment B, the concentration and electrical forces would be equal but opposite in direction.
7. The concentration gradient is from A to B. There is a tenfold difference in concentration, which is equivalent to 60 mV.
8. The electrical gradient is from B to A (like charges repel), and the magnitude is 40 mV.
9. The concentration force is 60 mV A to B, but the electrical force is 40 mV B to A. The net force is thus 20 mV A to B.
10. Because there is a net force of 20 mV A to B, chloride ions will diffuse into B. More negative charges moving into B will make that compartment more negative.
11. As the chloride ions move from A to B, there will not be a significant change in the concentration gradient; therefore, the concentration force will not change. It is the electrical force that will change. As chloride ions diffuse into B, the original -40 mV will become more negative. It will continue to change until the electrical force becomes equal and opposite to the concentration force. When the potential in B is -60 mV, the electrical force will be equal but opposite in direction to the concentration force.
12. The chloride ion equilibrium potential for the model would be -60 mV. If this potential existed in compartment B, the concentration and electrical forces would be equal but opposite in direction.

Group B

The following is an expanded version of the figure shown in the question, using vectors to demonstrate the direction of the individual forces.

X	Y
100 K+ (C)=> (E)=>	10 K+
10Na+ (E)=*	<=(C) 100 Na+
no cr	**no cr** -60 mV

C = concentration force (tenfold difference in concentration equals a force of 60 mV)

E = electrical force (= 60 mV)

1. Electrical force: Because the electrical potential is -60 mV in compartment Y, the electrical force on all ions is 60 mV. Positive ions will be attracted to compartment Y, and negative ions will be repelled from Y.
2. Concentration force: Because K^+ and Na^+ have a tenfold difference in concentration across the membrane, the concentration force of each is equivalent to a force of 60 mV (see Nernst equation).
3. Net force: The net force on K^+ is 120 mV directed toward Y. If there were open K^+ channels in the membrane, K^+ would diffuse from X to Y, depolarizing compartment Y. If the membrane had conductance only to K^+, the electrical potential of Y would move toward +60 mV. Once it reached +60 mV, K^+ would be at equilibrium. Therefore, the equilibrium potential for K+is+60 mV.

The equilibrium potentials:

For sodium ion: The net force on Na^+ is zero because the concentration and electrical forces are equal and opposite. Thus, under the initial conditions, regardless of the membrane conductance to Na^+, there would be no net diffusion across the membrane. The equilibrium potential for Na^+ is the initial potential of -60 mV.

For chloride ion: With Cl~ there is no concentration force, only an electrical force (magnitude 60 mV directed toward X). The electrical force is the net force. With only membrane chloride channels open, chloride ion would diffuse to X until the electrical potential of Y reached 0 mV. The equilibrium potential for ChisthusOmV.

All the preceding conclusions assume no significant changes in ion concentrations as a result of diffusion to the equilibrium point.

Group C

1. For X~: Because the membrane potential and the X equilibrium potential are the same, there will be no net movement and no change in the resting membrane potential. Answer C.
2. For Y~: Y ions will diffuse, and the membrane potential will move toward the Y equilibrium potential. The membrane potential can eventually reach but cannot go beyond the Y equilibrium potential. Answer B.
3. For Z^+: Z ions will diffuse, and the membrane potential will move toward the Z equilibrium potential. This is in the opposite direction from the Y equilibrium potential. The membrane potential can eventually reach but cannot go beyond the Z equilibrium potential. Answer D.

Use of the Nernst Equation

Although the theory relating to the Nernst equation is rarely tested as a separate question, it does have relevance for the USMLE. Important points are discussed below.

If the **oienibranepotenlial (Emjjias been measured** or given in an example and **the equiybriwn potential of aqjon (Exjcalculated** by using the Nernst equation, the following conclusions can be drawn:

If Ex equals the measured membrane potential (Em), the ion is at equilibrium, i.e., the concentration and electrical forces are equal and opposite. If they are not identical, the ion is not at equilibrium, which means if channels in the membrane are open to that ion, there will be a net diffusion of the ion across the membrane.

The difference between Ex and the measured membrane potential (Em) represents the net force on the ion.

The ion will always diffuse in a direction that brings the membrane potential (Em) toward its Ex.

> The **rate** at which an ion will diffuse across a membrane is directly proportional to the net force and membrane conductance to that particular ion. Note that as an ion diffuses and the membrane potential approaches the equilibrium potential for that ion, the net force on the ion decreases. When the membrane potential reaches the ion's equilibrium potential, the net force is zero.

Consider the following example:

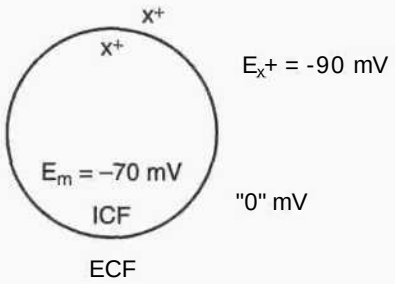


Figure 11-1-4

Because the membrane potential is not at -90 mV, the ion is not at equilibrium. If channels in the membrane to x are open, there will be a net diffusion of x across the membrane.

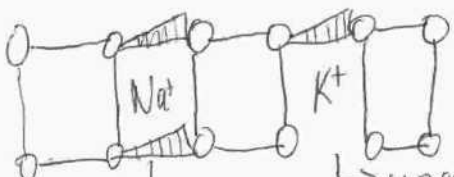
The difference between the membrane potential and the ion's equilibrium potential is 20 mV. This is the net force on the ion.

We know that the positive ion x will flow across the membrane to make the membrane potential approach -90 mV, which means it will become more negative. The only way a positive ion can do that is to flow out of the cell. Thus, when x channels are open, there will be an efflux of x and the membrane potential will move toward -90 mV, assuming no other ions are diffusing in opposition. As the membrane potential gets closer to -90 mV, the net force is decreasing, and if the membrane potential reaches -90 mV, the net force is zero and the net diffusion of x will cease, regardless of the ion's conductance.

V. Whenever $E_x = E_m$ there is equilibrium
2. $E_x - E_m$ = net force on ion
3. the ion will move to cause E_m to go towards E_x

X will efflux the cell drive 6 D force of 25mV.

X moving into cell w/25



↳ ungated so K^+ can leave cell at all times

↳ when cell at rest gates are closed

RESTING MEMBRANE POTENTIAL

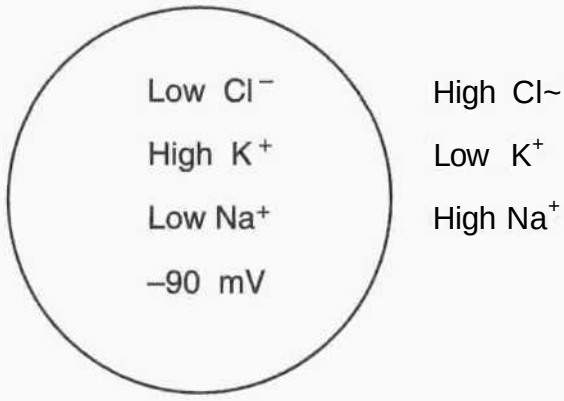


Figure 11-1-5

Figure II-1-5 represents a typical cell. If the concentrations of specific ions inside and outside the cell are known, the Nernst equation can be utilized to calculate the equilibrium potential for each ion. Although each cell will be slightly different, assume the following are fairly representative for most cells *in vivo.*

E_{Cr} = -90 mV
E_{K+} = -105 mV
E_{Na^+} = +45 mV

Important Points Regarding Cl"

Because the measured membrane potential and the calculated equilibrium potential are the same in magnitude and charge, the chloride ions are at equilibrium. No matter what the membrane conductance to chloride is, there will not be a net diffusion of chloride ions, nor will a change in the conductance of chloride in a steady-state situation alter the cell's membrane potential.

Important Points Regarding K+

The potassium ion is not at equilibrium. The net force on the potassium ions is 15 mV. Because this is a small force, the potassium ions can be considered close to but not quite at equilibrium.

Because all cells at all times have open potassium channels (ungated), there must be a net flux of potassium ions across the membrane. Also, because the ion will always diffuse to bring the membrane potential closer to the ion's equilibrium potential, the flux must be an efflux from the cell.

Increasing potassium conductance will accelerate the efflux of potassium ions and hyperpolarize the cell.

Increased extracellular potassium ions will reduce the efflux of the potassium ions or even create an influx of potassium ions, the net result of which will be depolarization.

Decreased extracellular potassium ions will accelerate the efflux of the potassium ions, the net result of which will be hyperpolarization.

Thus, a cell's resting membrane potential is very sensitive to changes in the extracellular potassium ion concentration.

Important Points Regarding Na^+

The sodium ion is not at equilibrium. The net force on the sodium ions is jj5 mV. This is considered a large force; therefore, the sodium ions are a long way from equilibrium.

In most cells, including excitable cells under resting conditions, there is not a significant number of open sodium channels (conductance close to zero). Thus, even though there is a large net force, flux is minimal.

An increase in membrane conductance to sodium ions will produce an influx of sodium ions and depolarization.

Because sodium channels are closed under resting conditions, changes in extracellular sodium will not affect the resting membrane potential.

Thus, a cell's resting membrane potential is not sensitive to changes in extracellular sodium.

Definitions

Depolarization: The negative intracellular potential moves toward zero (becomes more positive); e.g., Na^+ influx depolarizes a cell.

Hyperpolarization: The negative intracellular potential becomes more negative, e.g., increased K^+ efflux from a cell.

Transmembrane Potential: Potential difference across a cell membrane (sign not involved).

If the membrane potential is -70 mV, the transmembrane potential is 70 mV. As a cell undergoes depolarization and the membrane potential approaches zero, the transmembrane potential decreases in magnitude.

Pumping Na^+ Out of the Cell

Figure II-1-6 shows the steady-state resting relationship between ion diffusion and the Na/K-ATPase pump.

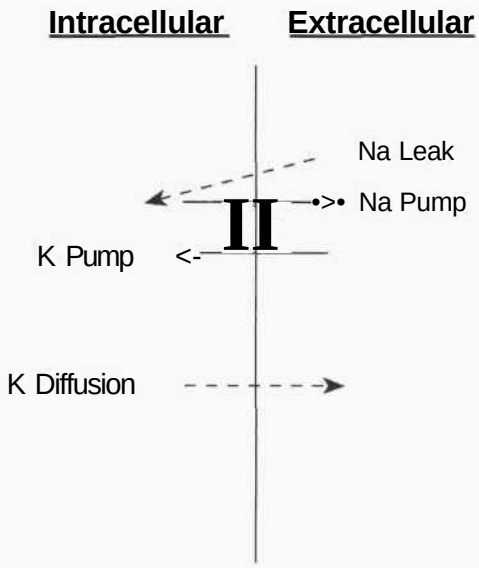


Figure 11-1-6

Even though sodium conductance is normally close to zero, the large inward force causes a sodium ion leak. This inward passive leak is balanced by an outward active pumping of sodium ions in exchange for potassium ions. The potassium ions pumped into the celldifruse~out through the ungated potassium channels. If these ungated potassium channels would be suddenly not available, the continued inward pumping of potassium ion would cause a gradual membrane depolarization.

Chapter Summary

Membrane conductance indicates whether channels are opened or closed.

Channels can be classified as ungated, voltage-gated, or ligand-gated.

The net force on an ion is the sum of the concentration and electrical forces.

A state of equilibrium represents equal but opposite concentration and electrical forces.

Equilibrium potential is the electrical potential required inside the cell for an ion to be at equilibrium. It is determined by the ion's charge and its concentration gradient across the membrane.

Comparing the membrane potential with an ion's equilibrium potential will reveal the net force on the ion, the directional change in the membrane potential as the ion diffuses across the membrane, and whether the diffusion will be an influx or efflux.

Potassium is close to equilibrium under resting conditions, and because ungated potassium channels are always present, there will be a slow efflux of potassium ion from the cell. A continuous efflux occurs because potassium ion is cortimjojis^Djjm£e^jDto_ltlfi_celL

Sodium ions are a long way from equilibrium under resting conditions, but the conductance is close to zero. Even so, there is a slow inward leak of sodium ion. This is countered by the Na/K-ATPase pump.

The Neuron Action Potential

2

THE ACTION POTENTIAL

Conduction of nerve signals is done by a rapid membrane depolarization that changes the normal resting negative potential to a positive potential. This is followed by a repolarization back to the normal negative membrane potential. These phenomena define an action potential. Excitable cells, nerves and muscle, have action potentials with distinguishing sizes and shapes.

Figure II-2-1 shows the action potential in three types of excitable cells. Even though the following is a description of the neuron action potential, almost identical events occur in skeletal muscle. However, the cardiac ventricular action potential is very different and will be discussed in another chapter.

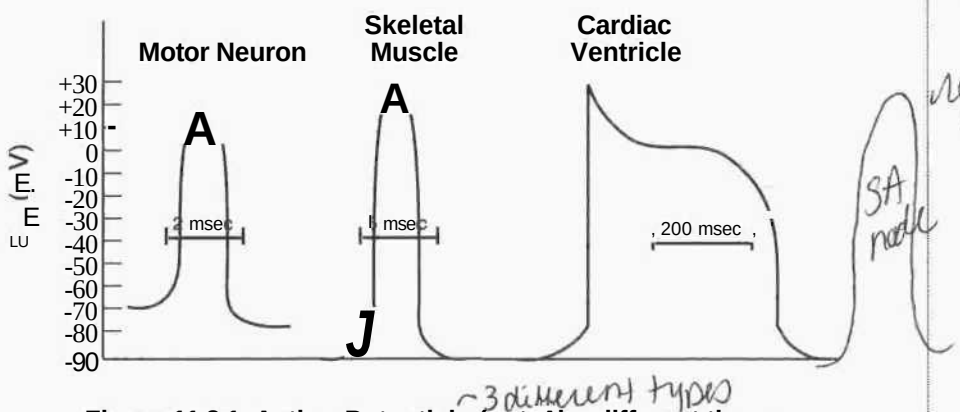


Figure 11-2-1. Action Potentials (note^he different times scales) From Three Vertebrate Cell Types. *(Redrawn from Flickinger, C.J., et al.: Medical cell biology, Philadelphia, 1979, W.B. Saunders Co.)*

What the USMLE Requires You to Know

- Mechanisms generating the neuronal and skeletal muscle action potential
- Mechanism and significance of the absolute refractory period

depolarization - make cell more positive

repolarization - make cell more negative

~3 different types

Skeletal Muscle

Figure II-2-2 shows the responses of a neuronal membrane to increasing pulses of depolarizing current. When the cell is depolarized to threshold, it fires an action potential. Subthreshold potentials of all types are referred to as *electrotonic* potentials.

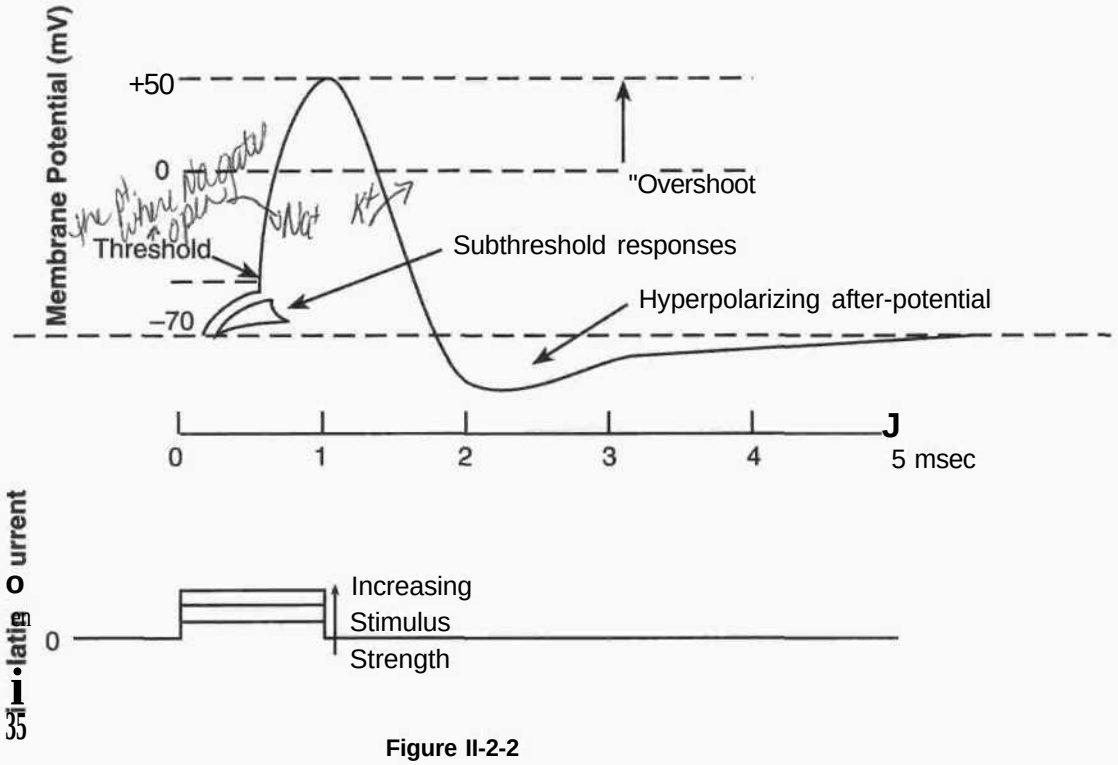


Figure II-2-2

Table II-2-1. Subthreshold Potential Change versus Action Potential

Subthreshold potential change	Action potential
Proportional to stimulus strength (graded)	Independent of stimulus strength (all or none)
Not propagated but decremental with distance	Propagated unchanged in magnitude
Exhibits summation	Summation not possible

MEMBRANE CHANNELS INVOLVED IN THE NEURON ACTION POTENTIAL

Because the action potential is produced by the diffusion of ions through channels, all the resulting events are passive.

Ungated Potassium Channels

These channels are always open, and unless the membrane potential reaches the potassium equilibrium potential (~ -103 mV), a potassium ion efflux is maintained through these channels.

Voltage-Gated (Dependent) Sodium Channels

These channels are closed under resting conditions. Membrane depolarization is the signal that causes these channels to quickly open and then close. They will not respond to a second stimulus until the cell almost completely repolarizes.

Voltage-gated sodium channels are required for the depolarization phase and thus the generation of an action potential in neurons and skeletal muscle. Preventing the opening of these channels in response to depolarization will prevent the development of an action potential.

Voltage-Gated (Dependent) Potassium Channels

These channels are closed under resting conditions. As is the case for the voltage-gated sodium channel, membrane depolarization is the signal that causes these channels to open. However, they open more slowly than the sodium channels, and thus opening peaks later during the action potential. These channels provide a rapid repolarization phase. Preventing their opening slows repolarization.

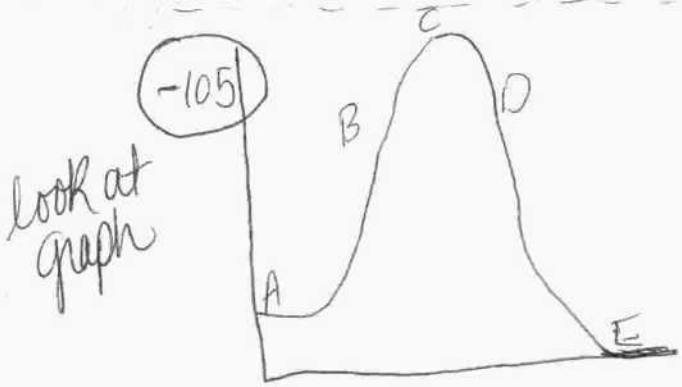
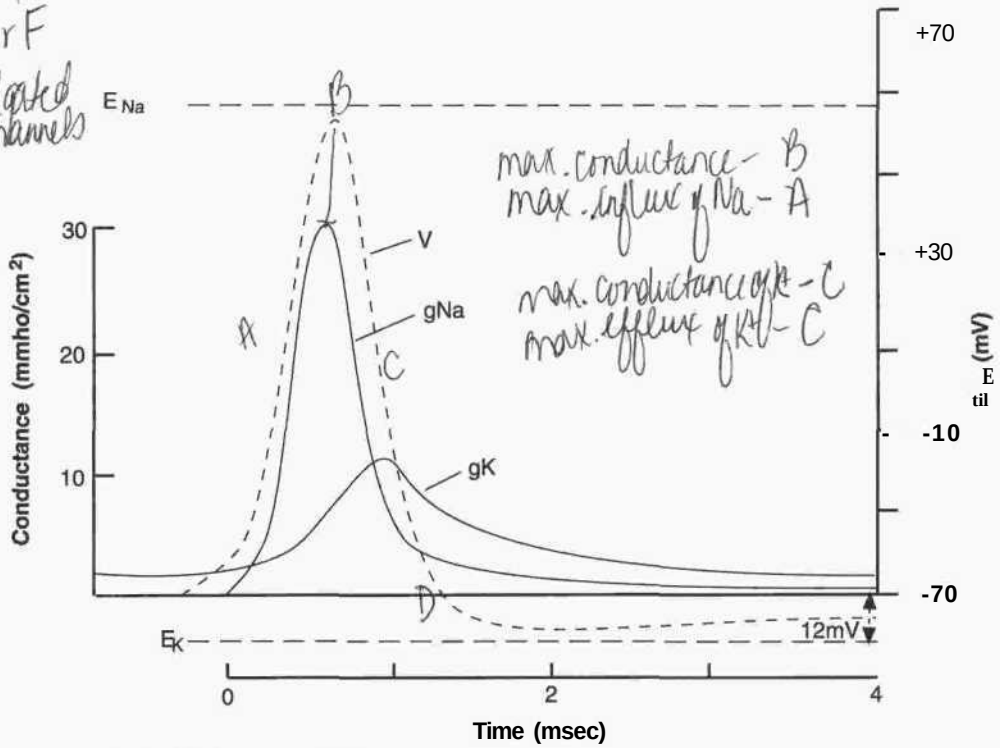


Figure II-2-3 shows the conductance changes in sodium and potassium ions in relation to the action potential.



V = membrane potential (action potential)

gNa^+ = sodium ion conductance

gK^+ = potassium ion conductance

Figure 11-2-3. Axon Action Potential and Changes In Conductance

Depolarization Phase

Initial depolarization is the stimulus that causes the opening of the voltage-gated sodium channels (open fast, close fast).

Opening of the sodium channels increases the membrane conductance to sodium ion, permitting a rapid sodium ion influx.

The sodium ion influx depolarizes the membrane close to the sodium equilibrium potential.

Sodium channels are opening throughout depolarization, and peak sodium conductance is not reached until just before the peak of the action potential. Even though peak sodium conductance represents a situation with a large number of open sodium channels, influx is minimal because the membrane potential is close to the sodium ion equilibrium potential.

Repolarization

During early repolarization, the voltage-gated sodium channels are rapidly closing. This eliminates a sodium ion flux across the membrane.

The voltage-gated potassium channels are still opening, increasing potassium conductance beyond the value under resting conditions.

Because at the beginning of repolarization the membrane potential is a long way from potassium ion equilibrium and the membrane conductance to potassium ion is high, there is a rapid potassium ion efflux that repolarizes the cell.

Peak potassium conductance does not occur until about mid-repolarization. At this point, even though the force on the potassium ions is less than at the beginning of repolarization, there is greater efflux because of the much greater conductance.

If the voltage-gated potassium channels do not open during repolarization, the cell will still repolarize through the ungated potassium channels. However, the process will be slower.

The original gradients are reestablished via the (active) Na/K-ATPase pump.

PROPERTIES OF ACTION POTENTIALS

Refractory Periods

AbsoluteRefractoryPeriod(FunctionalRefractoryPeriod)

The absolute refractory period is that period during which no matter how strong the stimulus, it cannot induce a second action potential.

The absolute refractory period is due to voltage inactivation of sodium channels. Also, it is the length of this period that determines the maximum frequency of action potentials. The shorter the absolute refractory period, the greater the maximum frequency.

The relative refractory period is that period during which a greater than normal stimulus is required to induce a second action potential.

Figure II-2-4 shows both the absolute and relative refractory periods of the neuron action potential.

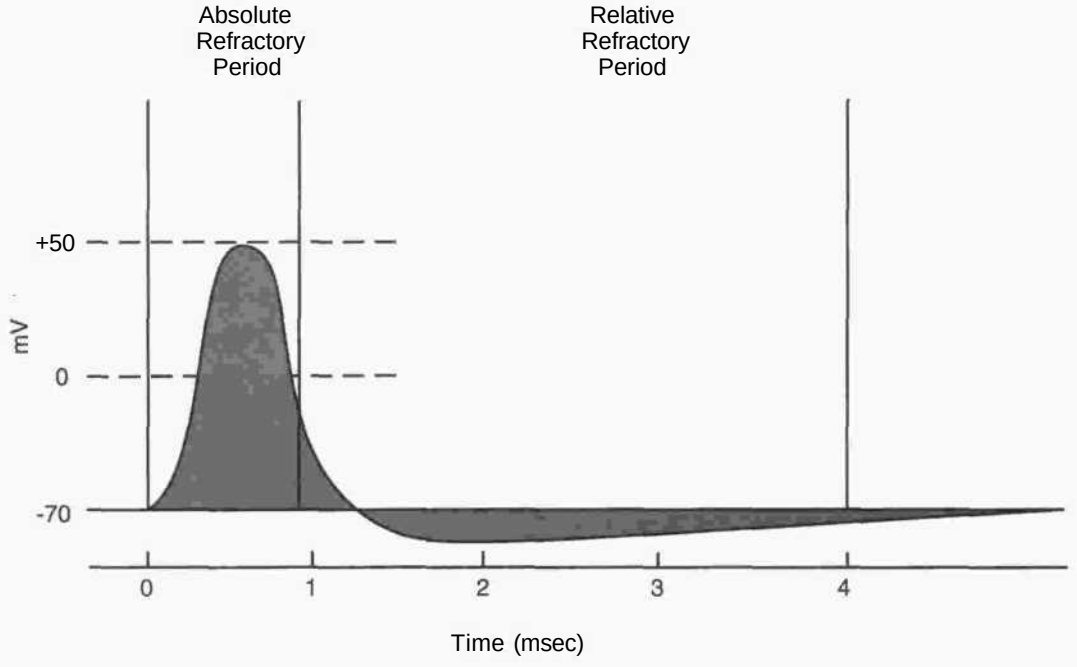


Figure 11-2-4

Conduction Velocity of the Action Potential

The Main Factors

Cell diameter: The greater the cell diameter, the greater the conduction velocity.

Myelin: The greater the myelination, the greater the conduction velocity.

- Large myelinated fibers = fast conduction
- Small unmyelinated fibers = slow conduction

Chapter Summary

The action potential is produced by the simple diffusion of ions through channels.

Depolarization is via sodium ion influx through voltage-gated channels. These channels are required for neuron and skeletal muscle action potential. Maximum sodium conductance is at the peak of the action potential. Because at this point the membrane potential is close to sodium equilibrium, there is little influx of sodium.

Repolarization is via potassium ion efflux, mainly through voltage-gated channels.

Without the opening of potassium voltage-gated channels, repolarization would be a slow process via the ungated channels.

The absolute refractory period is due to the unresponsiveness of the voltage-gated sodium channels.

Synaptic Transmission

3

NEUROMUSCULAR (CHOLINERGIC) TRANSMISSION

The Neuromuscular Junction

The synapse between the axons of a motor neuron and a skeletal fiber is called the *neuromuscular* junction.

Figure II-3-1 diagrammatically represents the neuromuscular junction.

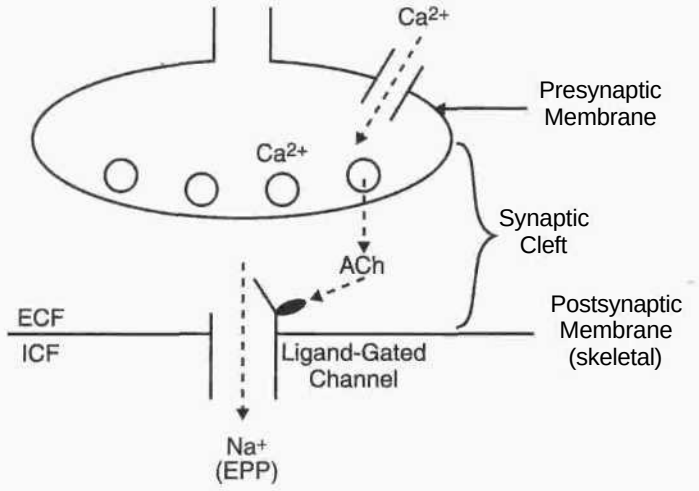


Figure 11-3-1. Neuromuscular Transmission

What is function of synapse in presynaptic cells opn Ca^{2+} channels

Summary of Events Occurring During Neuromuscular Transmission:

Action potential travels down the axon, ends in the presynaptic motor axon terminal, and **opens voltage-gated calcium channels.**

4

Increase in Ca^{2+} permeability of the axon terminal causes **an influx of extracellular Ca^{2+}** into the axon terminal.

⇓

The **rise in intracellular free Ca^{2+} causes the release of acetylcholine** from synaptic vesicles into the synaptic deft.

Diffusion of **acetylcholine** to the postjunctional membrane, which represents a **major time component.**

⇓

Combination of acetylcholine with cholinergic receptors on the postjunctional membrane: These receptors are part of a ligand-dependent channel. The channels open when acetylcholine attaches to the receptor, and they remain open until the acetylcholine is removed.

⇓

Opening of ligand-dependent channels results in an **increased conductance to Na^+** and K^+. Because of the greater net force on sodium, an influx of sodium dominates.

⇓

Influx of Na^+ causes local depolarization of the postjunctional membrane. This depolarization is referred to as the end-plate potential (or EPP). The more acetylcholine that is released, the greater the depolarization (the greater the end-plate potential). Because the skeletal muscle membrane in the synaptic region does not have voltage-gated sodium channels, the action potential cannot be initiated in this region.

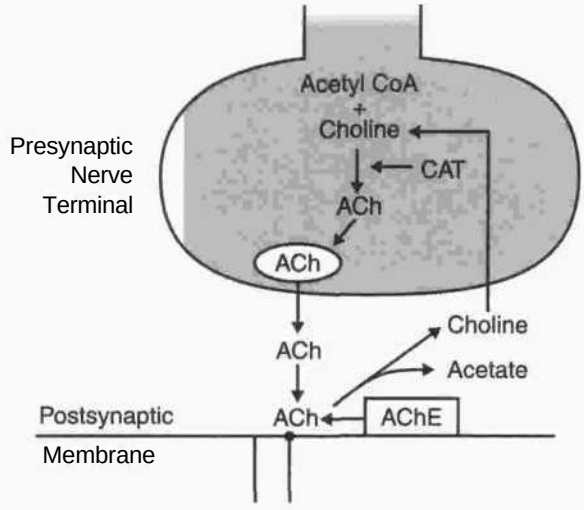
The EPP spreads, causing **depolarization of areas of muscle membrane adjacent to the end plate,** where voltage-gated sodium channels are present. Their opening causes the initiation of an action potential that spreads across the surface of the skeletal muscle cell.

Single quanta of acetylcholine are released randomly under resting conditions. Each produces a small depolarization of the postsynaptic membrane, called a miniature end-plate potential (MEPP). MEPPs do not generate action potentials.

Acetylcholine Synthesis and Choline Recycling

Biochemical Events Occurring at the Cholinergic Synapse

Figure II-3-2 summarizes the biochemical events at the cholinergic synapse. The most important aspects are described below.



ACh = acelylcholine
CAT = choline acetyltransferase
AChE = acetylcholinesterase

Figure 11-3-2

- Acetylcholine is an acetyl ester of choline.
- Synthesis takes place in the cytoplasm and is catalyzed by choline acetyltransferase.
- Acetylcholine is then taken up into synaptic vesicles by an active vesicular transport mechanism.
- Acetylcholinesterase, which is weakly associated with the postsynaptic membrane and is located within the synaptic cleft, terminates the action of the transmitter via hydrolysis to acetate and choline.
- The active reuptake of choline from the extracellular fluid into the nerve terminal recycles the choline.

Adrenergic Transmission

The release of transmitter from adrenergic nerve endings is similar to the calcium-dependent scheme described earlier for the cholinergic terminal.

The biochemical details are shown in Figure II-3-3. Note the major differences between it and the cholinergic system.

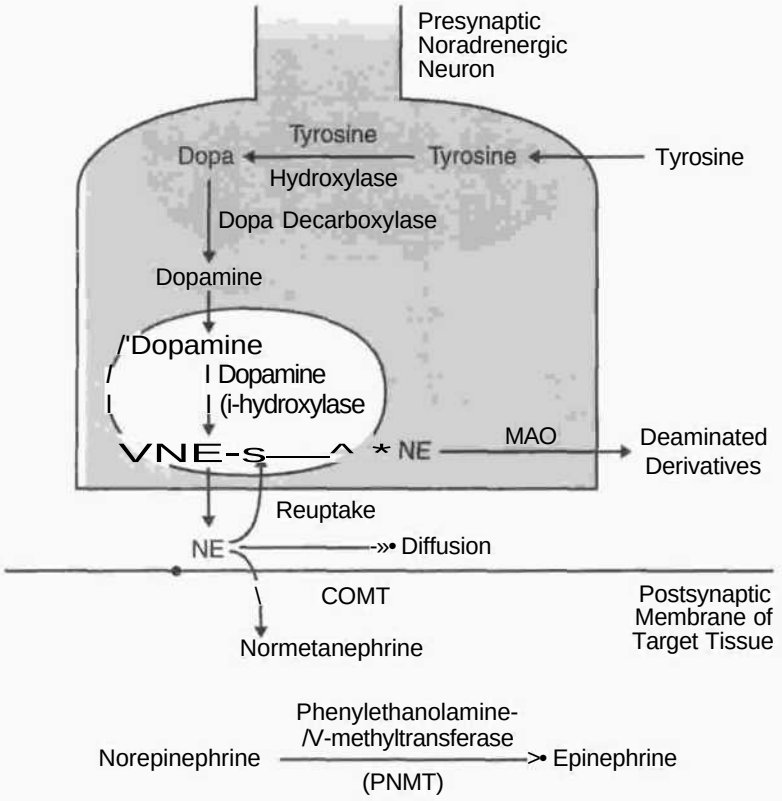


Figure 11-3-3

The most important aspects associated with adrenergic transmission are listed below:

- The transmitters are formed by the hydroxylation and decarboxylation of the amino acid tyrosine, which is taken up by the neuron and the adrenal medullary cells.
- Conversion of tyrosine to dopamine takes place in the cytoplasm. The first step, the conversion of tyrosine to dopa, is considered the main rate-limiting step in the synthetic pathway.
- After vesicular uptake, dopamine is converted into norepinephrine via the action of dopamine p-hydroxylase.

- Some norepinephrine is transferred to the cytoplasmic compartment, and the high activity of monoamine oxidase (MAO) here in the nerve terminal maintains a significant turnover.
- Norepinephrine is stored in association with ATP, which is released along with the norepinephrine and dopamine P-hydroxylase into the synaptic cleft.
- Reuptake is a major mechanism to terminate transmitter activity, with diffusion away from the synapse a second significant contributor.
- Metabolism is not the primary mechanism terminating transmitter activity, but the wide distribution of catecholamine O-methyl transferase (COMT) makes it responsible for the inactivation of circulating catecholamines.
- COMT is found in smooth muscle and in liver and kidney tissue, but it is not found in adrenergic nerve endings.

SYNAPSES BETWEEN NEURONS

General Features

Figure II-3-4 illustrates synaptic junctions between neurons. The most important aspects associated with synaptic junctions are listed below:

- Synapses are located on the cell body and dendrites.
- The cell membrane in these regions is specialized for chemical sensitivity and thus dominated by ligand-dependent channels, producing excitatory postsynaptic potentials (EPSPs) and inhibitory postsynaptic potentials (IPSPs) in response to the different transmitters.
- These voltage changes are conducted electronically along the dendritic and cell body membranes to the axon hillock-initial segment region.
- The closer the synapse is to this region, the greater its influence in determining whether an action potential is generated.
- The axon hillock-initial segment region has a particularly low threshold (voltage-gated channels).
- If the sum of all the inputs reaches threshold, an action potential will be generated and conducted along the axon to the nerve terminals.

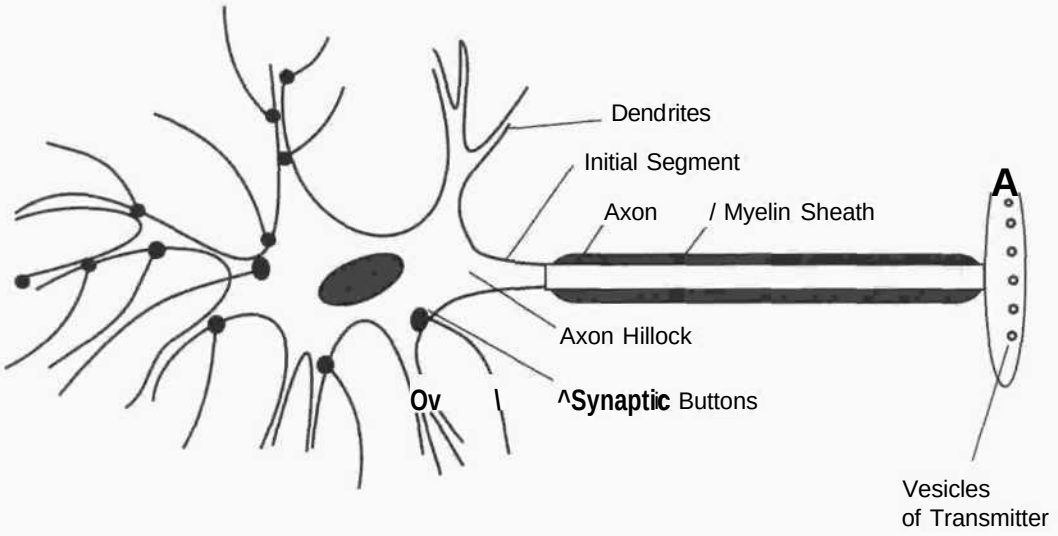


Figure II-3-4

Characteristics of EPSPs

Transient depolarizations

- Excitatory because Em moves closer to threshold
- Increase in conductance to Na^+ and K^+
- Na^+ influx causes depolarization.
- EPSPs at synapses between neurons are similar to the EPPs at neuromuscular junctions.

Characteristics of IPSPs

Transient hyperpolarizations

- Inhibitory because Em moves farther away from its threshold
- Increased conductance to *Or*
- Cl~ influx causes hyperpolarization
- Also can be produced by increased K^+ conductance and an accelerated K+efflux

ELECTRICAL SYNAPSES

Action potential is transmitted from one cell to another by the direct flow of current.

- Conduction can occur in both directions, and there is essentially no synaptic delay.
- Cells with electrical synapses are joined by gap junctions.

SUMMARY OF NEUROTRANSMITTERS

Acetylcholine

A transmitter used by all motor axons, autonomic preganglionic neurons, postganglionic parasympathetic fibers, and some cells of motor cortex and basal ganglia.

Enzymatic destruction is a major factor terminating transmitter action.

Biogenic Amines

Biogenic amines include norepinephrine, epinephrine, dopamine, serotonin, and histamine.

Norepinephrine is the primary transmitter for postganglionic sympathetic neurons.

Epinephrine is released by chromaffin cells of the adrenal medulla.

Serotonin is found in high concentration in brain stem cells.

Histamine is present in neurons of the hypothalamus.

Reuptake by presynaptic membrane is a major factor in terminating transmitter action of the biogenic amines.

Amino Acids

Amino acids include glycine, y-aminobutyric acid (GABA), glutamine, and aspartate.

- Glycine is an inhibitory transmitter in spinal interneurons.
- GABA is an inhibitory transmitter of the central nervous system.
- GABA and glycine generate IPSPs via ligand-gated Cl^- channels.
- Glutamine and aspartate are excitatory transmitters of the central nervous system that generate EPSPs.
- Nonpeptide transmitters are synthesized in nerve terminals, but peptide transmitters are synthesized in the neuron cell body, packaged in vesicles, and then transported to nerve terminals.

Reuptake by presynaptic membranes is a major factor terminating transmitter action of the amino acids.

Nitric Oxide (NO)

- NO is neither packaged in vesicles nor released by exocytosis.
- Unlike other transmitters, NO is a gas that, once synthesized, readily diffuses across cell membranes to adjacent target tissue.
- NO is an inhibitory transmitter in the central and enteric nervous system.
- NO also functions as a cellular signal transduction molecule in neural tissue and vascular smooth muscle (endothelial-derived relaxing factor).

NEUROMODULATORS

These compounds are not transmitters. The most important features of neuromodulators are listed below:

They alter the sensitivity of the synaptic membranes to transmitter stimulation or inhibition.

Neuromodulators are frequently peptides.

They can act at very low concentrations but often have a long duration.

PRESYNAPTIC INHIBITION

Presynaptic inhibition can occur when axon collaterals of inhibitory neurons synapse on excitatory nerve terminals, as shown in Figure II-3-5.

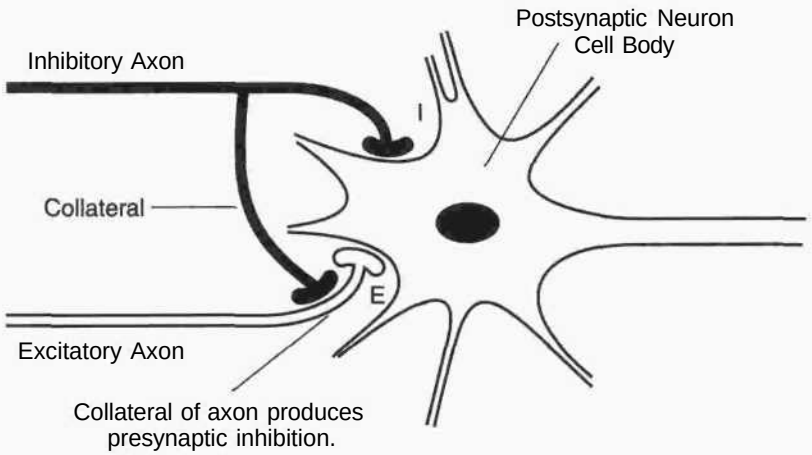


Figure II-3-5

Presynaptic inhibition decreases the entry of Ca^{2+} into the neuron terminal and thus decreases the release of transmitter. This may involve increasing the conductance to either chloride or potassium ions, which reduces the effectiveness of the action potential in increasing calcium conductance. GABA is the first transmitter causing presynaptic inhibition to be identified. In addition, norepinephrine is known to act presynaptically on a_2 receptors to inhibit further transmitter release.

Chapter Summary

Synaptic transmission involves the entry of extracellular calcium into the nerve terminal. This then triggers the release of transmitter.

The postsynaptic membrane is dominated by ligand-gated channels. In most cases, this allows either an influx of sodium (EPP or EPSP) or an influx of chloride (IPSP).

Nonpeptide transmitters are synthesized at nerve terminals, but peptide transmitters are synthesized in the neuron cell body.

Termination of acetylcholine action is mainly by enzymatic destruction, whereas with other transmitters it is reuptake by the presynaptic membrane and/or diffusion away from the site of action.

Electrical synapses are bidirectional and faster than chemical synapses, which are unidirectional.

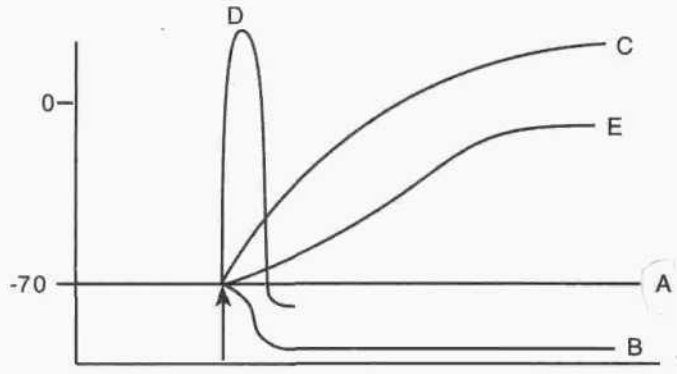
Neuromodulators function by altering synaptic sensitivity to the transmitter.

EXCITABLE TISSUE

Review Questions

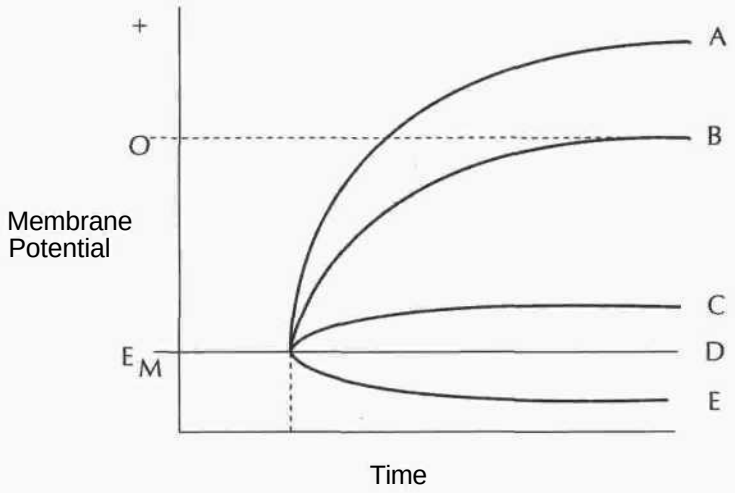
Directions: Select the ONE best answer.

1. The membrane potential of an alpha motoneuron axon is measured (below). At the arrow a sodium-channel blocker is injected into the axon and into the bath. Choose the labeled line which best illustrates the results.



Questions 2-3

For questions 2 and 3 choose from the diagram below the labeled line which best illustrates the change in resting membrane potential of a neuron resulting from:



2. A two-fold decrease in extracellular potassium concentration

3. Maximal increase in sodium conductance

4. If the permeability of a resting skeletal muscle cell to K^+ is increased while the permeability of the cell to Na^+ stays constant, then:
   A. the transmembrane potential would decrease
   B. the cell would become more excitable
   C. the cell would become more excitable because of a decrease in the transmembrane potential
   HD. the transmembrane potential would increase
   E. the transmembrane potential would not change

5. Which of the following changes in extracellular ion concentrations would be expected to hyperpolarize a skeletal muscle cell?
   A. increased sodium concentration
   B. decreased chloride concentration
   C. increased potassium concentration
   I–D. decreased potassium concentration

6. Which of the following changes would be expected to make the membrane potential of a muscle cell more positive than the normal (resting) level?
   A. increased conductance to potassium
   i-B. decreased conductance to potassium
   C. decreased conductance to sodium

7. The resting membrane potential of a somatic nerve axon should be altered significantly (greater than 20 mV) by which of the following agents?
   [1]-A. potassium-channel blocker
   B. tetrodotoxin
   C. norepinephrine
   D. calcium-channel blocker

8. Sodium concentration inside a mammalian cell is measured to be 10 mEq/L, while the extracellular concentration is determined to be 100 mEq/L. Which of the following values represents the equilibrium potential for sodium? (Hint: use vectors.)
   A. +30 mV
   B. +60 mV
   C. -60 mV
   D. -30 mV
   E. +120 mV

9. The resting membrane potential of the cell described in the previous question:
   A. would be -90 mV
   B. would be +71.7 mV
   C. would be -71.7 mV
   D. would be +43.5 mV
   L E. cannot be determined from the data given

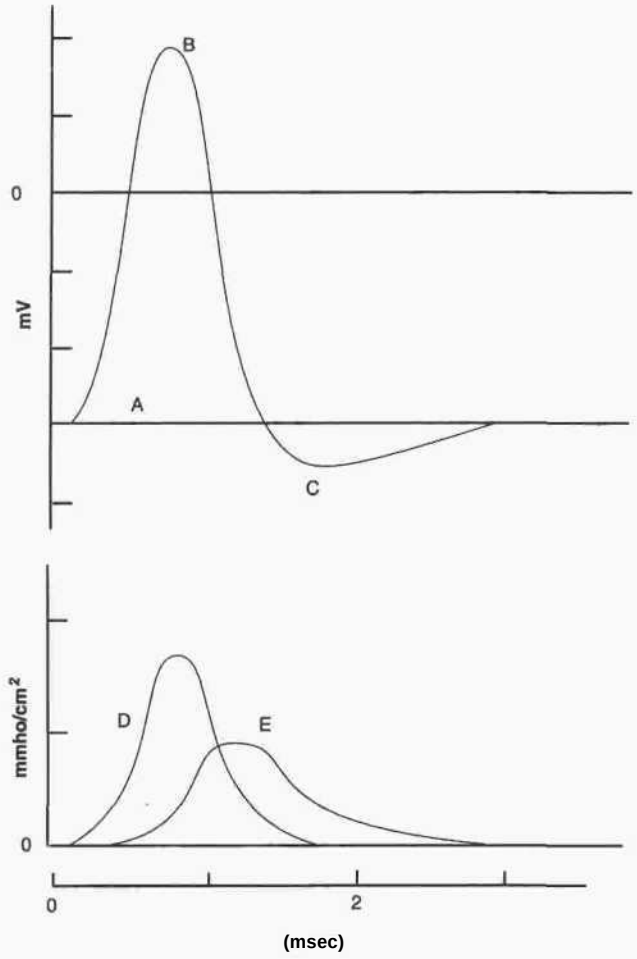
10. A drug that opens sodium channels in a motoneuron would also:
   u-A. cause the membrane potential to move toward the sodium equilibrium potential.
   B. cause the membrane potential to move toward the potassium equilibrium potential.
   C. increase the sodium equilibrium potential.
   D. increase the potassium equilibrium potential.

11. Which of the following is **inconsistent** with a resting alpha motoneuron?
   A. The electrical gradient for potassium is directed inward, but the concentration gradient is directed outward.
   ^ B. The electrical gradient for sodium is directed inward, but the concentration gradient is directed outward.
   C. Potassium efflux is impeded by the electrical gradient.
   D. Increasing sodium influx would in itself accelerate potassium efflux.

ACTION POTENTIAL

Review Questions

Directions: Select the ONE best answer.



The diagrams above depict characteristics of a mammalian spinal motoneuron measured by intracellular microelectrode.

1. From the diagrams above, choose the letter closest to the equilibrium potential for Na^+-
2. From the diagrams above, choose the letter that best represents K+ conductance.

3. Which of the following characteristics of a neuron is not associated with increased conduction velocity?

   A. increased axon diameter
   B. myelination
   C. increased transmembrane resistance
   D. decreased fiber size

Questions 4 and 5: Answer using the following **options:**

   A. rising phase of action potential
   B. falling phase of action potential
   C. both A and B are correct
   D. resting membrane potential

4. Is/are included in the absolute refractory period of a nerve fiber.

5. Period of lowest sodium conductance in a nerve fiber.

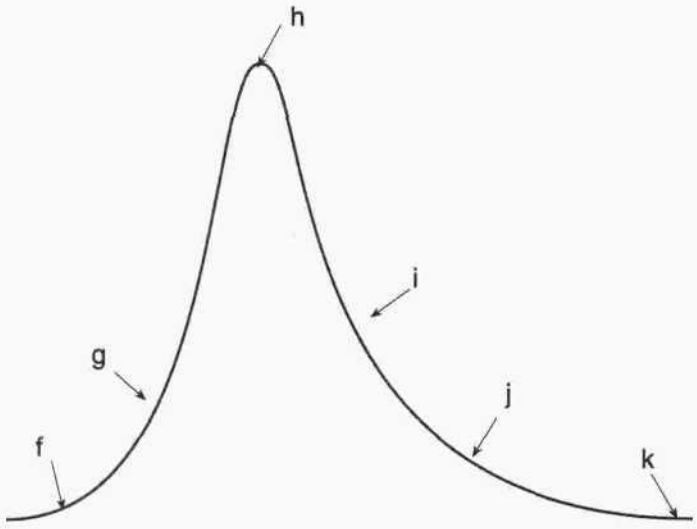
6. In excitable cells, repolarization is most closely associated with which of the following events?

   A. Na+efflux
   B. Na+influx
   C. K+efflux
   D. K+influx
   E. decreased excitability

7. The molecular basis of an axonal action potential includes:

   A. increased potassium conductance followed by increased sodium conductance
   B. increased sodium conductance followed by increased potassium conductance
   C. decreased sodium conductance
   D. decreased potassium conductance
   E. decreased calcium conductance

Questions 8-10



8. In the action potential illustrated above:

A. interval g-h is caused by an active transport of Na^+ into the cell
B. interval g-h is caused by a diffusion of Na^+ into the cell
C. interval g-h is caused by pinocytosis
D. interval h-i is caused by active transport of K^+
E. interval h-i is caused by active transport of Na^+

9. In the transmembrane potential illustrated above:

A. point f represents the threshold potential or firing level for the cell
B. the movement of the transmembrane potential from point f toward point g is called depolarization
C. the movement of the transmembrane potential from point f toward point g is associated with a decreased excitability
D. the cell is refractory during interval j-k
E. all of the above statements are true

10. The above action potential is recorded from a somatic efferent neuron:

At what interval would the O_2 consumption in milliliters of O_2 most exceed the resting level?

A. interval f-g
B. interval g-h
C. interval h-i
D. interval i-j
E. interval j-k

JUNCTIONAL TRANSMISSION

Review Questions

Directions: Select the ONE best answer.

1. A miniature end-plate potential results from:
   ^A. spontaneous release of a quantal package of acetylcholine
   B. presynaptic inhibition
   C. recruitment of motor units
   D. postsynaptic atropine blockade
   E. stimulation of A-alpha fibers

2. Which of the following occurs during an inhibitory postsynaptic potential (IPSP)?
   A. decreased potassium conductance
   --B. increased chloride conductance
   C. increased sodium conductance
   D. decreased calcium conductance

3. Which of the following is NOT associated with electronic neuron-to-neuron transmission?
   A. faster than chemical transmission
   B. involves direct cell-to-cell communication
   C. potentially bidirectional
   *-D. receptor dependent

4. The end-plate potential of skeletal muscle is best characterized as:
   A. a local reversal of charge originating at the end-plate
   B. a reversal of charge originating at the end-plate and propagated throughout the cell
   C. a decrease in the transmembrane potential that is propagated throughout the cell
   D. a local decrease in the transmembrane potential that is caused by an increased permeability to Na^+ and K^+
   E. a local decrease in the transmembrane potential that is associated with little or no increase in Na^+ conductance

5. The end-plate of a normally innervated skeletal muscle cell can be distinguished from the rest of the cell membrane in that **only** the end-plate:

<--A. will initiate a contraction in response to the local application of acetylcholine
B. will depolarize when exposed to an excess of extracellular K^+
C. will depolarize in response to an excess of extracellular Ca^{2+}
D. has all of the above characteristics
E. has none of the above characteristics

6. The inhibitory postsynaptic potential:

A. probably occurs only in the brain
B. is a local depolarization caused by an increase in Ca^{2+} conductance
C. is a local hyperpolarization caused by a decrease in Ca^{2+} conductance
D. is a local depolarization caused by an increase in C~ conductance
<E. is a local hyperpolarization caused by an increase in Cl~ conductance

EXCITABLE TISSUE

Answers

1. Ans A The resting membrane potential of the neuron is -70 mV. If a sodium-channel blocker is added to the medium you would be blocking closed channels and nothing should happen to the resting membrane potential. Line A represents a constant membrane potential of -70 mV.

2. Ans E A decrease in the extracellular concentration of potassium would accelerate the potassium efflux from the cell. Removing positive charges from the cell would produce hyperpolarization, line E.

3. Ans A A large increase in sodium conductance would produce sodium influx and depolarize the cell to a value close to the equilibrium potential for sodium. Since this is a positive potential, it would cross the zero potential line. Therefore, line A (not B) is the best answer.

4. Ans D An increase in potassium permeability would accelerate K^+ efflux and hyperpolarize the cell. This is also an increase in transmembrane potential (number without the sign). A hyperpolarization moves the membrane potential away from threshold and thus the cell becomes less excitable.

5. Ans D An increase in extracellular sodium would have no effect on the resting membrane potential (sodium channels closed). Decreased chloride, if anything, would cause an efflux of chloride (negative charges) and depolarize the cell. Increased extracellular potassium would slow the potassium efflux or reverse it to an influx. Positive potassium ions moving into the cell would cause a depolarization. Decreasing extracellular potassium would accelerate potassium efflux and hyperpolarize the cell.

6. **Ans B** Increased conductance to potassium accelerates potassium efflux and hyperpolarizes the cell. Decreased conductance to potassium would reduce potassium efflux. Since we continue to pump potassium into the cell (Na/K pump), these positive ions would accumulate intracellularly and cause a depolarization. The conductance to sodium under resting conditions is zero.

7. **Ans A** A potassium-channel blocker would decrease K^+ efflux. The continued pumping of positive ions into the cell would cause a progressive depolarization of the cell. Sodium-channel blockers would just block the closed sodium channels. A nerve axon does not have

receptors for norepinephrine. If no receptors are there, norepinephrine will be unable to act. Nerve axons also have no calcium channels in the membrane, hence no effect.

8. **Ans** B If the extracellular sodium concentration is 100 and inside the cell it is 10, there is a 10-fold concentration gradient directed into the cell. The force of this concentration gradient has the same magnitude as an electrical force of 60 mV. For sodium to be at equilibrium, there must be an electrical force directed outward with a magnitude of 60 mV. Thus, the equilibrium potential must be 60 mV. Since the force must act to push sodium out of the cell, it must be a positive 60 mV. If there was a positive 60 mV charge inside the cell repelling the sodium, this would balance the concentration force directed inward and the sodium would be at equilibrium.

9. **Ans** E As far as we are concerned, the resting membrane potential must be given or it is unknown. It is not possible without a complex calculation to predict a resting membrane potential.

10. **Ans** A Whenever channels are open to a particular ion, the membrane potential will move toward the equilibrium potential of that particular ion. Until the membrane potential reaches this equilibrium potential, the ion will continue to diffuse through the open channels. Based upon the numbers given in class you should realize that opening sodium channels will cause the membrane potential to move away from the potassium equilibrium potential. Opening channels will not change the equilibrium potential for a particular ion. The equilibrium potential is determined by the concentrations inside and outside the cell. Only if these concentrations change significantly will the equilibrium potential change. Assume that ions diffusing through channels under physiological conditions will not significantly alter intracellular or extracellular concentrations.

11. **Ans** B In answer B the electrical gradient for sodium is directed inward. Since membrane potentials are negative, the electrical gradient for all positive ions is directed inward (unlike charges attract). Since the concentration of sodium is greater on the outside of the cell, the concentration gradient is also directed inward. The concentration of potassium is greater inside the cell, therefore the concentration gradient is directed outward. In answer C the negative intracellular potential attracts the potassium and thus impedes its efflux. Finally, increasing the sodium influx will depolarize the cell. This will move the membrane potential away from the potassium equilibrium potential and thus increase the net force causing potassium efflux.

ACTION POTENTIAL

Answers

1. AnsB — For these two graphs the x axis is time. For the upper graph, the y axis is mV and the curve depicted is the action potential. In the lower graph, the y axis represents conductance changes during the action potential. Curve D is close to the expected changes for sodium and curve E depicts potassium. The equilibrium potential for sodium is a positive number measured in mV. The best answer is point B on the first curve.

2. AnsE — Potassium conductance increases during the action potential with peak conductance occurring during repolarization, curve E (see question 1 for further information).

3. AnsD — Conduction velocity is directly related to axon diameter and the amount of myelin. Myelination increases membrane resistance. Small diameter fibers will be slow conducting fibers.

4. AnsC — The absolute refractory period is that time interval after threshold is reached where a second stimulus will not invoke a second action potential. This includes all of the depolarization phase of the action potential and most of repolarization.

5. AnsD — The lowest conductance to sodium would represent the phase with the fewest open sodium channels . All sodium channels are closed during the resting phase. During repolarization, sodium channels are closing but some are still open in the early part of this phase.

6. AnsC — The most prominent event during repolarization is potassium efflux. It is the efflux of potassium the causes repolarization. There is still some sodium influx in the initial stage of repolarization but this quickly ceases. In repolarization the cell is moving through the relative refractory period back toward the resting phase. Thus, during this phase the cell is regaining its excitability.

7. AnsB — The depolarization phase is associated with an increased sodium conductance, resulting in a sodium influx, and repolarization, by an increased potassium conductance, resulting in an accelerated potassium efflux. There are no changes in calcium conductance during the axonal action potential.

8. Ans B The action potential is caused by the simple diffusion of ions through channels. Therefore, the answers explaining any aspect on the basis of active transport (or pinocytosis) are incorrect. Interval g-h is the depolarization phase which is caused by the inward diffusion of sodium.

9. Ans B In depolarization the membrane potential becomes more positive. Thus f to g is depolarization, g to h is also depolarization. Point f to g represents an increase in excitability since the membrane potential is moving toward threshold. The best answer for threshold is point g. When the word refractory is used, assume absolute refractory period unless the relative refractory period is specified. The absolute refractory period is best represented by g to i.

10. Ans E The point of this question is that the action potential itself is a passive event caused by first, the inward diffusion of sodium, then by a large outward diffusion of potassium. The Na/K pump then reestablishes the gradients via active transport, which is an energy demanding event and increases the oxygen consumption of the cell. Thus, the last labeled interval would be the best answer.

JUNCTIONAL TRANSMISSION

Answers

1. Ans A For some reason, single packets of acetylcholine are released into the synaptic cleft independent of action potentials. This causes a very small end-plate potential (referred to as miniature), too small to initiate an action potential. The mechanism is not well understood, thus the release is considered spontaneous.

2. Ans B The increased conductance to chloride is the only possible answer. Presumably this would produce an influx of chloride ions and hyperpolarization. Decreased conductance to potassium would depolarize because of the reduced efflux of potassium ions.

3. Ans D Receptors are associated with chemical transmission. Because with electronic transmission the electrical activity moves directly from cell to cell, it is faster. A direct transmission can move in either direction. Remember chemically mediated synapses are unidirectional.

4. Ans D An end-plate potential is a local depolarization caused by an influx of sodium ions. The channels that open to allow the passage of sodium also permit the passage of potassium. However, the main flux is the movement of sodium. The depolarization is not great enough to produce a reversal of the membrane charge.

5. **Ans A** The end-plate region of the skeletal muscle cell is the only region with receptors to acetylcholine. The end-plate potential produced in this region can lead to an action potential and muscle contraction. All regions of the muscle membrane will be depolarized by increases in extracellular potassium and neither region will be dramatically affected by calcium.

6. Ans E An inhibitory postsynaptic potential is a hyperpolarization making the cell less excitable. There is no closure of calcium channels involved and the only possibly listed correct choice is an increased chloride conductance.

SECTION III

Peripheral Circulation

General Aspects of the Cardiovascular System

1

GENERAL FEATURES OF THE CARDIOVASCULAR SYSTEM

Organization

Figure III-1-1 illustrates the general organization of the cardiovascular system.

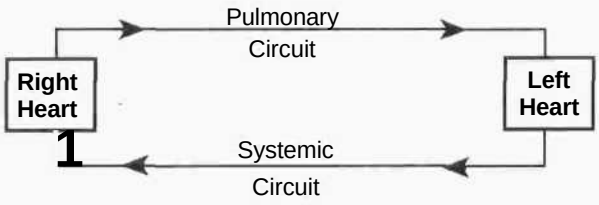


Figure Iii-1-1

The cardiovascular system consists of two pumps (left and right ventricles) and two circuits (pulmonary and systemic) connected in series. When circuits are connected in series, flow must be equal in the two circuits.

Cardiac output is the output of either the left or right ventricle, and because of the series system, they are equal.

What the USMLE Requires You to Know

- General features of the cardiovascular system
- The changes in pressure, cross-sectional area, velocity, and blood volume from the aorta to the vena cava
- The application of the Poiseuille equation to a vessel, organ, and, most important, the systemic circuit
- Factors affecting resistance
- Series versus parallel circuits
- Factors determining vessel wall tension
- The implications for differences in vessel compliance
- Effects of gravity on the cardiovascular system
- Factors affecting capillary filtration versus reabsorption

Also, the chemical composition of pulmonary venous blood is very close to the chemical composition of systemic arterial blood, and systemic mixed venous blood entering the right atrium has the same composition as puhnonary arterial blood.

Table III-l-l. Pressure Differential

Pressures in the Pulmonary Circulation		Pressures in the Systemic Circulation	
Right ventricle	25/0 mm Hg	Left ventricle	120/0 mm Hg
Pulmonary artery	25/8 mm Hg	Aorta	120/80 mm Hg
Mean pulm. art.	15 mm Hg	Mean art. blood p	93 mm Hg
Capillary	7-9 mm Hg	Capillary: skeletal renal glomerular	30 mm Hg 45-50 mm Hg
Pulmonary venous	5 mm Hg	Peripheral veins	15 mmHg
Left atrium	5-10 mm Hg	Right atrium (central venous)	0 mm Hg
Pressure gradient	15-5= 10 mm Hg	Pressure gradient	93 - 0 = 93 mm Hg

STRUCTURE-FUNCTION RELATIONSHIPS OF THE SYSTEMIC CIRCUIT

General Features

Figure III-1-2 shows that the systemic circuit is a branching circuit. It begins as a large single vessel, the aorta, and branches extensively into progressively smaller vessels until the capillaries are reached. The reverse then takes place in the venous circuit.

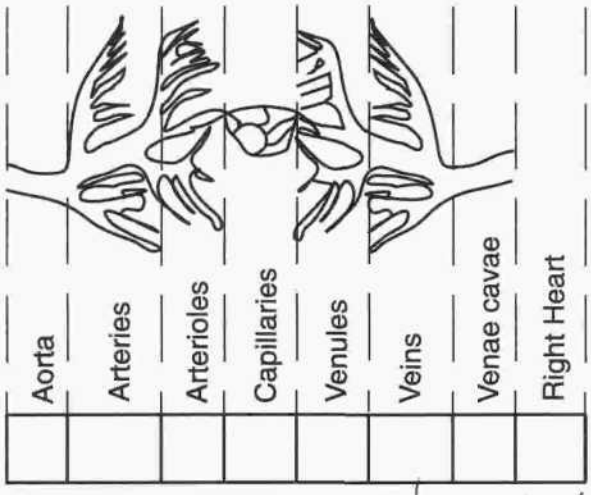


Figure III-1-2

Pressures in the Systemic Circuit

Figure III-1-3 shows, in a horizontal subject, the phasic and mean pressures from the aorta to the vena cava.

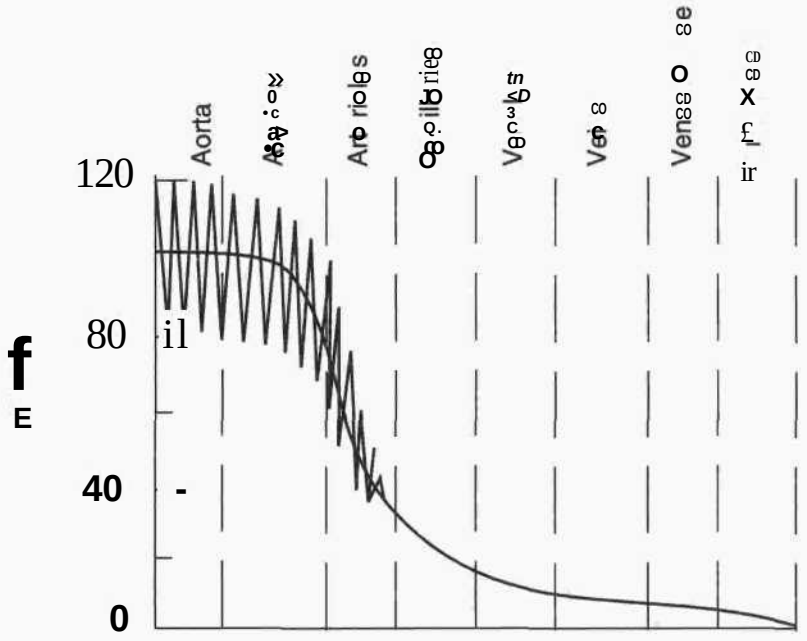


Figure MM-3

Pressure in the aorta is normally just below 100 mm Hg (about 93 mm Hg) and decreases toward the right atrium.

The pressure dissipates, overcoming resistance. The amount of pressure lost in a particular segment is proportional to the resistance of that segment.

There is a small pressure drop in the major arteries (low-resistance segment); the largest drop is across the arterioles (highest resistance segment), and another small pressure drop occurs in the major veins (low-resistance segment).

Local arteriolar dilation decreases arteriolar resistance, which increases flow and pressure downstream (more pressure and more flow get downstream).

Likewise, local arteriolar constriction increases arteriolar resistance, and flow and pressure decrease downstream.

Cross-Sectional Area

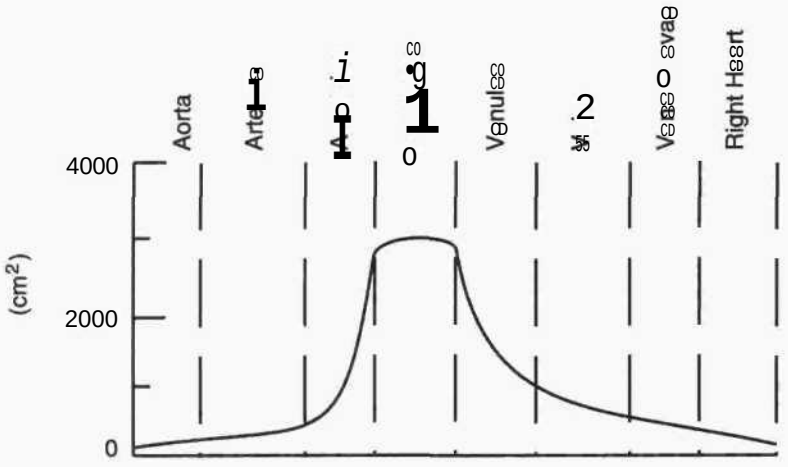


Figure III-1-4

The aorta is a large-diameter vessel, but it is still represents the systemic segment with the smallest cross-sectional area.

- As the aorta branches, the cross-sectional area of each individual vessel decreases, but collectively the cross-sectional area increases to reach a maximum in the capillaries.
- The cross-sectional area then decreases through the venous system.

Velocity

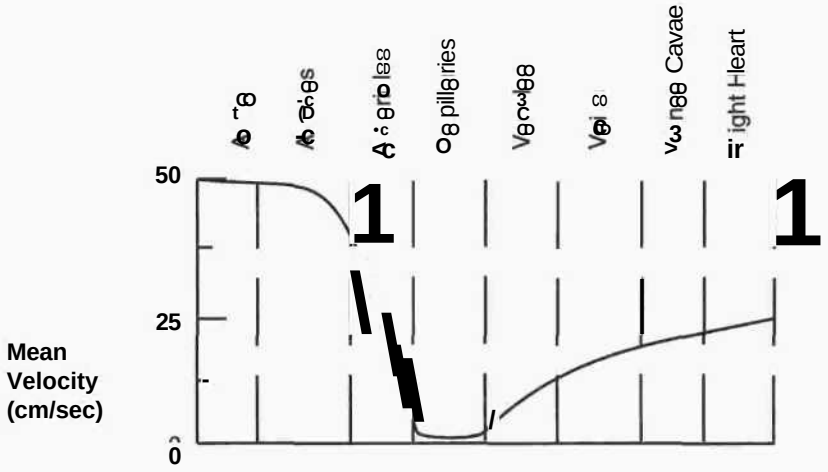


Figure 111-1-5

Velocity is inversely related to the total cross-sectional area of all vessels of a particular segment.

Velocity is greatest in the aorta, decreases to a minimum in the capillaries, and then increases from the venules to the right atrium.

Blood Volume

The largest blood volume in the cardiovascular system is in the systemic veins. The second largest blood volume is in the pulmonary system. Both represent major blood reservoirs.

HEMODYNAMICS

The Poiseuille equation: the relationship of flow, pressure, and resistance.

The following equation can be applied to a single vessel (Figure III-1-6), an organ, or an entire circuit.

$$Q = \frac{P1 - P2}{R}$$

Q:flow

Pi: upstream pressure for segment or circuit

P_2: pressure at the end of the segment or circuit

R: resistance of vessels between Pj and P_2

Figure III-1-6 illustrates how the Poiseuille equation applies to a single vessel.

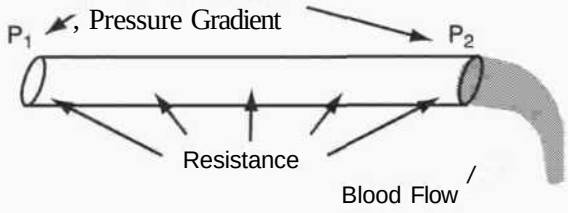


Figure 111-1-6

The flow to an organ such as the kidney, for example, could be calculated as mean arterial pressure minus renal venous pressure divided by the resistance of all vessels in the renal circuit.

Determinants of Resistance

Resistance $\frac{P1-P2}{\dot{Q}}$ Units of Resistance = $\frac{\text{mm Hg}}{\text{mL/min}}$ = $\frac{\text{pressure}}{\text{volume/time}}$

The resistance of a vessel is determined by three major variables: $R \propto \frac{vL}{r^4}$

Vessel Radius (r)

The most important factor determining resistance is the radius of the vessel.

- Resistance of a vessel is inversely proportional to the fourth power of the radius.
- This is how resistance is varied in the arterioles, which are the main regulators of flow distribution and make up the greatest component of total peripheral resistance (TPR).
- A slightly greater contraction of the smooth muscle surrounding an arteriole creates a small decrease in radius but a very large increase in vessel resistance.
- If the radius is decreased by half, the resistance increases 16-fold.
- If the radius doubles, the resistance decreases to 1/16 of the original.

Blood Viscosity (v)

Viscosity is a property of a fluid that is a measure of the fluid's internal resistance to flow:

- The greater the viscosity, the greater the resistance.
- The prime determinant of blood viscosity is the hematocrit.
  Figure III-1-7 shows how viscosity varies with hematocrit.

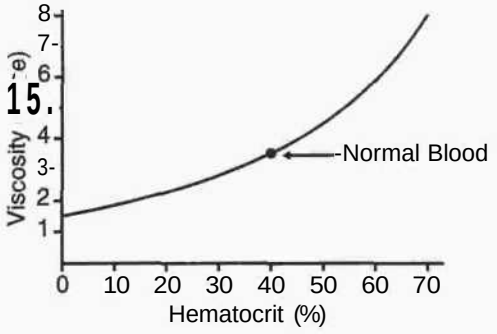


Figure II1-1-7

Anemia decreases viscosity. Polycythemia increases viscosity.

Vessel Length (L)

The greater the length, the greater the resistance.

- If the length doubles, the resistance doubles.
- If the length decreases by half, the resistance decreases by half.

Laminar Flow versus Turbulent Flow

There can be two types of flow in a system: laminar and turbulent.

Characteristics of laminar flow:

- As shown in Figure III-1-8, laminar flow is flow in layers.
- Laminar flow occurs throughout the normal cardiovascular system, excluding flow in the heart.
- The layer with the highest-velocity is in the-ceritgr of the tube.

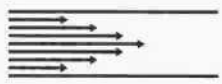


Figure 111-1-8. Laminar Flow

Characteristics of turbulent flow:

As shown in Figure III-1-9, turbulent flow is nonlayered flow.

- It creates murmurs.
- It produces more resistance than laminar flow.

Figure 111-1-9.
Turbulent Flow

Relation of Reynolds Number to Laminar and Turbulent Flow

Reynolds number = $\frac{(\text{diameter K velody (density)}}{\text{Viscosi}}$

>2000 = turbulent flow

<2000 = laminar flow

The following promote the development of turbulent flow (i.e., increase Reynolds number):

- Increasing tube diameter
- Increasing velocity
- Decreasing blood viscosity, eg, anemia

The following also promote turbulence:

- Vessel branching
- Narrow orifice (severe stenosis)

The vessel in the systemic circuit that is closest to the development of turbulent flow is the aorta. It is a large-diameter vessel with high velocity. This is where turbulence should appear first in anemia.

During inspiration and expiration, the conducting airways of the respiratory tree represent mainly a turbulent system. There is high velocity in large tubes with extensive branching.

Series versus Parallel Circuits

The following represent the consequences of connecting resistors in series.

Figure III-1-10 is a model of three resistors connected in series.

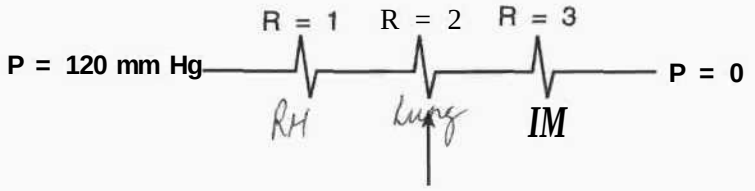


Figure 111-1-10

A major feature is that flow must be equal at all points in a series system. If the flow changes, it changes equally at all points in a series system.

The total resistance is the sum of the individual resistances:

$$R_T = R_1 + R_2 + R_3 \ldots$$

Therefore, the total is always **greater** than any of the individual resistances.

- Adding a resistor in series increases the resistance of the system.
- Connecting resistors in series results in a high-resistance system.

If Pin and P_{out} are kept constant, as in Figure III-1-10, the following will occur if the central resistance (R = 2) increases:

- Flow through the series system decreases equally at all points.
- Pressure immediately upstream from R_2 increases toward the perfusing pressure of 120 mm Hg.
- Pressure immediately downstream from R_2 decreases toward 0 mm Hg.

If Pj_n and P_{out} are kept constant, as in Figure III-1-10, the following will occur as the central resistance (R_2) decreases:

- Flow through the series system increases equally at all points.
- Pressure immediately upstream from R_2 decreases.
- Pressure immediately downstream from R_2 increases.

See the "Flow through a Single Nephron" discussion in the Renal Section (Section VII) for a practical application of this information.

Figure III-1-ll represents a simple model of the systemic circuit.

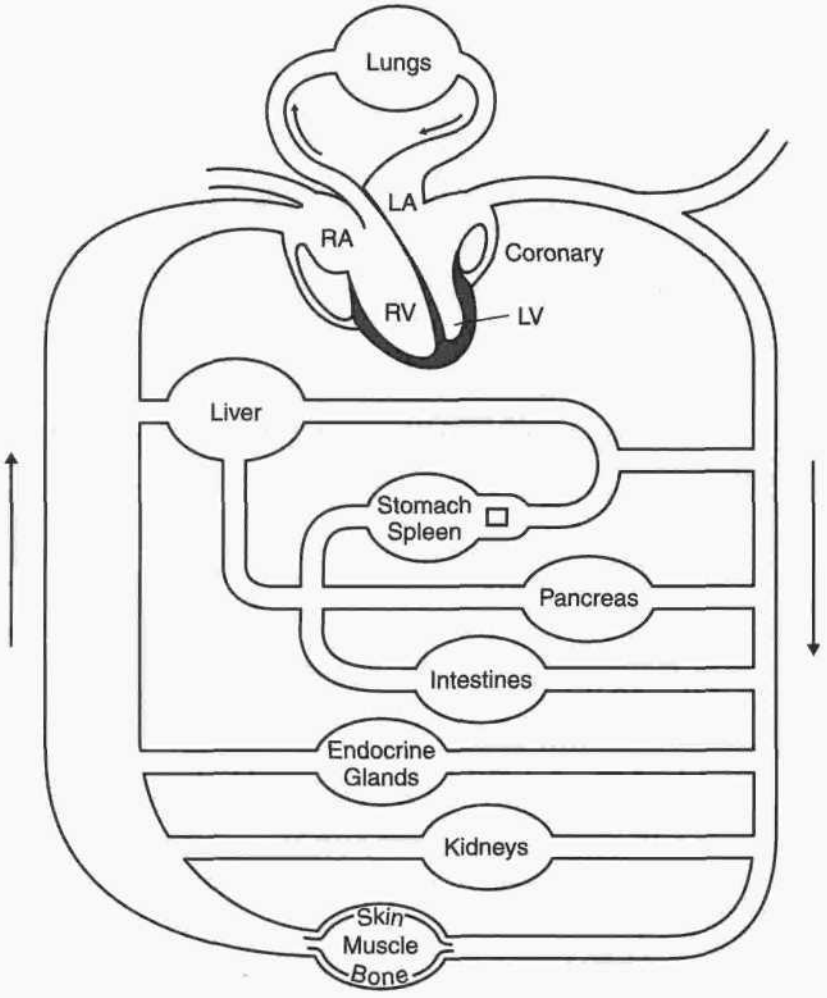
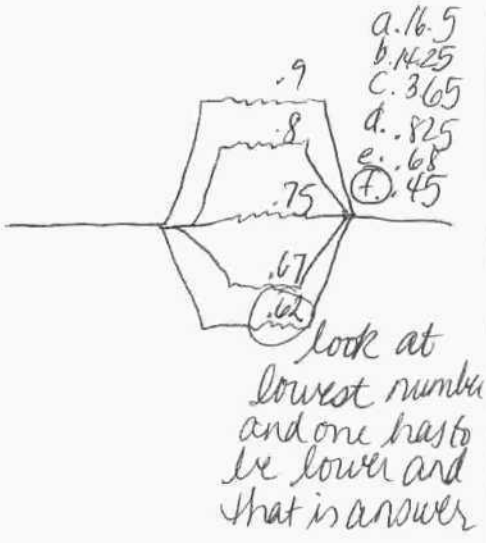


Figure 111-1-11. Systemic Circuit

As shown in Figure III-l-l 1, most systemic organs are connected in parallel. For example, the cerebral, cutaneous, coronary, and renal circuits are all in parallel.

When resistors are connected in parallel, the reciprocal of the total resistance is the sum of the reciprocals of the individual resistances.

$$\frac{1}{R_f} = \frac{1}{R_j} + \frac{1}{R_2} + \frac{1}{R_3} + \frac{1}{R_4} \ldots$$



If the resistance of each tube is 2 mm Hg/ml/min, then:

$$\frac{1}{R_T} = \frac{1}{2} + \frac{1}{2} + \frac{1}{2} + \frac{1}{2} = \frac{9}{2}$$

$$R = \frac{1}{2}$$

Therefore:

- Connecting resistors in parallel results in a low-resistance system.
- The total resistance is always less than any of the individual resistances.
- Adding a resistance in parallel lowers the resistance of the system.

Also, if blood pressure is kept constant, altering the resistance and thus the flow in one parallel circuit will not change the flow in the remaining parallel circuits.

- When structures are connected in parallel, flows can be independently regulated.
- This is not the case for structures connected in series.

The removal of a parallel resistance in the systemic circuit increases total resistance and consequently tends to increase blood pressure.

A dramatic example of this occurs at birth. Fifty-five percent of the fetal cardiac output goes through the placenta. At birth, the loss of the placental circulation increases systemic resistance. The subsequent rise in aortic blood pressure (as well as the fall in pulmonary arterial pressure caused by the expansion of the lungs) causes a reversal of flow in the ductus arteriosus, which leads to a large enough increase in left atrial pressure to close the foramen ovale.

WALL TENSION

Laplace relationship:

T °e Pr T = wall tension
P = pressure
r = radius

Development of an Arterial Aneurysm

Figure III-1-12 shows a developing arterial aneurysm. The pressures at points A, B, and C will be approximately the same.

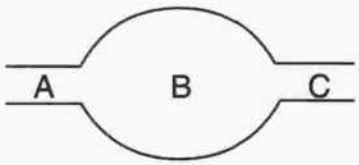


Figure IIM-12. Aortic Enlargement

Thus, because the aneurysm has a greater radius, its wall tension will be greater than that of the surrounding normal vessel segments.

Also, as the aneurysm enlarges, wall tenskmjncreases, and the vessel is more likely to burst

The aorta is the artery with the greatest wall tension (greatest pressure and radius^""

Vessel Compliance

$$\frac{\Delta V}{\Delta P}$$

Compliance of a vessel can be calculated, but the resulting number is, for all practical purposes, meaningless. It is much more important to simply have a good concept of compliance and understand the differences in compliance among the vessels that make up the cardiovascular system.

Compliance is essentially how easily a vessel is stretched. If a vessel is easily stretched, it is considered very compliant. The opposite is noncompliant or stiff.

QUESTIONS

1. Which of the following circuits represents the lowest resistance pathway?
   A. cerebral circulation
   B. coronary circulation
   C. renal circulation

2. Which of the following circuits represents the lowest resistance pathway?
   A. cerebral circulation
   B. coronary circulation
   C. renal circulation
   D. liver
   E. pulmonary circulation

Questions 3-7 follow and are based on Figure III-1-13, a hemodynamic model with three single tubes connected in series. Note that this does not represent the systemic circuit, which is a branching circuit.

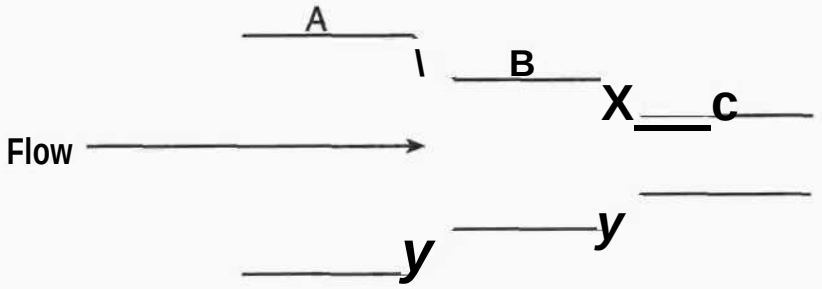


Figure 111-1-13. Hemodynamic Model

3. How does flow compare in A, B, and C?
4. Which section has the greatest wall tension?
5. Which section has the greatest velocity? G
6. Which section has the greatest resistance?
7. Which section will have the greatest pressure loss?

ANSWERS

1. c. This is based on the cardiac output delivered to each circuit. The renal circuit receives 20 to 25% of cardiac output, which is considerably more than the other two choices.
2. e. The pulmonary circuit receives 100% of cardiac output, thus it must be a low-resistance circuit. In addition, the pulmonary circuit is a low-pressure circuit. High-flow, low-pressure circuits must have very low resistance.

3. The flow will be the same. All points in a series system have the same flow.
4. Section A. It has the greatest pressure and the greatest radius.
5. Section C. Velocity is always inversely related to cross-sectional area.
6. Section C. Of the three tubes that are connected in series, it has the smallest radius.
7. Section C. Pressure will drop from A to C, but the amount of pressure lost will be proportional to the resistance of each segment.

CHARACTERISTICS OF SYSTEMIC ARTERIES

Figure III-1-14 shows a pressure pulse for a major systemic artery.

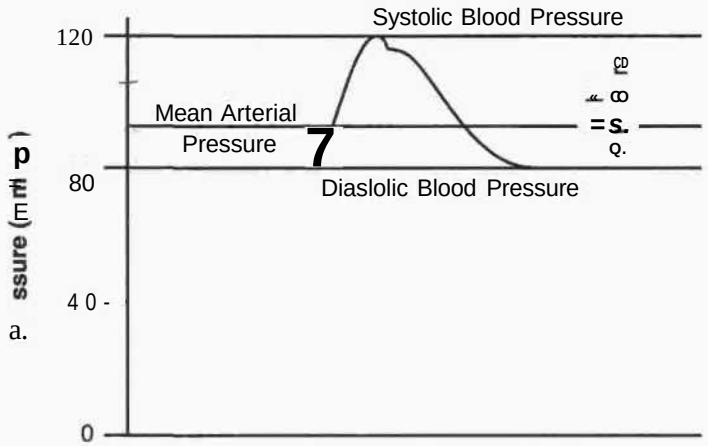


Figure MM-14

Systolic pressure is the peak pressure reached during systole. The following will increase arterial systolic pressure:

- An increase in stroke volume
- A decrease in vessel compliance
- A decrease in heart rate (via increased stroke volume)

Diastolic pressure is the lowest pressure, which is at the end of arterial diastole. The following will decrease arterial diastolic pressure:

- A decrease in total peripheral resistance
- A decrease in heart rate
- A decrease in stroke volume

Pulse pressure is the difference between systolic and diastolic pressure.

Pulse pressure = systolic - diastolic

The following will increase (widen) pulse pressure:

- An increase in stroke volume (systolic increases more than diastolic)
- A decrease in vessel compliance (systolic increases and diastolic decreases)

The aorta is the most compliant artery in the systemic system. Peripheral arteries are more muscular and less compliant. Based on the preceding information, in Figure III-1-15 the pressure record on the left best represents the aorta, whereas the one on the right best represents the femoral artery.

Figure III-1-15

The figure demonstrates that a compliant artery has a small pulse pressure and that a stiff artery has a large pulse pressure. Also, pulse pressure increases with age because compliance is decreasing.

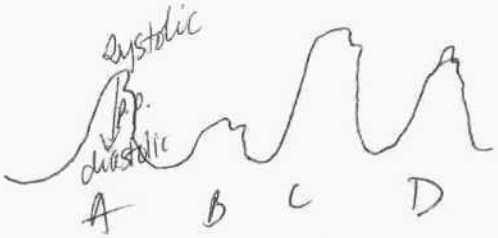
Mean pressure is the average pressure, but it is closer to diastolic pressure than to systolic pressure. Therefore, diastolic pressure is a better index of mean pressure than is systolic.

Mean pressure can be approximated by the following formulas:

$$\text{mean pressure} = \text{diastolic} + 1/3\ \text{pulse pressure}$$

$$= 2/3\ \text{diastolic pressure} + 1/3\ \text{systolic pressure}$$

Any formula that calculates mean pressure must give a value between systolic and diastolic but closer to diastolic than systolic.



femoral - A.
popliteal - D
pedal - C
iliac - B

pulse pressure ↑ as we go peripherally.

compliance ↑ as we go closer to heart.

Factors that affect mean pressure (the application of the Poiseuille equation to the systemic circuit):

$\dot{Q}$ = cardiac output

Pj = aortic pressure (mean arterial pressure)

P_2 = pressure at the entrance of the right atrium

R = resistance of all vessels in the systemic circuit. This is referred to as total peripheral resistance (TPR).

Because the major component of TPR is the arterioles, TPR can be considered an index of arteriolar resistance.

Because Pj is a very large number (100 mm Hg) and P_2 is a very small number that doesn't change dramatically in most situations, we can simplify the equation if we approximate P_2 as zero. Then:

$$CO = \frac{MAP}{TPR}$$

MAP = mean arterial pressure

CO = cardiac output

TPR = total peripheral resistance

or

$$MAP = CO \times \mathbf{TPR}$$

This equation simply states that:

Mean arterial pressure (MAP), which is maintained close to 100 mm Hg, is determined by only two variables: cardiac output and total peripheral resistance.

Cardiac output can be considered circulating volume. The blood stored in the systemic veins and the pulmonary circuit would not be included in this volume.

Total peripheral resistance (TPR) is the resistance of all vessels in the systemic circuit. By far the largest component is the resistance in the arterioles.

MAP= **CO* TPR**
HR x SV

↑ TPR through α_1 receptors
↑ HR by β stimulation
α + β
sympathetic

Hemorrhage

The problem is the loss of cardiac output or circulating blood volume. The increase in TPR via the carotid sinus reflex minimizes the loss of blood pressure. Because the reflex increase in TPR almost completely compensates in early hemorrhage, blood pressure is not a good index of blood loss following a hemorrhage.

Exercise

Exercise produces minimal changes in blood pressure. The decrease in TPR, mainly due to the dilation of arterioles in the exercising muscle, is accompanied by an equivalent increase in cardiac output. For example, a threefold increase in cardiac output would be the response if TPR decreased to a third of the resting level.

CHARACTERISTICS OF SYSTEMIC VEINS

Systemic veins are about 20 times more compliant than systemic arteries.

Veins also contain about 70% of the systemic blood volume and thus represent the major blood reservoir.

In the venous system then, a small change in pressure causes a large change in venous volume. For example, in a hemorrhage, venous pressure decreases. Because veins are very compliant vessels, this loss of distending pressure causes a significant passive constriction of the veins and a decrease in blood stored in those veins.

- The blood removed from the veins will now contribute to the circulating blood volume (cardiac output), a compensation for the consequences of hemorrhage.
- The sympathetic nerves innervating the veins will cause an active constriction and a further reduction in stored blood volume.

Volume loading (infusion of fluid) increases venous pressure. The increased pressure distends the veins; this is a passive dilation. The volume of fluid stored in the veins increases, which means that some of the infused volume will not contribute to cardiac output.

The actual venous return to the heart is determined by the venous pressure gradient. The large volume and compliant nature of the veins act to buffer changes in venous return and cardiac output. This effect is summarized in Figure III-1-16.

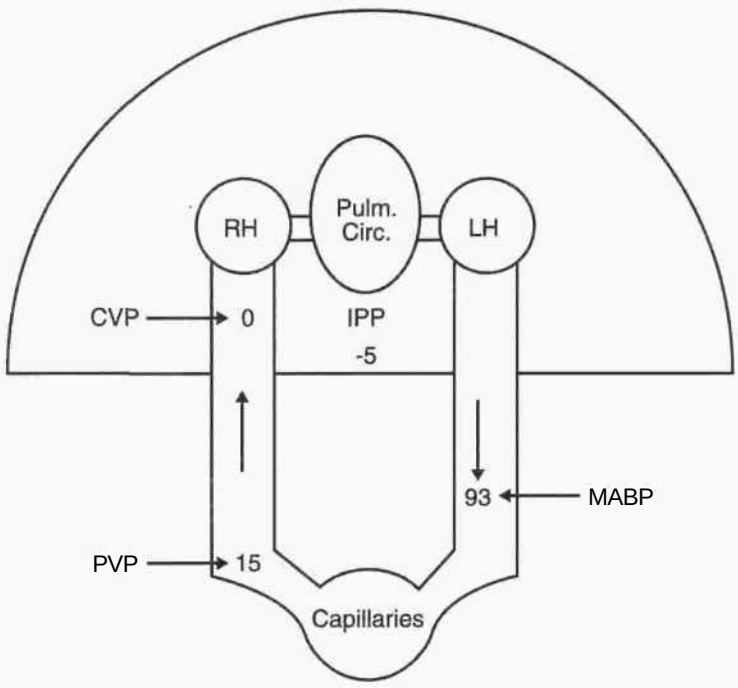


Figure 111-1-16

ABBREVIATIONS

CVP = Central venous pressure
IPP = Intrapleural pressure
LH = Left heart
MABP = Mean arterial blood pressure
PVP = Peripheral venous pressure
RH = Right heart

THE EFFECT OF GRAVITY

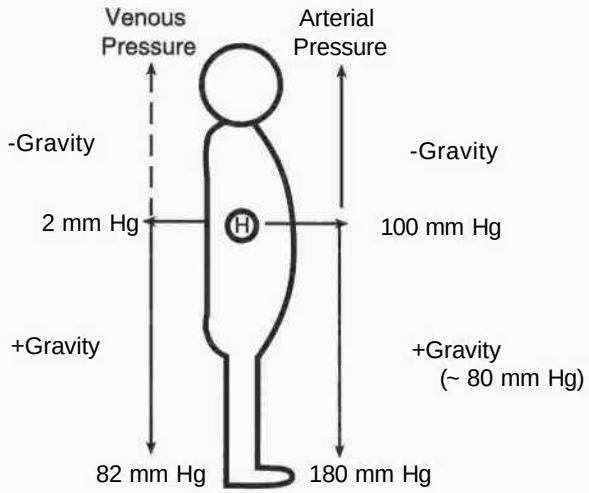


Figure 111-1-17

Upright Individual Summary

Below heart level, there are equal increases in systemic arterial and venous pressures (assuming no muscular action). Thus, the pressure difference between arteries and veins does not change.

Because veins are very compliant vessels, the higher pressures in the dependent veins mean a significant pooling of blood, a volume that is not contributing to cardiac output.

Above heart level, systemic arterial pressure progressively decreases.

Because venous pressure at heart level is close to zero, venous pressure quickly becomes subatmospheric (negative).

Surface veins above the heart cannot maintain a significant pressure below atmospheric; however, deep veins and those inside the cranium supported by the tissue can maintain a pressure that is significantly below atmospheric.

A consequence of the preceding is that a severed or punctured vein above heart level has the potential for introducing air into the system.

When a person goes from supine to an upright posture, the following important changes take place:

- Pressure in the dependent veins increases.
- Blood volume in the dependent veins increases.

- Circulating blood volume (cardiac output) decreases.
- Blood pressure decreases.

Compensation via the carotid sinus reflex will include:

- Total peripheral resistance increases.
- Heart rate increases.

The changes induced by the carotid sinus returns blood pressure toward the value in the supine position, but in most cases compensation will not be complete.

QUESTIONS

Based on your understanding of the effects of gravity:

1, Which of the following vessels will have the highest absolute pressure in an upright individual?

A. aorta

\-B."femoral artery

C. brachial artery

D. femoral vein

E. brachial vein

2. Which of the following vessels will have the greatest change in pressure when going from a supine to an upright posture?

A. cerebral artery

B. brachial artery

C. cerebral vein

D. brachial vein

E. aorta

VF. femoral vein

ANSWERS

1. B, femoral artery

   The best answer is always the artery farthest below heart level.

2. F, femoral vein

   The best answer is always the vessel farthest away from the heart. Femoral artery and femoral vein cannot both be given because they are equidistant from the heart. Moving to the upright position would cause a greater pooling of blood in the vein than in the artery.

EFFECTS OF INTRAPLEURAL PRESSURE ON PULMONARY BLOOD FLOW AND VOLUME

Inspiration

Intrapleural pressure becomes more negative (decreases).

Systemic venous return and right ventricular output are increased.

An increase in the output of the right ventricle will delay the closing of the pulmonic valves and may result in a splitting of the second heart sound.

Pulmonary vessels expand, and the volume of blood in the pulmonary circuit increases.

Blood returns, and the output of the left ventricle is decreased, causing decreased systemic arterial pressure.

Expansion of the right atrium and the ensuing drop in blood pressure cause a reflex increase in heart rate (sinus arrhythmia).

Expiration

Intrapleural pressure becomes more positive (increases).

Systemic venous return and output of the right ventricle are decreased.

Pulmonary vessels are compressed, and the volume of blood in the pulmonary circuit is decreased.

The return of blood and output of the left ventricle are increased, causing increased systemic arterial pressure.

The right atrium is compressed, and the blood pressure is increased, causing a reflex decrease in heart rate.

A Valsalva maneuver will also increase intrapleural pressure and central venous pressure and decrease venous return.

THE MICROCIRCULATION

General Characteristics

Flow and pressure within the system is controlled by varying the radius (resistance) of the arterioles.

Dilation of the arterioles causes an increase in flow and pressure in the capillaries, and constriction of the arterioles causes a decrease in pressure and flow in the capillaries.

Capillaries are generally permeable to all dissolved substances except plasma proteins. Even so, proteins slowly leak out into the interstitium.

One function of the lymphatic system is the removal of interstitial proteins.

Capillary Exchange

Diffusion is the main process involved in the exchange of nutrients and gases between blood and tissue.

The only dissolved substance in the plasma that does not exchange freely with the interstitium by diffusion is protein and substances attached to protein.

Net diffusion across a capillary membrane is driven by concentration differences, and the rate depends on the factors discussed in membrane transport (Section I) and summarized again in the following equation:

$$D \propto \frac{\text{APX\&4X } SOL}{T \text{ X } \sqrt{MW}}$$ where*:

D = diffusion rate

A P = pressure gradient

SA = surface area

SOL = solubility of the substance in the membrane

T = membrane thickness

MW = molecular weight

The exchange of an individual substance across a capillary membrane is by simple diffusion.

Exchange does not take place by protein-mediated transport.

If it is a lipid-soluble substance, it will diffuse through the endothelial cells (e.g., oxygen); if the substance cannot penetrate cell membranes, it will diffuse between the endothelial cells (e.g., sodium).

Filtration and reabsorption are the main processes by which fluid moves between plasma and interstitium. These two processes are driven by osmotic and hydrostatic pressure differences and thus would be classified as bulk flow.

Figure III-1-18 illustrates the four factors that affect filtration and reabsorption.

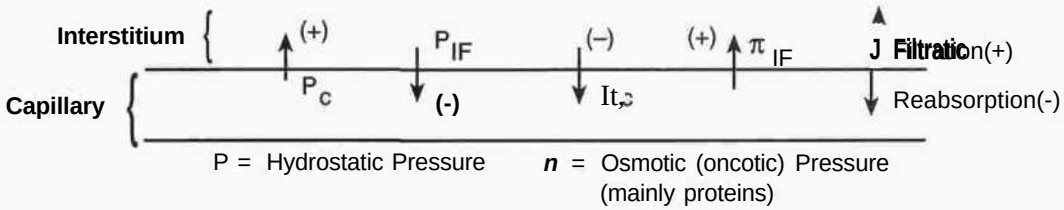


Figure III-1-18

P_c = hydrostatic pressure in the capillary

Pjp = hydrostatic pressure in the interstitial fluid

π_c = colloid osmotic pressure or oncotic pressure of plasma. This is the osmotic pressure of plasma solutes that cannot diffuse across the capillary membrane. The only natural substances are the plasma proteins, and the osmotic pressure is determined by the protein concentration in the plasma.

TTjp = determined by the concentration of protein in the interstitial fluid

Fluid movement = $k(?_c - P_{IF})$ - a(iTc - Tip)

Where *k* = filtration coefficient; cr = reflection coefficient

QUESTIONS

1. Given the following values, calculate a net pressure:
   P_c = 25 mm Hg
   P_{IF} = 2 mm Hg
   π_c = 20 mm Hg
   π_{IF} = 1 mm Hg
2. Calculate a net pressure if the interstitial hydrostatic pressure is -2 mm Hg.

ANSWERS

1. +4 mm Hg
2. +8 mm Hg

VARIATIONS IN THE FACTORS THAT AFFECT FILTRATION AND REABSORPTION

Capillary Hydrostatic Pressure

Capillary hydrostatic pressure is increased by arteriolar dilation (upstream arterioles) and venous constriction (a point constriction, which raises venous pressure).

It is decreased by arteriolar constriction. Essential hypertension that is the result of an increase in TPR will raise blood pressure but lower the downstream capillary pressure. Hemorrhage will also lower capillary pressure and promote the reabsorption of interstitial fluid. Under normal conditions, this is the main factor affecting filtration versus reabsorption.

Capillary Oncotic Pressure

Capillary oncotic pressure is increased by dehydration as a result of excessive sweating.

It is decreased by liver and renal disease and by saline infusion (not plasma and whole blood, which contain protein).

Interstitial Oncotic Pressure

Interstitial oncotic pressure is increased by chronic lymphatic blockage and by greater capillary permeability (e.g., burns).

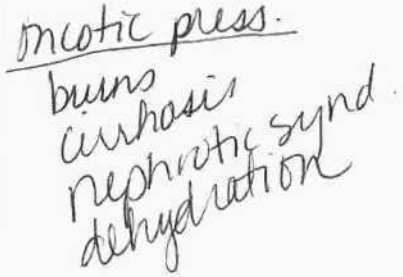
Interstitial Hydrostatic Pressure

Clinically significant changes are mainly restricted to the pulmonary circuit. More negative thoracic pressures will increase filtration (e.g., respiratory distress syndrome).

Note

Pulmonary Edema

The pulmonary capillaries are normally surrounded by a subatmospheric pressure, which promotes filtration. The tendency to develop pulmonary edema increases when intrathoracic pressures become more negative, such as in respiratory distress syndrome.



Chapter Summary

The cardiovascular system consists of two circuits and two pumps connected in series.

Systemic pressure decreases slightly through the arteries, decreases markedly through the arterioles, and then decreases only slightly more through the major veins. The loss of pressure is determined by regional resistance.

The cross-sectional area increases from a minimum in the aorta to a maximum in the capillaries. Velocity of the blood is inversely related to a region's cross-sectional area.

The main blood reservoir is the systemic veins.

Of the factors affecting a vessel's resistance, radius is the most important. The radius of the arterioles determines total peripheral resistance (TPR).

The cardiovascular system is a laminar flow system. The factors that promote turbulence include decreased fluid viscosity, large-diameter tubes, increasing fluid velocity, and vessel branching.

Structures connected in series produce high resistance, and flow is dependent and equal at all points.

Mean arterial pressure is determined only by the circulating blood volume (cardiac output) and the resistance of the arterioles.

Systemic organs are connected in parallel, which permits independent regulation of flow.

Vessel wall tension is directly proportional to pressure and radius.

The aorta is the most compliant artery, but veins are more compliant than arteries.

Gravity causes the pooling of blood in the dependent veins. This blood does not contribute to cardiac output.

Capillary filtration is supported by capillary hydrostatic pressure and interstitial oncotic pressure.

Reabsorption is supported by capillary oncotic pressure and interstitial hydrostatic pressure.

The subatmospheric thoracic pressure supports filtration.

Regulation of Blood Flow and Pressure

2

MEASUREMENT OF CARDIAC OUTPUT USING THE FICK PRINCIPLE

The Fick principle can be utilized to calculate the blood flow through an organ.

Calculation of flow through the pulmonary circuit provides a measure of the cardiac output.

$$\text{Flow} = \frac{\text{Uptake}}{\text{A - V oxygen content difference}}$$

Required data are: oxygen consumption of the organ

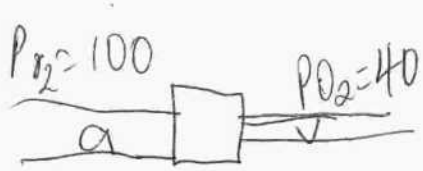
A - V oxygen content (concentration) difference across the organ (not PO2)

Pulmonary venous (systemic arterial) oxygen content = 20 vol%

= 20 volumes O_2 per 100 volumes blood

= 20 ml O_2 per 100 ml

= 0.2 ml O_2 per ml blood



What the USMLE Requires You to Know

- Measurement of cardiac output using the Fick principle
- Autoregulation and the metabolic hypothesis
- Extrinsic mechanisms regulating systemic blood flow
- The control of blood flow to resting versus exercising muscle
- The characteristics of the coronary, cerebral, cutaneous, renal, and splanchnic circulations
- The unique characteristics of the pulmonary circulation
- The fetal circulation

Figure III-2-1 illustrates the situation in a normal resting individual.

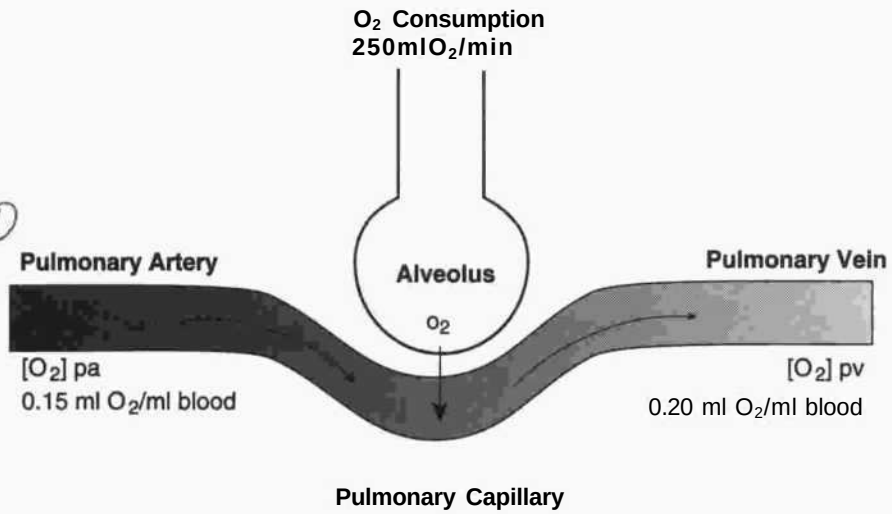


Figure III-2-1

$$\dot{Q}(\text{flow}) = \frac{\text{oxygen consumption}}{[O_2]pv - [O_2]pa}$$

$$= \frac{250 \text{ ml/min}}{0.20 \text{ ml/ml} - 0.15 \text{ ml/ml}} = 5000 \text{ ml/min}$$

Note

Pulmonary venous oxygen = systemic arterial

Pulmonary arterial oxygen = systemic venous

REGULATION OF BLOOD FLOW AT THE ORGAN LEVEL

Flow is regulated by constricting and dilating the smooth muscle surrounding the arterioles.

I. Intrinsic Regulation (Autoregulation)

The control mechanisms regulating the arteriolar smooth muscle are entirely within the organ itself.

- What is regulated is blood flow, not resistance. It is more correct to say that resistance is changed in order to regulate flow.
- No nerves or circulating substances are involved in autoregulation. Thus, the autonomic nervous system and circulating epinephrine have nothing to do with autoregulation.

There are two main theories that attempt to explain autoregulation. Of the two, the metabolic hypothesis has more support.

MetabolicHypothesis

Tissue produces a vasodilatory metabolite that regulates flow, e.g., adenosine in the coronary circulation.

A dilation of the arterioles is produced when the concentration of these metabolites increases in the tissue. The arterioles constrict if the tissue concentration decreases.

MyogenicHypothesis

Increased perfusing pressure causes stretch of the arteriolar wall and the surrounding smooth muscle.

Because an inherent property of the smooth muscle is to contract when stretched, the arteriole radius decreases, and flow does not increase significantly.

This explanation cannot stand alone unless overcompensation to the stretch occurs.

MajorCharacteristicsofanAutoregulatingTissue

Blood flow should be independent of blood pressure.

This phenomenon is demonstrated for a theoretically perfect autoregulating tissue in Figure III-2-2.

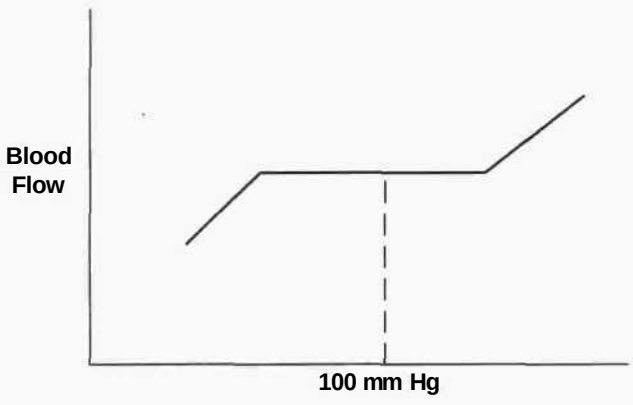


Figure III-2-2

Blood flow in most cases is proportional to tissue metabolism.

Blood flow is independent of nervous reflexes (e.g., carotid sinus).

Know what signals are found to regulate lung CO_2 & H^+

Ang. I
ACE in lungs & elsewhere
Ang. II

0

Autoregulating tissues include (tissues least affected by nervous reflexes):

- Cerebral circulation
- Coronary circulation
- Skeletal muscle vasculature during exercise

Extrinsic Regulation

These tissues are controlled by nervous and humoral factors originating outside the organ, e.g., resting skeletal muscle.

Figure III-2-3 illustrates an arteriole in skeletal muscle and the factors regulating flow under resting conditions.

Figure III-2-3

The main mechanism controlling flow in resting skeletal muscle and all other major extrinsically regulated systemic circuits is tonic changes in sympathetic adrenergic activity, i.e., norepinephrine acting on a receptors, causing constriction.

When present, P receptors can contribute to the regulation; that is, circulating epinephrine acting on fi_2 receptors can cause dilation.

Generally, the parasympathetic system does not affect arterioles, and thus it has little or no influence on total peripheral resistance (exception: the penis).

Circulations with mainly extrinsic regulation (those most affected by nervous reflexes):

- Cutaneous circulation-^ A *dh* sympathetic cholinergic
- Resting skeletal muscle

Control of Resting versus Exercising Muscle

Resting Muscle

Flow is controlled mainly by increasing or decreasing sympalhfiicjx-adrenergic activity. But (3_2 receptors can contribute to the regulation of blood flow.

Exercising Muscle

The increase in flow is mainly via vasodilatory metabolites, but this cannot occur without a significant contribution via an increase in cardiac output.

- fi_2 activation via circulating epinephrine can contribute to the increase inflow.
- Sympathetic adrenergic nerves have no effect on flow in exercising muscle, (a receptors are unresponsive to norepinephrine.)
- Thus, if there was an increase in sympathetic activity to an exercising muscle, flow would not change.

Coronary Circulation

Coronary Flow Patterns

Coronary flow patterns are demonstrated in Figure III-2-4.

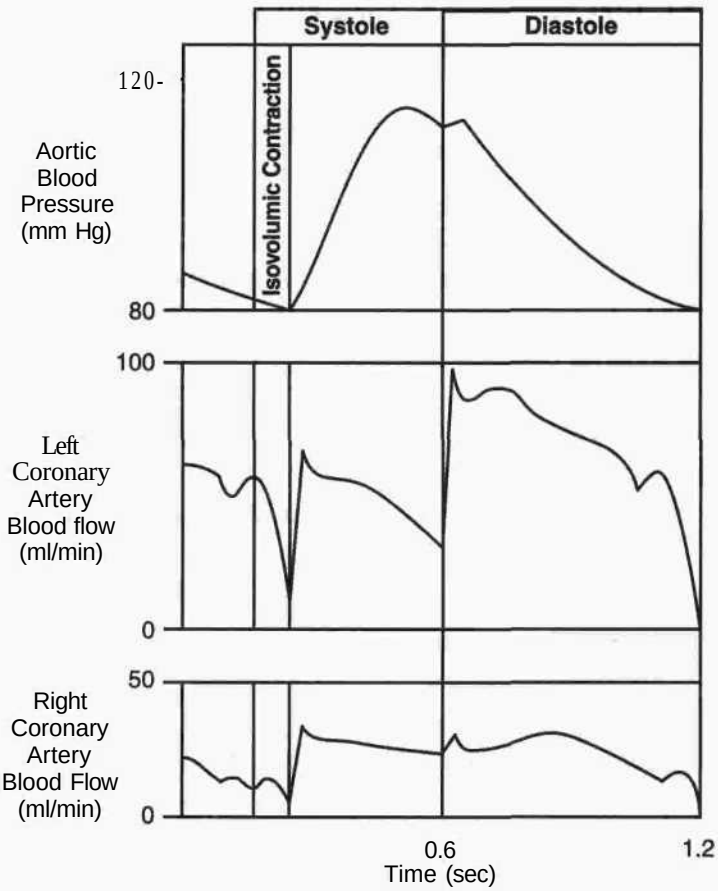


Figure III-2-4

Characteristics of left coronary flow (flow to the left ventricular myocardium):

Left ventricular contraction causes severe mechanical compression of intramyocardial vessels. Therefore:

- Very little if any blood flow occurs during systole.
- Most of the blood flow is during diastole.

Characteristics of right coronary blood flow (flow to the right ventricular myocardium):

Right ventricular contraction causes modest mechanical compression of intramyocardial vessels. Therefore:

- Significant flow can occur during systole.
- The greatest flow under normal conditions is still during diastole.

Oxygenation

In the coronary circulation, the tissues extract almost all the oxygen they can from the blood, even under "basal" conditions. Therefore:

- The venous PO_2 is extremely low. It is the lowest venous PO_2 in a resting individual.
- Because the extraction of oxygen is almost maximal under resting conditions, increased oxygen delivery to the tissue can be accomplished only by an increased blood flow.
- In the coronary circulation, flow must match metabolism.

Pumping Action

Coronary blood flow (ml/min) is determined by the pumping action of the heart.

Increased pumping action means increased metabolism, which means increased production of vasodilatory metabolites, which means increased coronary flow.

Increased pump function occurs with:

- Exercise: increased volume work (more volume pumped at the same pressure)
- Increased arterial pressure (hypertension): increased pressure work (a similar volume pumped against a greater pressure)

Cerebral Circulation

Flow is proportional to arterial PCO_2.

Under normal conditions, arterial PCO_2 is the main factor regulating cerebral blood flow.

The final effector is cerebrospinal fluid (CSF) hydrogen ions.

- Hypoventilation increases arterial PCO_2, thus it increases cerebral blood flow.
- Hyperventilation decreases arterial PCO_2, thus it decreases cerebral blood flow.

As long as arterial PO_2 is normal or above normal, cerebral blood flow will be regulated via arterial PCO_2. Therefore:

- If a normal person switches from breathing room air to 100% oxygen, there will be no significant change in cerebral blood flow.
- However, a (large) decrease in arterial PO_2 will increase cerebral blood flow. Under these conditions, it is the low arterial PO_2 that is determining flow.
- Baroreceptor reflexes do not affect flow.

A-V is very high in coronary vessels.

In MI the first intervention is to give vasodilator

Beginning of hyperten sion you feel good. It takes years to start feeling effects

I J

Cutaneous Circulation

Almost entirely controlled via sympathetic adrenergic nerves.

Large venous plexus innervated by sympathetics.

A-V shunts innervated by sympathetics.

Sympathetic stimulation to the skin will cause:

- Constriction of arterioles and a decrease in blood flow
- Constriction of the venous plexus and a decrease in blood volume in the skin
- Increase in velocity of blood (decreased cross-sectional area)
- Sympathetic activity to the skin varies mainly with the body's need for heat exchange with the environment.

TemperatureRegulation

Sensor represents the temperature-sensitive neurons in the anterior hypothalamus, whose firing rate reflects the temperature of the regional blood supply.

Normal set point: oral 37° C (rectal + 0.5° C)

Orcadian rhythm: low point, morning; high point, evening

As illustrated in Figure III-2-5, the body does not lose the ability to regulate body temperature during a fever. It simply regulates body temperature at a higher set point.

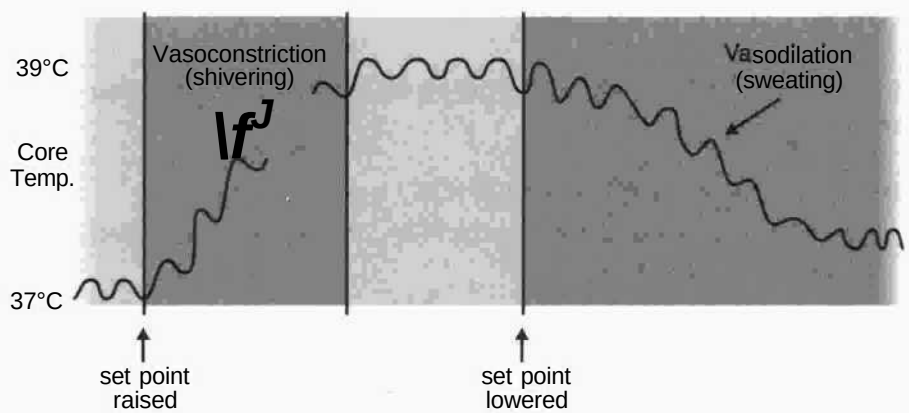


Figure 111-2-5

When a fever is developing, body temperature is rising toward the new higher set point. Under these conditions, heat-conserving and heat-generating mechanisms include:

- Shivering
- Cutaneous vasoconstriction

After a fever "breaks," the set point has returned to normal, and body temperature is decreasing. Heat-dissipating mechanisms include:

- Sweating (sympathetic cholinergics)
- Cutaneous vasodilation

Renal and Splanchnic Circulation

A small change in blood pressure will invoke an autoregulatory response to maintain renal blood flow.

Thus, under normal conditions, the renal and splanchnic circulations demonstrate autoregulation.

Situations in which there is a large increase in sympathetic activity (e.g., hypotension) usually cause vasoconstriction and a decrease in blood flow.

Renal circulation is greatly overperfused in terms of nutrient requirements, thus the venous PO_2 is high.

Pulmonary Circuit

Characteristics

Low-pressure circuit, arterial =15 mm Hg, venous = 5 mm Hg

High flow, receives entire cardiac output

Low-resistance circuit

Passive circuit; total flow not regulated

Very compliant circuit; both arteries and veins are compliant vessels

Hypoxic vasoconstriction (low alveolar PO_2 causes local vasoconstriction)

Blood volume proportional to blood flow

- Because of the passive nature of the pulmonary circuit, pulmonary pressures are proportional to the output of the right ventricle.
- Because of the very compliant nature of the pulmonary circuit, large changes in the output of the right ventricle are associated with only small changes in pulmonary pressures.

PulmonaryResponsetoExercise

A large increase in cardiac output means increased volume pumped into the circuit. This will produce a rise in pulmonary pressures.

Because of the passive, compliant nature of the circuit, the response to a rise in pressure is vessel dilation.

This response leads to apical blood vessel recruitment. The overall response is a large decrease in resistance.

Consequently, during exercise, there is only a slight increase in pulmonary pressures.

- If the pulmonary circuit was not a passive, very compliant circuit, increasing the output of the right ventricle would cause pulmonary hypertension.

PulmonaryResponsetoHemorrhage

A large decrease in cardiac output means decreased volume pumped into the circuit. This will produce a decrease in pulmonary pressures.

Because of the passive, compliant nature of the circuit, the response to a decrease in pressure is vessel constriction. This results in a large increase in resistance.

Consequently, during hemorrhage, there is often only a slight decrease^ in pulmonary pressures.

Vessel constriction also means less blood is stored in this circuit.

FETAL CIRCULATION

The general features of the fetal circulatory system are shown in Figure III-2-6.

Numbers in parentheses refer to the percent hemoglobin (%HbO_2) saturation.

rt. ventricle JUT) main pump and goes to pulmonary artery

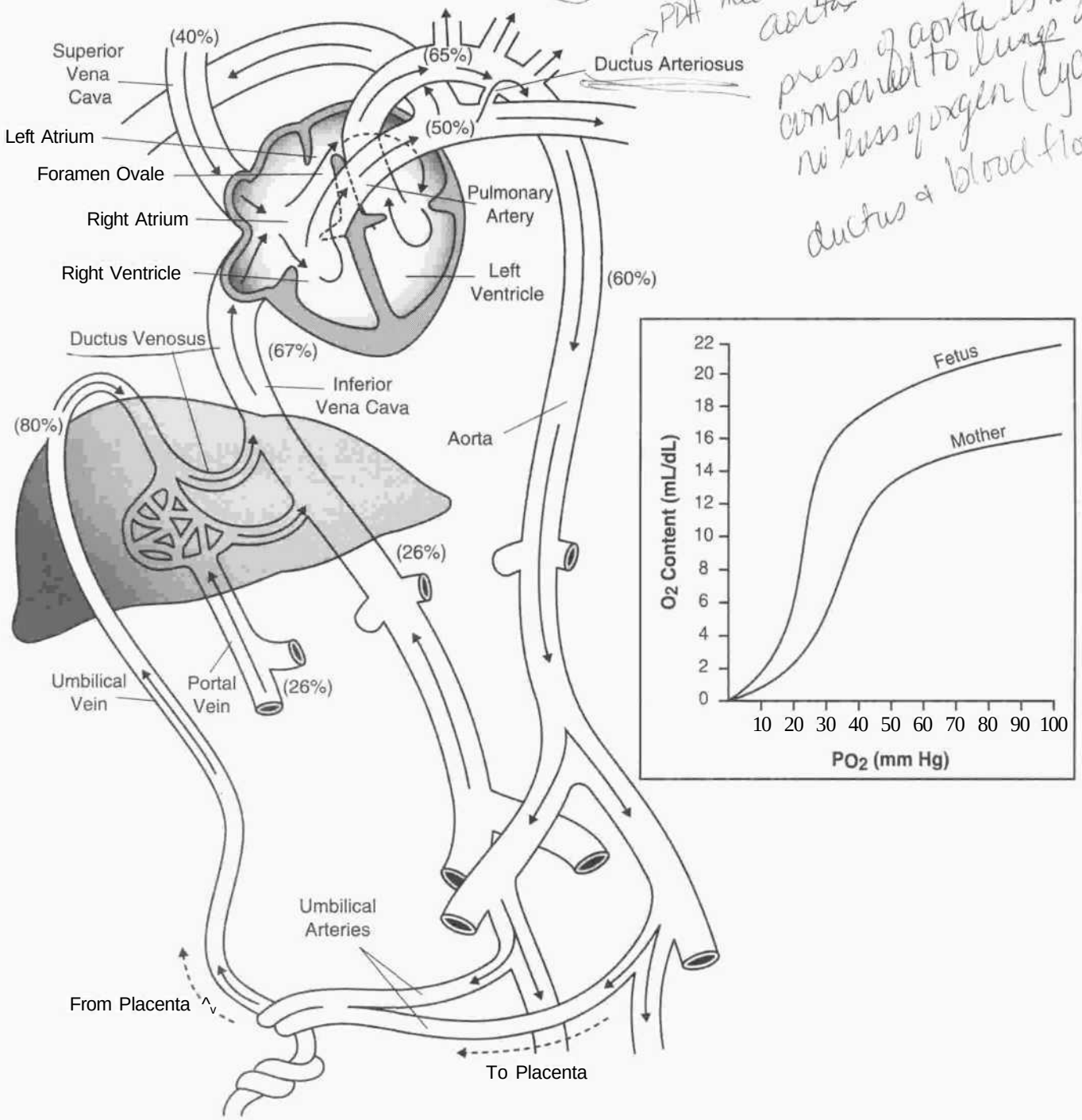


Figure 111-2-6. Fetal Circulatory System

Of the fetal cardiac output, 55% goes to the placenta.

The umbilical vein and ductus venosus have highest %HbO_2 saturation (80%).

When mixed with inferior vena caval blood (26% HbO_2), the %HbO_2 saturation of blood entering the right atrium is 67%.

This blood is directed through the foramen ovale to the left atrium, left ventricle, and ascending aorta to perfuse the head and the forelimbs.

Superior vena caval blood (40% HbO_2) is directed through the tricuspid valve into the right ventricle and pulmonary artery and shunted by the ductus arteriosus to the descending aorta.

The HbO_2 saturation of aortic blood is 60%.

ARTERIAL-VENOUS DIFFERENCES (A SUPPLEMENTAL TOPIC)

General Principle

Figure III-2-7 illustrates the principle of calculating an A-V difference.

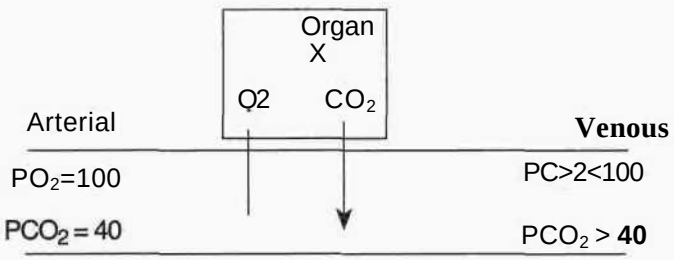


Figure 111-2-7

Arterial-venous differences:

= " + " if substance extracted by the organ, e.g., O_2, substrates like glucose, lactate in heart muscle

= " - " if substance produced by the organ, e.g., CO_2, glucose in liver, lactate in skeletal muscle and ischemic heart muscle

Skeletal Muscle

Resting muscle venous PO_2 ~ 45 mm Hg

Exercising muscle venous PO_2 ~ 20 mm Hg

QUESTIONS

1. What is the A-V PO_2 difference in this resting muscle?
2. What is the A-V PO_2 difference in exercising muscle?
3. What happens to the A-V difference with exercise?
   A. increase
   B. decrease
   C. no change
4. During exercise, increased oxygen delivery to the muscle is accomplished by:
   A. increased blood flow
   B. increased extraction
   C. both
5. With exercise, which increases more in skeletal muscle, flow or metabolism?
6. How does flow versus metabolism change in the heart with exercise?
7. How does the A-V PO_2 difference in the renal circuit compare with the coronary circuit?
8. Assuming no effect on metabolism, what consequences does a vasodilatory drug have on the PO_2 A-V difference in resting skeletal muscle?
9. What are the direct effects of an a agonist on the A-V PO_2 difference in resting skeletal muscle?

ANSWERS

1. (Same for question 2.) The systemic arterial PO_2 is close to 100 mm Hg under resting conditions and does not change significantly during exercise.

   Thus, the resting A-V difference is:

   100 - 45 = 55 mm Hg

   During exercise, it will be:

   100-20 = 80 mm Hg

3. A. The greater extraction of oxygen during exercise increases the A-V difference.

4. C. During exercise, vasodilatory metabolites lower skeletal muscle vascular resistance, and flow increases. Increased flow means increased oxygen delivery. Even though flow increases, oxygen extraction increases. Therefore, C is the best answer.
5. If flow (oxygen delivery) kept pace with increased tissue demands during exercise, there would be no change in extraction; that is, if both flow and metabolism doubled, venous PO_2 would be unchanged. If metabolism increased more than flow, increased extraction would be necessary to meet tissue oxygen demands. Because extraction does increase in exercising muscle, there is a greater rise in metabolism than blood flow.
6. In the coronary circuit, oxygen extraction is close to the maximum under resting conditions. Therefore, increased extraction cannot be utilized effectively to meet any increased tissue oxygen demands. Flow must increase in proportion to metabolism in order to meet tissue demands. These two variables are directly proportional in the healthy heart.
7. In the coronary circuit, because oxygen extraction is maximal, there is a large A-V difference.

   i.e., PaO_2 = 100 mm Hg; coronary sinus PO_2 = 20 mm Hg

   A-V = 100 - 20 = 80 mm Hg

   The renal circuit is overperfused in terms of nutrient supply. Much more oxygen than is required flows through the renal circulation. Thus, less oxygen is extracted per ml of blood. Under these conditions, venous PO_2 will be higher than most systemic tissues. This will translate into a low A-V difference.
8. Vasodilation increases flow and oxygen delivery. If metabolism does not change, the amount of oxygen needed per unit of time remains unchanged. This oxygen will now be removed from a greater volume of blood. Thus, less oxygen is removed from each ml of blood, and the venous PO_2 will be higher. A higher venous PO_2 means a lower A-V difference.
9. The a agonist will constrict arterioles and reduce blood flow and oxygen delivery. The only way to maintain the same flow of oxygen to the tissue would be to increase extraction. This reduces venous PO_2 and increases the A-V difference.

Chapter Summary

The production of vasodiiatory metabolites best explains the control of blood flow in autoregulating systemic tissues.

Sympathetic adrenergic nerves represent the main control in extrinsically regulated systemic tissues.

Resting skeletal muscle exhibits extrinsic regulation, but exercising muscle autoregulates.

Mechanical compression of the intramyocardiai vessels restricts perfusion to the myocardium during systole.

Because oxygen extraction is almost complete from the blood perfusing the myocardium, coronary flow must match myocardial metabolism.

The main factor regulating cerebral blood flow is arterial carbon dioxide.

The cutaneous circulation exhibits extrinsic regulation, and flow responds to the need for heat exchange with the environment.

Normally, the kidney exhibits strong autoregulation but constricts, resulting in a loss in renal function, with a large decrease in blood pressure.

The passive, compliant nature of the pulmonary circuit minimizes changes in pulmonary pressures with large changes in cardiac output.

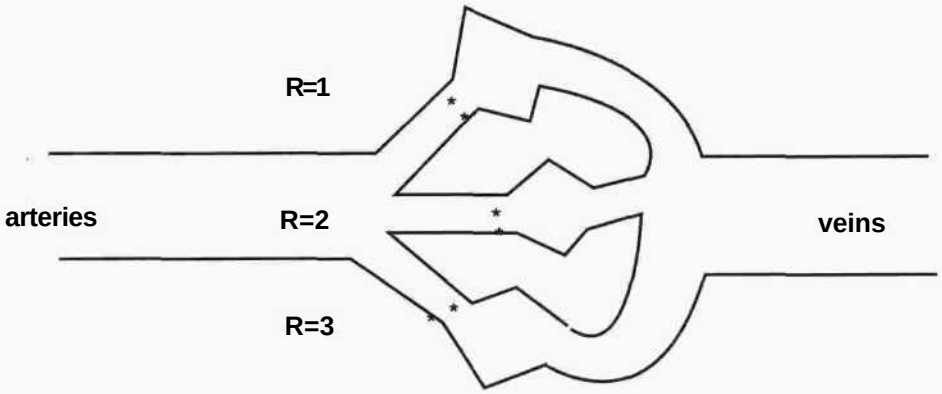
HEMODYNAMICS

Review Questions

DIRECTIONS: Select the one best answer.

1. Under which one of the following conditions is an increase in arterial pressure associated with a decrease in peripheral resistance?

A. when there is turbulence
B. when there is an increased hematocrit
C. when there is vasoconstriction
D. when there is vasodilation
u-E. when there is an increased cardiac output



2. In the above diagram, the resistance to blood flow in the three organs arranged in parallel are indicated. Calculate the total resistance in these vascular beds.

A. 9
v#. 6/11
C. 11/6
D. 3
E. 6

3. The variable that is most responsible for the change in resistance to blood flow in a healthy individual is the:

A. length of the vessel
B. viscosity
'-C. radius of the arterioles
D. radius of the aorta
E. radius of the capillaries

4. The cardiac output of an individual with the following hemodynamic status would be (liters/min):

Pulmonary arterial pressure = 24 mm Hg
Right atrial pressure = 2 mm Hg
Left atrial pressure = 4 mm Hg
Pulmonary vascular resistance = 2 mm Hg/liter/min
Systemic vascular resistance = 20 mm Hg/liter/min
HINT: Use values for pulmonary circuit.

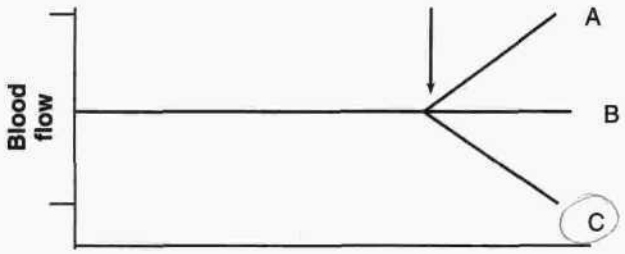
A. 1.0
B. 1.1
-C 10
D. 11
E. cannot be determined from the above information

MAP = CO · TPR

$CO = \frac{MAP}{TPR}$

$F = \frac{P_1 - P_2}{R}$

$\frac{24-4}{2}$



5. The above figure shows a recording of blood flowing through an organ at a constant perfusion pressure. At the arrow, the resistance to blood flow suddenly increases. Which tracing indicates the blood flow occurring after the increase in resistance?

6. Which of the following units would be correct for the measurement of resistance to flow?
   A. cmH_2O
   B. cm H_2O/hter/second
   C. cm H_2O X liter X second
   D. ml/min/mm Hg
   E. dimensionless (no units appropriate)

7. Calculate the total peripheral resistance of an individual from the following measured variables:

   100 = 5 · TPR

   Mean arterial pressure = 100 mm Hg
   Central venous pressure = 0 mm Hg
   Cardiac output = 5 L/min
   In peripheral resistance units (mm Hg/L/min), the total peripheral resistance of this individual is:
   A. 100
   B. 50
   C. **20**
   D. 5
   E. 2.67

DIRECTIONS: Choose the false statement for questions 8 to 11.

8. A. The vascular resistance of the lower extremities (or renal circulation) is lower than the resistance of the cutaneous vasculature of the left thumb (or coronary circulation).

   B. In a normal individual the compliance of the aorta is greater than the femoral artery (measured at a pressure close to 100 mm Hg).

   y/Q. The blood volume of the systemic veins is approximately equal to the blood volume of the entire pulmonary circulation.

   D. Doubling the radius of a vessel will alter resistance more than doubling the length of a vessel.

9. A. The large pressure drop across the arterioles is related to the large resistance in these vessels.

   ^"B. Proceeding from the aorta peripherally to the arterioles, resistance to flow will increase and total cross-sectional area will decrease.

   C. Adding a resistance in series will always increase the overall resistance in the system.

   D. Adding a parallel circuit to a given system will always decrease the resistance in the system.

10. A pattern of turbulent rather than laminar flow in a systemic artery:

   A. is more likely to occur in the aorta than in the femoral artery
   B. is more likely to occur when there is a reduction in blood viscosity, as in anemia
   C. results in a higher pressure gradient for a given flow
   ^•*D.* is associated with flow in distinct layers

11. The pressure gradient across a long tube with a flow of 5 L/min (mm Hg/L/min = PRU):

   A. would be 10 mm Hg if the resistance was 2 PRU
   B. would be less if a parallel circuit of high resistance was added
   C. would be lower if flow was lowered to 2 L/min
   \J>. would decrease if an 80% stenosis which raised resistance was added in the middle of the tube

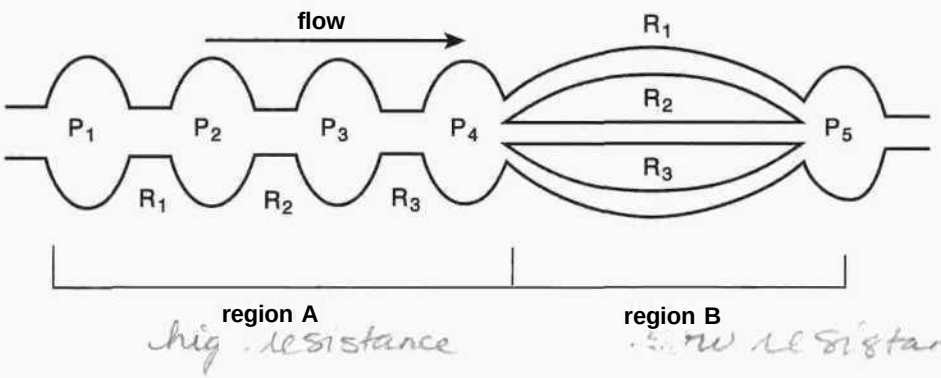
DIRECTIONS: Select the one best answer.

12. Turbulent flow in an artery can be induced by:

A. an increase in hematocrit
B. a decrease in velocity of blood
C. a decrease in diameter of the blood vessel
D. a decrease in the viscosity of the blood

13. In the diagram below, flow is constant, P = pressure, and R = resistance.

Rj in region A = Rj in region B, likewise R_2 in region A = R_2 in region B, R_3 in region A = R_3 in region B



high resistance low resistance

Which of the following statements is correct?

A. The total resistance of region A is the same as total resistance of region B.
B. The pressure drop across Rj ($P_j - P_2$) in region A will equal the pressure drop across all of region B ($P_4 - P_5$).
C. The pressure drop across region A ($P_j - P_4$) will equal the pressure drop across region B ($P_4 - P_5$).
D. MT P_4 will be less than P_3 but greater than P_5.

Flow goes from higher pressure to lower pressure

14. What would be the total resistance of the following three resistances in parallel with each other?

HINT: do not calculate, pick the best answer using your understanding of the consequences of resistances in parallel.

- resistance f: 0.2 PRU
- resistance g: 0.4 PRU
- resistance h: 0.2 PRU

A. 0.8 PRU
B. 0.4 PRU
C. 0.3 PRU
D. 0.2 PRU
•*J&,* 0.08 PRU

15. In going from a lying down to an upright position, the change in pressure will be greatest in which of the following vessels?

A. aorta
B. pulmonary artery
^C. femoral artery
D. subclavian artery (large artery, shoulder area)
E. pulmonary vein

16. The blood pressure of a person who is standing up is highest in the:

A. femoral artery
i-B. dorsalis pedis artery (an artery in the feet)
C. radial artery (an artery in the arms)
D. cerebral artery
E. aorta

17. A saccular aneurysm in the abdominal aorta is more likely to rupture than one in the normal aorta because:

A. more tension is exerted on the wall of the aneurysm
B. there is less pressure in the aneurysm
C. there is less turbulence in the aneurysm
D. there is more tension exerted on and less turbulence in the aneurysm
E. there is more pressure and less turbulence in the aneurysm

18. A 70-kg, 6-foot, normal, healthy subject standing quietly erect for 30 seconds has a mean arterial pressure of 100 mm Hg in the ascending aorta and a venous pressure of 2 mm Hg in the superior portion of the inferior vena cava. What is the pressure in the veins of the dorsum of the foot?

A. less than 0 mm Hg (i.e., below atmospheric pressure)
B. 2 mm Hg
C. 4 mm Hg
D. about 20 mm Hg
E. above 40 mm Hg

19. In a horizontal subject, the greatest pressure head (i.e., Pj - P_2) exists between the:

A. ascending aorta and the anterior tibial artery
B. anterior tibial artery and the anterior tibial vein
C. anterior tibial vein and the right atrium
D. pulmonary artery and the pulmonary vein
E. efferent renal arteriole and the renal vein

MICROCIRCULATION

Review Questions

DIRECTIONS: Select the ONE best answer.

Questions 1 and 2

In the following example, determine the filtration or reabsorption pressures in a capillary subjected to the following conditions:

capillary hydrostatic pressure at the arterial end = 30 mm Hg
capillary hydrostatic pressure at the venous end = 10 mm Hg

plasma oncotic (colloidal) pressure = 23 mm Hg
tissue hydrostatic pressure = 1 mm Hg
tissue oncotic pressure = 0 mm Hg

1. The capillary filtration pressure at the arterial end in mm Hg is:
   A. 2
   B. 4
   vG: 6
   D. 8

2. The capillary reabsorption pressure at the venous end in mm Hg is:
   A. 7
   B. 12
   US: 14
   D. 3

3. If the hydrostatic pressure in the capillary is 10 mm Hg, interstitial pressure is 2 mm Hg, colloid osmotic pressure of blood 25 mm Hg and interstitial fluid colloid osmotic pressure is 5 mm Hg, which of the following is correct for this situation?
   A. filtration with a net pressure of 18 mm Hg
   B. filtration with a net pressure of 12 mm Hg
   C. reabsorption with a net pressure of 18 mm Hg
   Y,B. reabsorption with a net pressure of 12 mm Hg

4. Net movement of fluid from the intravascular space to the interstitial space occurs with all the following conditions EXCEPT:
   A. constriction of postcapillary venules
   B. decreased plasma albumin concentration
   C. lymphatic obstruction
   Iff. constriction of precapillary arterioles
   E. activation of bradykinin

5. If the colloid osmotic pressure of the blood is 25 mm Hg and the interstitial fluid is 5 mm Hg and the hydrostatic pressures in the capillary and interstitial space are 20 and 0 mm Hg, respectively, which of the following statements is true?

   A. there is a net movement of fluid from the capillary to the interstitial space with a net pressure of 10 mm Hg
   B. there is a net movement of fluid from the capillary to the interstitial space with a net pressure of 5 mm Hg
   C. there is a net movement of fluid from the interstitial space to the capillary with a net pressure of 10 mm Hg
   D. there is a net movement of fluid from the interstitial space to the capillary with a net pressure of 5 mm Hg
   IE. filtration and reabsorption factors are balanced and no net movement of fluid across the capillary is occurring

6. Edema formation can occur from all of the following EXCEPT:

   A. an increase in interstitial fluid pressure
   B. an increase in venous pressure
   C. a increase in capillary filtration
   D. a decrease in plasma oncotic pressure

7. Lymph capillaries differ from systemic blood capillaries in that they:

   A. are less permeable
   B. are not lined by endothelium
   C. lack valves
   D. are absent in the central nervous system

8. Which of the following will not cause edema?

   A. decreased plasma concentration of albumin
   B. decreased venous pressure
   C. damage to capillary endothelium
   D. blockage of lymph ducts

9. A FALSE statement concerning fluid exchange across the microvascular bed is:

   A. fluid exchange follows the laws of pressure filtration across a semipermeable membrane
   B. fluid is filtered outward at the arterial end of the vascular bed
   C. edema occurs if the plasma protein concentration is reduced drastically
   D. edema occurs if the arterial blood pressure decreases

REGULATION OF ORGAN FLOW

Review Questions

DIRECTIONS: Select the ONE best answer.

1. Local control of the circulation predominates over neural control in which of the following organs?

   vA. brain
   B. skin
   C. skeletal muscle
   D. GI tract

2. During vigorous exercise, skeletal muscle blood flow increases tremendously. The circulatory adjustment most responsible for this change is:

   A. increased (3-adrenergic receptor stimulation in skeletal muscle blood vessels
   *-B. local vasodilation in skeletal muscle
   C. increased stroke volume
   D. increased cardiac parasympathetic stimulation

3. Which of the following represents exercising as opposed to resting skeletal muscle?

   A. lower lymph flow
   B. lower arteriovenous oxygen difference
   C. lower capillary hydrostatic pressure
   vB. lower vascular resistance

4. Which of the following best describes the pulmonary circulation?

   A. operation in parallel with the systemic circuit
   B. pressure is lower but resistance is higher than in the systemic circuit
   C. contains more than 80% of the individual's blood volume
   D. the ratio of flow in the pulmonary artery to flow in the aorta is normally 1.0

5. Which of the following is **least likely** to influence cerebral blood flow?

   A. PO_2 of the arterial blood
   B. cerebrospinal fluid pressure
   C. pH of the interstitial fluid of the brain
   D. PCO_2 of the arterial blood
   uE. vasomotor reflexes

6. Which of the following variables is most similar in the pulmonary circulation and the systemic circulation?

   A. mean arterial pressure
   B. resistance to flow
   C. capillary pressure
   <&. blood flow
   E. diastolic arterial pressure

7. The cause of the increased blood flow to skeletal muscles during exercise is:

   A. adrenal release of epinephrine
   B. increased resistance to flow in other muscles
   C. stimulation of cholinergic vasodilator nerves
   D. increased cardiac output
   K local production of vasodilatory metabolites

8. A hypothetical drug given intravenously caused a decrease in mean arterial pressure and at the same time a decrease in heart rate. Which of the following could explain the action of this drug? (If you cannot answer the question now, wait for the discussion of baroreceptors.)

   A. stimulation of fij and (3_2 receptors
   B. stimulation of a receptors
   C. blocking parasympathetic effects in heart muscle
   D. activating histaminergic receptors
   uE. increases in the firing rate of the baroreceptor nerves

DIRECTIONS: True or false (Questions 9-10).

9. An injection (IV) of epinephrine, which increases systemic arterial pressure and heart rate, will also result in an increase in coronary blood flow.

10. The ratio of diastolic coronary blood flow to systolic coronary blood flow is greater for the left than for the right coronary artery.

Questions 11 and 12: Select all the correct answers.

11. In the heart, brain, skeletal muscle, liver, kidney, and intestine, 1 minute of vascular occlusion is followed by which of the following changes when the occlusion is removed?
HINT: this is reactive hyperemia (check the two correct answers).
    1. a period of 15 to 30 seconds during which flow progressively increases to the preocclusion value
    2. a rapid (less than 2 seconds) return to the preocclusion flow
    3. a period of 15 seconds or more during which the flow is markedly higher than it was prior to occlusion
    4. a change in flow produced primarily by adrenergic sympathetic neurons
    5. a change in flow produced primarily by cholinergic sympathetic neurons
    6. a change in flow produced primarily by the accumulation of vasodilator metabolites
    7. a change in flow produced primarily by local heating of the tissue

12. The pulmonary circulation differs from the systemic circulation in that in the pulmonary circulation (check each correct statement):
    1 the veins do not contain an important reservoir of blood for the heart
    2. the arterial system is more distensible
    3. adrenergic sympathetic neurons are less important in controlling arteriolar and precapillary resistances
    4. the capillaries have a higher transmural pressure
    5. the arteries serve as more important blood reservoirs
    6. obstruction of blood flow is much more likely to cause a retrograde ventricular failure

13. Systemic arterial pressure in the adult is approximately six times that of pulmonary arterial pressure because (select the one best statement):
    A. left ventricular stroke volume is greater than right ventricular stroke volume
    B. systemic blood volume exceeds pulmonary blood volume
    C. systemic resistance exceeds pulmonary resistance
    D. pulmonary compliance exceeds systemic compliance
    E. intra-abdominal pressure exceeds intrathoracic pressure

14. During early ventricular systole, coronary blood flow:
    A. is more likely reduced at the subepicardial surface than the subendocardial surface
    B. is markedly reduced because the cusps of the aortic valve occlude the coronary arteries and therefore protect them from excess pressure
    C. in the left coronary artery goes to near 0 or below
    D. in the right coronary artery goes to near 0 or below
    E. is well characterized by all of the above statements

EXERCISE

Review Questions

Questions 1-5: Select the ONE best answer.

1. Which one of the following is most likely to occur in a healthy subject in response to running?

A. an increased coronary flow due to decreased cardiac adrenergic tone
B. a generalized increase in blood flow (i.e., in the kidneys, muscle, stomach, etc.) due to an increased cardiac output
C. both A and B occur during exercise
D. a decreased velocity of flow in the capillaries of the lungs
^E. a decreased cardiac parasympathetic tone

2. During strenuous running, the cardiac output of a subject increased fourfold, the systemic A-V oxygen difference changed from 4 to 12 volumes percent, and the mean pulmonary arterial pressure changes from 15 mm Hg to 18 mm Hg. Check each of the conclusions that can be drawn from this typical response to exercise.

A. The increased pressure was caused by an increased pulmonary resistance to flow.
B. The pulmonary artery blood had a lower PO_2 during exercise.
C. Changes in the pulmonary artery blood PO_2 are, for the most part, responsible for the changes in the pulmonary peripheral resistance.
D. None of the above are true.

3. Which of the following is most likely to occur in a healthy subject in response to strenuous running?

A. A decrease in.the ejection fraction of the ventricles
B. A decrease in the maximum dp/dt of the left ventricle
C. An increase in circulation time
D. A decrease in the systemic arteriovenous O_2 difference
E. An increase in the arterial lactate concentration

4. In a healthy subject, running is usually associated with a decrease in the end-systolic volume of the right and left ventricles and with an increase in their stroke volume. The mechanism for this response is probably the following:

A. Starling's law of the heart
B. an increase in sympathetic tone to the ventricles
C. an increase in parasympathetic tone to the ventricles
D. a decrease in venous return of blood to the heart
E. an increase in pulmonary and systemic resistance

5. Which of the following is **not** an important mechanism for increasing the blood flow to active skeletal muscle during exercise?

   A. an increased cardiac output
   B. an increased concentration of epinephrine in the vicinity of the blood vessels of active skeletal muscle
   C. an increased concentration of norepinephrine in the vicinity of the blood vessels of active skeletal muscle
   D. an increased concentration of acetylcholine in the vicinity of the blood vessels of active skeletal muscle
   E. the action of metabolites on skeletal muscle blood vessels

HEMODYNAMICS

Answers

1. AnsE This question relates to the formula MAP = CO X TPR. If there is a decrease in TPR and no other changes are occurring, blood pressure will decrease (Ans D). The only way to prevent a decrease in blood pressure if TPR decreases is to have a rise in cardiac output. This is what occurs during exercise. As skeletal muscle vessels dilate, the increase in cardiac output prevents a drop in blood pressure. If cardiac output rises more than the decrease in TPR, blood pressure will actually rise. In answers A, B, and C there will be an increase in resistance. Creating turbulence raises resistance and an increase in hematocrit increases viscosity. Viscosity affects resistance when there is laminar flow.

2. AnsB When resistors are connected in parallel, a low-resistance pathway is created. The total resistance will be lower than any of the individual resistances. Thus, the total must be lower than 1. Only one answer is a number lower than 1, therefore it must be the best answer. The actual calculation is shown in the hemodynamics section of the handout.

3.AnsC Although all of the factors listed will affect resistance, in the systemic circuit, resistance is varied by controlling the radius of the arterioles. Resistance is inversely proportional to the fourth power of the vessel radius.

4.AnsC To calculate cardiac output using systemic variables we must have mean arterial pressure and TPR to plug into the equation MAP = CO X TPR. The problem is we are not given MAP. Therefore we must calculate flow through the pulmonary circuit, which is also cardiac output. To do this, we must go back to the original equation:

$$F = \frac{P1-P2}{R}$$

Pj = pulmonary arterial pressure (24 mm Hg)
P_2 = is pulmonary venous or **left** atrial pressure (4 mm Hg)
R = pulmonary vascular resistance (2 mm Hg/liter/min)

5.AnsC The graph shows blood flow versus time. At the arrow, blood flow changes. In A there is an increase in flow, B shows no change in flow, and C, shows a decrease in flow. When resistance increases, flow goes down; therefore, C is the best answer.

6.AnsB If the hemodynamic equation is arranged with resistance on the left we have:

$$R = \frac{P1-P2}{F} = \frac{\text{pressure units}}{\text{flow units (volume/time)}}$$

Therefore, resistance units represent: pressure/volume/time
= cm H_2O/liter/second

7.AnsC The hemodynamic equation for the systemic circuit with resistance on the left side of the equation is:

$$TPR = \frac{MAP}{CO} = \frac{100 \text{ mm Hg}}{5 \text{ L/min}} = 20 \text{ mm Hg/L/min}$$

8. AnsC The blood volume of the systemic veins is greater than the blood volume of the pulmonary circuit. In answer A where the resistance of two different segments of the systemic circulation is involved, we simply compare the flows. The greater the flow a segment receives, the lower the resistance of the pathway. The renal circulation or the lower extremities receives more flow than the coronary circulation or the left thumb. Therefore, the renal circulation or lower extremities represents the lower resistance pathway. The aorta is the most compliant artery. The femoral is a more muscular and stiffer artery. Finally, radius is the most important factor determining the resistance of a vessel.

9.AnsB Proceeding peripherally from the aorta, resistance will increase, reaching a maximum in the arterioles. Also, cross-sectional area is increasing and reaches a maximum in the capillaries. Pressure is lost overcoming resistance, thus in answer A, a large pressure drop does occur across the arterioles because they are a high-resistance pathway. Adding a resistance in series increases the resistance of the system (high-resistance system), but when added in parallel, lowers the resistance of the system (low-resistance system).

10. **Ans D** Flow in layers is laminar flow. Disrupting the layers produces turbulence. The aorta is a larger diameter tube and has a higher velocity than the femoral artery, and because of this, turbulence is more likely to occur in the aorta (see factors that affect Reynolds number). Also, decreasing viscosity promotes turbulence. Any disruption of the laminar flow layers raises resistance, thus requiring a greater pressure to maintain a given flow.

11. Ans D All of these answers require the use of the hemodynamic equation:

Ans A 5 L/min = 10 mm Hg / 2 PRU. The statement is true.

Ans B If a parallel circuit was added to the system, the overall resistance would decrease, no matter what the resistance of that parallel circuit. If the resistance was less, then a smaller pressure would be required to maintain a flow of 5 L/min.

Ans C If the flow was decreased and the resistance remained unchanged, the pressure must be lower. If resistance is unchanged, the only way to lower the flow would be to lower the driving pressure.

12. Ans D Increasing the hematocrit will increase the viscosity, and this will promote laminar flow. Decreasing the viscosity as in answer D will promote turbulence. Both an increase in diameter and an increase in velocity will promote turbulence.

13. Ans D In region A, the three resistors are connected in series and thus represent a high-resistance pathway. In B they are connected in parallel and thus represent a low-resistance pathway. Ans A: In region A, because the resistors are connected in series, it will represent a greater resistance than region B. Ans B and C: Since pressure is lost overcoming resistance, most of the pressure decrease will be in region A. Rj in region A will be a greater resistance than all of region B, so a greater pressure drop will occur in Rj in region A. Ans D: This simply states that pressure decreases as we go downstream. This must be the case no matter what system we are dealing with because flow goes from a higher pressure to a lower pressure.

14. **Ans** E When resistors are connected in parallel, a low-resistance pathway is produced. The total resistance must also be lower than the lowest individual resistance in the circuit. In this circuit, the total resistance must be much lower than 0.2 PRU. There is only one answer lower than 0.2, Ans E. Therefore, this must be the best answer.

15. **Ans** C When going to an upright position, all vessels not at heart level will have a significant change in pressure. Those above the heart will lose pressure and those below the heart will gain pressure. This is a gravity effect, and the farther a vessel is from the heart vertically, the greater the change in pressure. Of the vessels listed, the femoral artery is the farthest from heart level and thus will have the greatest change in pressure. The femoral artery and vein will have an equal change in pressure since they are the same distance below the

heart. The above analysis will not work well for veins above heart level for reasons given in class.

16. **Ans** B The greatest pressure in an upright individual will be in the artery farthest below heart level. Of those listed, the artery in the foot is farthest below heart level and is thus the best answer.

17. **Ans** A Tension in the wall of a vessel represents a force which, if large enough, will cause the wall to rupture. In blood vessels, the source is the pressure inside the vessel, but the magnitude of wall tension also depends upon the radius of the vessel. The relationship is: T oc p X r. At a given pressure, the greater the vessel radius the greater the wall tension. Thus, because an aneurysm has a greater radius, it will have a greater wall tension and is more likely to rupture than the surrounding normal aorta.

18. **Ans** E In an upright individual, proceeding from the right atrium to the foot in the venous system, pressures will increase due to gravity. The main point here is that it is a fairly **large** increase. Thus, answers A, B, or C are not even reasonable choices. D and E are the only possibilities. If you have some idea of the magnitudes involved you should recognize that answer E is the better answer of the two possibilities.

19. **Ans** B We are looking for the largest difference between two pressures. This individual is horizontal; therefore gravity is not a factor. In choice A the aorta will have a pressure close to 100 mm Hg and because the systemic arteries are a low-resistance pathway there will be little change in pressure as we move to a smaller peripheral artery. Therefore, the difference will be only a few mm Hg, a very **small** number. However, in choice B we are going from a systemic artery to a systemic vein, which means we pass through arterioles. Arterioles are a high-resistance pathway and therefore produce a dramatic pressure decrease. The difference in pressure between a systemic artery and vein should be a **large** number (possibly 95 - 10 = 85). The systemic veins, like the arteries, represent a low-resistance pathway, and there should be only a small decrease in pressure between a peripheral vein and the right atrium. The pulmonary circuit is a low-pressure circuit, and the difference in pressure between the pulmonary artery and vein will be a much smaller number (15-5 = 10 mm Hg) than between an artery and vein in the systemic circuit. Finally, in choice E the efferent arteriole is downstream from the afferent arteriole, which means pressure is already below 100 mm Hg, thus the difference between the efferent arteriole and the renal vein must be a smaller number than that obtained in choice B.

MICROCIRCULATION

Answers

LAnsC This calculation requires the capillary hydrostatic pressure at the arterial end. The following would be the appropriate numbers and signs:

P_c = 30 (+)
P_{IF} = 1 (–)
π_c = 23 (-)
π_{IF} = 0 (+)

answer = +6 mm Hg

2. Ans C Here P_c will be the hydrostatic pressure at the venous end of the capillary. The following will be the numbers and signs:

P_C = 10 (+)
P_{IF} = 1 (–)
π_c = 23 (-)
π_{IF} = 0 (+)

answer = -14 mm Hg

A major aspect of these two questions is that the hydrostatic pressure decreases from the arterial to the venous end of the capillary. Thus, filtration at the beginning of the capillary can change to reabsorption at the end of the capillary.

3. Ans D The appropriate numbers and signs are:

P_c = 10 (+)
P_{IF} = 2 (-)
TT_C = 25 (-)
TT_{IF} = 5 (+)

answer = -12 mm Hg

4. Ans D Net movement from the intravascular space means filtration.

A. Constriction of postcapillary vessels would raise capillary hydrostatic pressure and promote filtration.
B. Decreased plasma proteins would lower plasma oncotic pressure, which is a force that promotes reabsorption. Thus, this would also promote filtration.
C. A small amount of protein is continuously leaking into the interstitium. Lymphatic obstruction would prevent the washout of these interstitial proteins. They would then accumulate in this compartment and raise interstitial colloid osmotic pressure, a force which promotes filtration.
D. Constriction of precapillary arterioles would lower hydrostatic pressure in the capillary. This would decrease filtration.
E. Bradykinin is a vasodilator. Dilating a systemic vascular bed, which means dilating arterioles upstream from capillaries, raises capillary hydrostatic pressures and promotes filtration.

5. **Ans** E The appropriate numbers and signs are:

P_c = 20 (+)
P_{IF} = 0 (–)
π_c = 25 (-)
π_p = 5 (+)
answer = 0 mm Hg

The forces are balanced and hence no net fluid movement occurs across the capillary wall.

6. **Ans** A Anything that promotes filtration promotes edema formation.

A. Pressure in the interstitial fluid promotes reabsorption, not filtration and is thus the correct answer.
B. An increase in venous pressure will raise capillary hydrostatic pressure and promote filtration.
C. Capillary filtration promotes edema formation.
D. Plasma proteins promote fluid reabsorption or fluid retention in the capillary. If the concentration of plasma proteins decreases, more fluid will be filtered.

7. **AnsD** Lymph capillaries are more permeable than systemic capillaries (they pick up interstitial proteins readily), are lined by endothelium, and have valves which promote a unidirectional flow. However, lymphatics are not present in the central nervous system.

8. **Ans** B A decrease in venous pressure will always tend to lower capillary pressure upstream and thus will decrease filtration. A rise in venous pressure will do the opposite. In many cases the development of peripheral edema can be traced to elevated venous pressures.

9. **Ans** D It is unlikely that if blood pressure drops, peripheral edema will develop. A decrease in blood pressure will generally cause a reflex peripheral vasoconstriction. The constriction of arterioles will lower capillary hydrostatic pressure and, if anything ,cause an increase in fluid reabsorption from the interstitium.

REGULATION OF ORGAN FLOW

Answers

1. **AnsA** The best answer for local control of blood flow is the cerebral circulation. The other circulations listed all have significant sympathetic adrenergic control.

2. AnsB The vasodilation and increased blood flow to exercising muscle is mainly via the local production of vasodilatory metabolites. Circulating epinephrine will stimulate P_2 receptors to contribute to the vasodilation. There is only a small increase in stroke volume during exercise, and cardiac parasympathetic stimulation would tend to decrease cardiac output and flow to the periphery.

3. **Ans** D Exercising muscle is vasodilated and thus has a lower vascular resistance. The vasodilation raises capillary pressure, filtration, and lymph flow. Since extraction of oxygen increases, there will be a greater A-V oxygen difference.

4. **Ans** D The systemic and pulmonary circuits are connected in series and thus the flow must be equal in the two circuits. Since the flows are the same, the flow ratio must be 1.0. The pulmonary circuit is a low-pressure, high-flow circuit and consequently must be maintained as a low-resistance pathway. Most of our blood volume is in the systemic circuit.

5. **AnsE** The cerebral circuit is a chemically regulated circuit, mainly responding to changes in arterial PCO_2. Nervous reflexes do not affect this circulation under normal conditions, thus the best answer is E.

6. **Ans** D The systemic and pulmonary circuits have very different characteristics except for flow. This must be equal in the two circuits, because they are connected in series.

7. **Ans** E The best answer is always the local production of vasodilatory metabolites. The second best answer, and it is a close second, is an increase in cardiac output. Answers A and B do provide a small contribution but are not major players.

8. **Ans** E Stimulation of (3_2 receptors will cause a vasodilation and a decrease in blood pressure, but fij stimulation will produce an increase in heart rate. Stimulation of a receptors will produce a vasoconstriction and raise blood pressure. Blocking parasympathetic effects on the heart will raise heart rate. Histaminergic receptors vasodilate and lower blood pressure, but the decrease in blood pressure would cause a reflex increase in heart rate. If a drug increased the firing rate of the baroreceptor nerves, that would be a signal to the brain that blood pressure was rising. The response would be to decrease sympathic outflow and increase parasympathetic outflow. This would lower blood pressure and heart rate.

9. **Ans True** Coronary flow is directly proportional to the work of the heart. Anything that increases the pumping action of the heart increases myocardial metabolism and the production of vasodilatory metabolites. The additional flow is necessary to supply more oxygen and nutrients to the tissues. An increase in blood pressure and heart rate means an increase in the pumping action and work of the heart.

10 **Ans Tine** Because of the severe mechanical compression of the left coronary circulation during left ventricular systole, very little blood flows to the left ventricular myocardium during this period. Systolic compression of vessels perfusing the right ventricular is less, permitting more flow during systole. Thus, because perfusion of the left ventricular myocardium is almost completely a diastolic process, it will have a greater diastolic to systolic ratio than the right ventricle.

11. **Ans** 3,6 In these tissues occlusion causes the accumulation of vasodilatory metabolites, which relax arteriolar smooth muscle. As a result, when the occlusion is released, flow increases to a value much higher than the preocclusion level. As the vasodilatory metabolites are washed out, flow gradually returns to the original level.

12. **Ans** 2,3>5 The pulmonary circuit is a very compliant circuit that serves as an important blood reservoir. This includes the arteries and the veins. It is also a passive system with little if any adrenergic control (sympathetics control airway smooth muscle). The low pressures in this circuit means a low capillary pressure, which is important to prevent significant filtration to the interstitium. Finally, the pulmonary circuit acts as a filter to prevent **small** clots from reaching the systemic circuit. A clot that reaches and lodges in the coronary circuit is a real threat to ventricular function.

13. **Ans** C Pressure is determined by flow and resistance. The flows in the systemic and pulmonary circuits are the same, therefore the reason for the higher pressures in the systemic must be due to the fact that it is a higher resistance pathway.

14. **Ans** C Because of the severe mechanical compression of the coronary vessels, flow to the left ventricle is close to zero during systole. The compression is most prominent in the subendocardium and decreases in magnitude toward the subepicardium. Because there is less compression in the subepicardium, more flow reaches this region during systole.

EXERCISE

Answers

1.AnsE The increased cardiac performance is facilitated not only by an increased sympathetic activity but by a decreased parasympathetic activity. The increased coronary flow is due to vasodilatory metabolites, and there is not a generalized increase in flow to systemic tissues but a selective increase to specific tissues. The increased blood flow through the pulmonary circuit also increases velocity. The increased velocity means blood spends less time in capillaries and thus less time is available for the exchange of O_2 and CO_2.

2.AnsB Since exercising muscle extracts more oxygen from blood, systemic venous PO_2 falls. Pulmonary arterial blood has the same composition as systemic venous blood. The increased pulmonary pressure was due to an increase in cardiac output. The passive stretch of the pulmonary vessels, caused by the increasing pressure, decreases pulmonary resistance and minimizes the increase in pulmonary pressures.

3.Ans E In strenuous running, skeletal muscle often becomes anaerobic and produces lactic acid. There is an increase in ejection fraction and dp/dt because of the increased contractility. Circulation time is decreased because of the increase in velocity in the circulation, and an increase in A-V O_2 difference occurs because of the increased extraction of oxygen in the exercising muscles.

4. **Ans** B The increased sympathetic tone to the ventricles increases contractility. Increased contractility is associated with an increased ejection fraction. This will tend to increase stroke volume, but in exercise, the increased venous return will also contribute to the increased stroke volume.

5. **Ans** C The arterioles of exercising muscle become unresponsive to norepinephrine. Thus, in the exercising muscle, sympathetic adrenergic activity plays **no** role in blood flow regulation. An increase in cardiac output is an important mechanism that maintains high blood flow in exercising muscle. Circulating epinephrine can activate (3_2 receptors and **contribute** to the elevated flow to exercising muscle. There are some sympathetic cholinergics that innervate skeletal muscle blood vessels. When activated, they would produce a vasodilation. The **main** mechanism that increases flow to exercising muscle is the production of vasodilatory metabolites.

SECTION IV

Skeletal Muscle

Excitation-Contraction Coupling

1

SKELETAL MUSCLE STRUCTURE-FUNCTION RELATIONSHIPS

Ultrastructure of a Myofibril

Figure IV-1-1 shows the basic organization of the sarcomere.

Contraction will produce the following:

A band: no change in length

I band: shortens

H zone (band): shortens

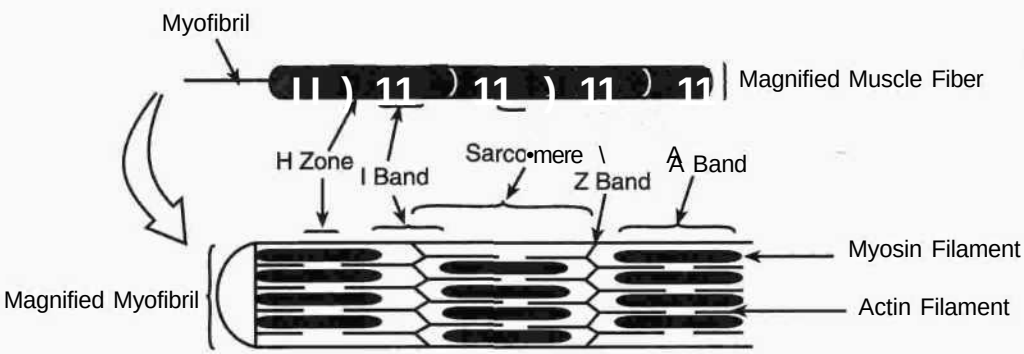


Figure IV-1-1

What the USMLE Requires You to Know

- Functional organization of the sarcomere
- Structural versus regulatory proteins of the thin and thick filaments
- The role of the two main ATPases involved in muscle contraction
- The sequence of events in excitation-contraction coupling
- Cross-bridge-actin interactions during muscle contraction

Ultrastructure of the Sarcoplasmic Reticulum

The external and internal membrane system of a skeletal muscle cell is displayed in Figure IV-1-2.

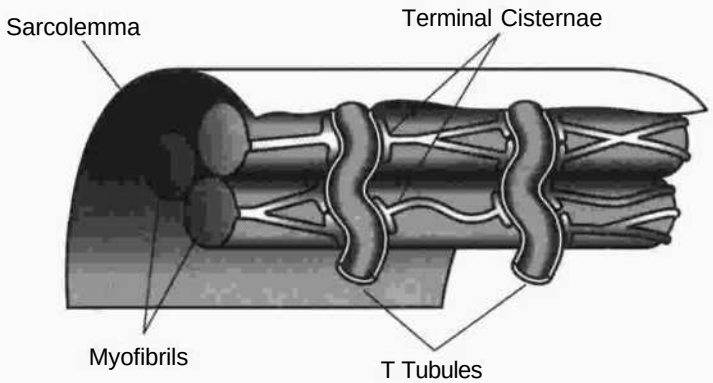


Figure IV-1-2

The T-tubular membranes are extensions of the surface membrane, and therefore the interiors of the T tubules are part of the extracellular compartment——

The saKx»plasrnic reticiihirn is part of the intemaljnembrane system, one function of which is to store calcium. In skeletal muscle, most of the calcium is stored in the terminal cisternae close to the T-tubular system.

Extracellular Ca^{2+} does not play a role in muscle contraction.

Dihydropyridine receptors

Organization of the Thin and Thick Filaments

Figure IV-1-3 shows the relationships among the various proteins that make up the thin and thick filaments and the changes that occur with contraction.

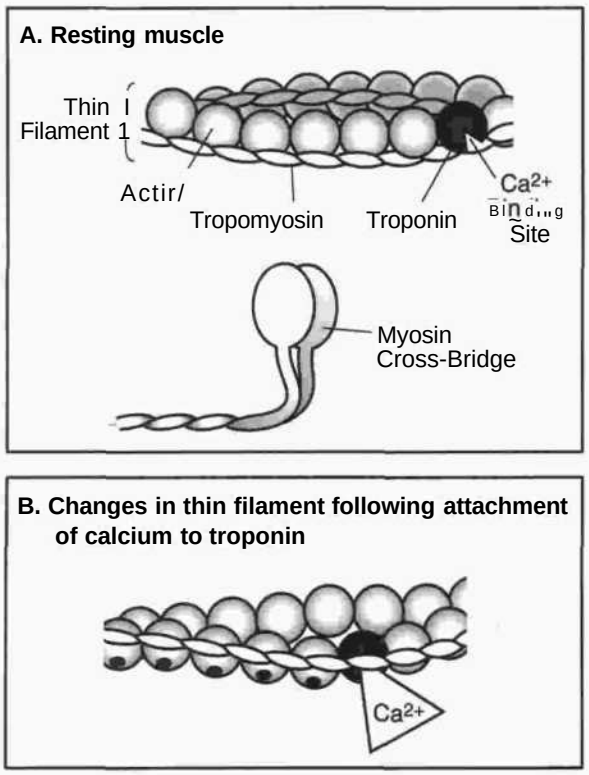
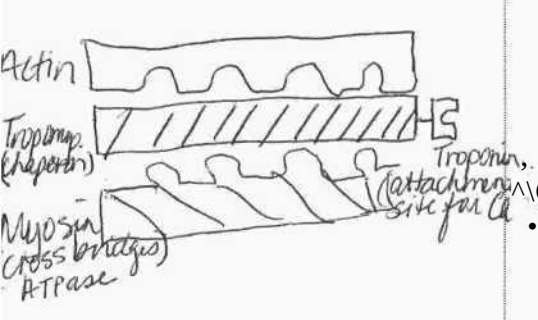


Figure IV-1-3



Proteins of the Thin Filaments

Actin

The structural protein of the thin filament

Possesses the attachment sites for the cross-bridges

Tropomyosin

Covers or makes the attachment sites of the cross-bridges unavailable in resting muscle

Troponin

Binds calcium

- Under resting conditions, no calcium is bound to the troponin, and the attachment sites on the actin are unavailable for cross-linking.
- Early in the contraction process, calcium attaches to the troponin, and it remains attached during cross-bridge cycling.
- When calcium binds to troponin, the troponin-tropomyosin complex moves, making the attachment sites for the cross-bridges on the actin available for cross-linking with myosin cross-bridges.
- Contraction is terminated (cycling is terminated) when calcium is removed from the troponin.

Proteins of the Thick Filaments

Myosin

Possesses the cross-bridges that can attach to the actin of the thin filaments

Cross-bridges possess ATPase activity.

The energy released from the breakdown of ATP on the cross-bridges during contraction is used to power the mechanical aspects of contraction.

This can be in the form of active tension and/or active shortening of the muscle.

Cross-Bridge Interactions (Chemical-Mechanical Transduction)

Figure IV-1-4 illustrates the major steps involved in cross-bridge cycling in a contracting muscle.

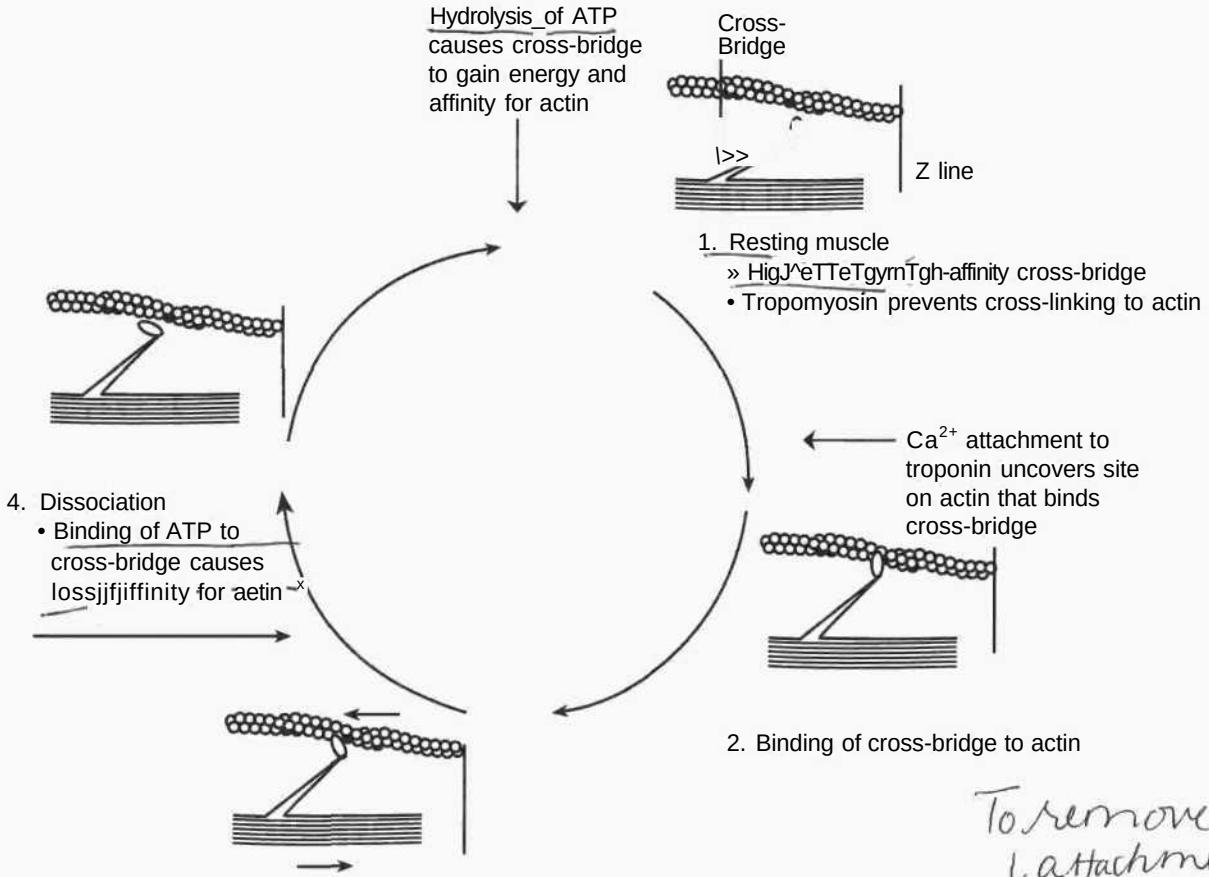


Figure IV-1-4

Contraction is the continuous cycling of cross-bridges.

Cycling starts when free calcium is available and attaches to troponin.

ATP is not required to form the cross-bridge linking to actin but is required to break the link with actin.

To remove Ca^{2+}
1. attachment of Ca^{2+} no ATP involved
2. removal of Ca^{2+} ATP is involved

1 contraction
2 PO_4 bonds broken
ATP → ADP → AMP

Every time a cross-bridge completes a single cycle, one ATP is hydrolyzed. This provides the energy for the mechanical aspects of contraction, that is, active shortening and/or the development of active tension.

Cross-bridge cycling continues (contraction continues) until there is either:

Withdrawal of Ca^{2+}: cycling stops at position 1 (normal resting muscle)

or

ATP is depleted: cycling stops at position 3 (rigor mortis). This would not occur under physiological conditions.

Intracellular Contraction-Relaxation Steps

Sequence

The action potential initiated at the neuromuscular junction travels over the surface of the skeletal muscle cell and down the_XJg|ples, where it terminates. The action potential does not spread across the surface of the sarcoplasmic reticulum, which is an internal membrane system.

41

Activation of djhydropyridin^recepjors in the T-tubular membrane. These receptorsjuncti^as volta^sensorsjhat pull the functional foot processes away from the ryanodine calcjunw-elease channels in the sarcoplasmic reticulum (Figure IV-1-5).

↓Ca^{2+}: motor neurons become hypersensitized => Threshold ↓ ↑action pot.#s → tetany

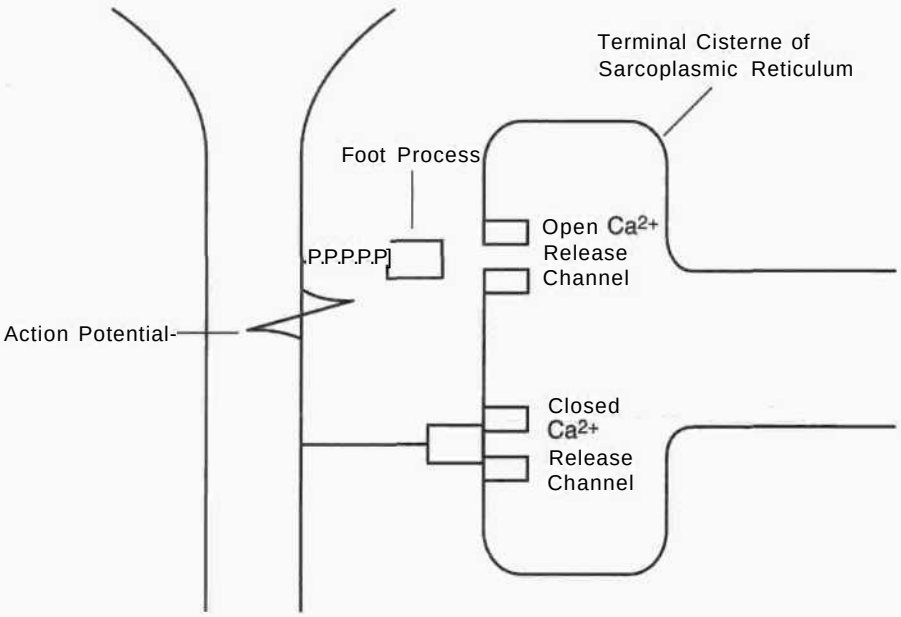


Figure IV-1-5

⇓

Calcium, which is stored in the sarcoplasmic reticulum (mainly terminal cisternae), is released into the intracellular environment and diffuses toward the troponin.

⇓

Calcium binds to the troponin, causing the tropomyosin to move and expose the attachment sites for the myosin cross-bridges. As long as the calcium remains attached to the troponin, the cross-bridge attachment sites remain available, and cross-bridge cycling continues. The ATP broken down on the cross-bridges produces energy that is utilized for the production of active tension and/or the active shortening of the muscle.

⇓

Contraction is terminated (cycling is terminated) by the pumping of the calcium back into its storage depot inside the sarcoplasmic reticulum. This is an energy-dependent active process. This is the normal process of muscle relaxation and ends with the actin and myosin not connected by cross-bridges.

DiGeorge 3rd/4th pharyngeal pouch hypocalcemia

Important Points

Two ATPases are involved in contraction:

- Myosin ATPase: supplies the energy for the mechanical aspects of contraction
- Sarcoplasmic calcium-dependent ATPase: supplies the energy to terminate contraction
- Therefore, both contraction and the process of relaxation are active events.

The source of the calcium that binds to the troponin in skeletal muscle is solely from the cell's sarcoplasmic reticulum.

- No extracellular calciumjs involved.
- The surface membrane of skeletaTmuscle does not possess voltage-gated calcium channels (this is not true for cardiac and smooth muscle).

ELECTRICAL VERSUS MECHANICAL EVENTS

Mechanical Response Elicited by Induction of a Single Action Potential

Figure IV-1-6 illustrates the mechanical contraction of skeletal muscle and the action potential on the same time scale.

1. Action Potential Duration is very narrow
2. Large time gap b/t action pot. & contraction of muscle

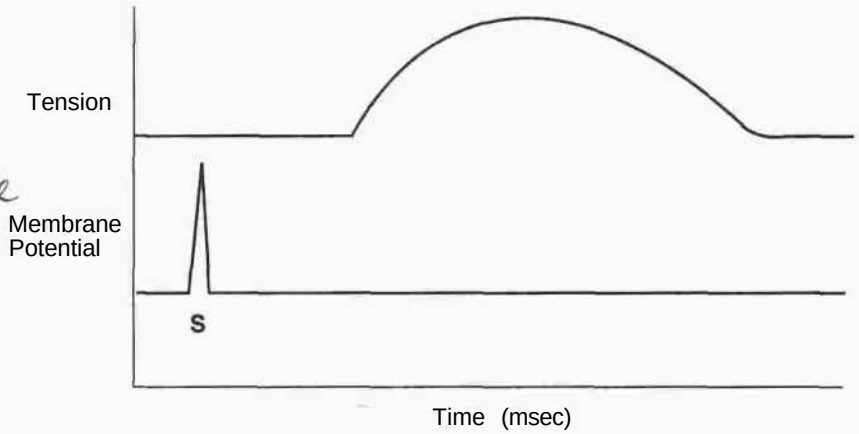


Figure IV-1-6

Because the electrical event (action potential) precedes the mechanical event and the refractory period has a very short duration, multiple action potentials can occur during the mechanical event.

- Increasing the frequency of action potentials causes the release of more calcium from the sarcoplasmic reticulum and the cycling of more cross-bridges for a longer period of time. This increases the magnitude of the mechanical response.
- Complete tetanus is obtained when sufficient free calcium is available for continuous cycling of all available cross-bridges.

Mechanical Response Elicited by Induction of Multiple Action Potentials

The mechanical response of increasing the frequency of action potentials is shown in Figure IV-1-7. This figure also demonstrates skeletal muscle wave summation and tetany resulting from increasing free intracellular calcium.

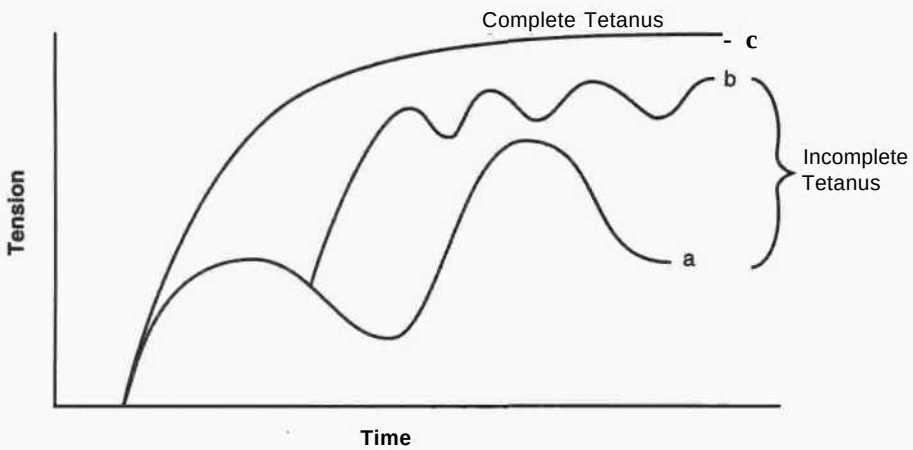


Figure IV-1-7

Complete tetanus will occur whenever the contractile machinery is saturated with calcium.

Chapter Summary

Actin is the structural protein of the thin filaments. The regulatory proteins are tropomyosin and troponin, which binds calcium. These proteins determine the availability of cross-linking sites on the thin filaments.

By definition, contraction is the continuous cycling of cross-bridges.

The passive release of calcium from the sarcoplasmic reticulum initiates cross-bridge cycling, and its active pumping (calcium-dependent ATPase) back into the sarcoplasmic reticulum terminates cycling.

The hydrolysis of ATP by the myosin ATPase provides the energy for the mechanical aspects of contraction.

Saturation of the skeletal muscle cell with free calcium causes tetanus, which is simply the continuous cycling of all available cross-bridges.

Skeletal Muscle Mechanics

2

PRELOAD AND AFTERLOAD

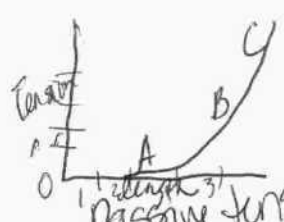
Preload

Preload is the load on a muscle in a relaxed state, that is, prior to contraction. Applying preload to muscle does two things:

- Causes the muscle to stretch. The greater the preload added, the greater the stretch of the muscle. Along with stretching the muscle, preload stretches the sarcomere. **Tjie greater the preload, the greater the pre-stretch of the sarcomere.**
- Causes the muscle to develop passive tension. If a 2-g weight is suspended from a muscle, a 2-g force also develops within that muscle. This force is the passive tension. **The^reaterthepreload,the greaterthepassive tension in the muscle.**

In muscle mechanics, there are two types of tension:

- Passive tension: produced by preload prior to contraction
- Active tension: produced by cross-bridge cycling during the process of contraction



TT
↓
PT + AT

1. ↑ length of m.
2. ↑ availability of cross bridges

A. What is preload of muscle at pt. A
B.
C

What the USMLE Requires You to Know

- Preload versus afterload
- Length-tension relationships in isolated muscle and their application *in vivo*
- Isometric versus isotonic contractions
- Characteristics of white versus red muscle
- Similarities and differences among skeletal, cardiac, and smooth muscle

Passive tension - tension in muscle before it contracts (preload) always some tension

Active tension -

Total tension

Afterload

Afterload is the load the muscle is working against or trying to move during stimulation.

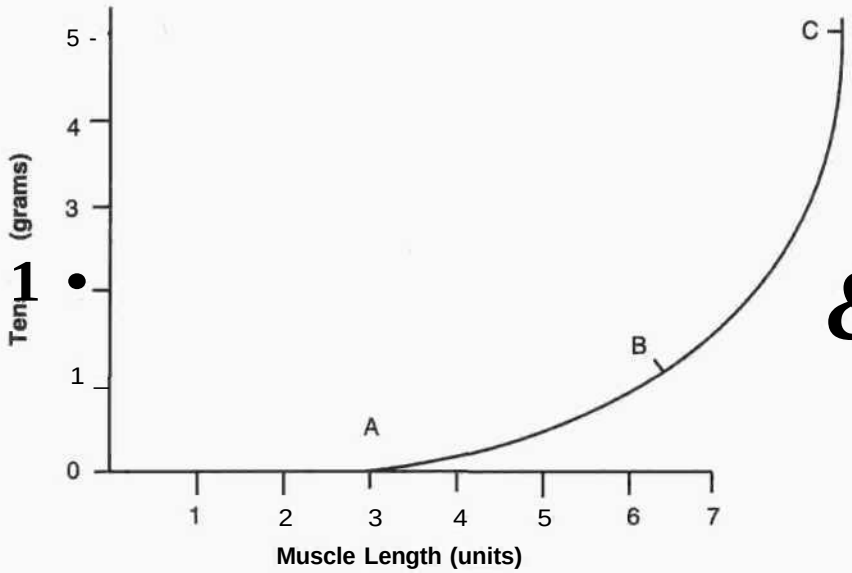
If the muscle is trying to lift 100 lb. during stimulation, then the after load is 100 lb. During contraction, the muscle does not necessarily lift or move the afterload.

LENGTH-TENSION CURVES

Length-tension curves are important in understanding how both skeletal and cardiac muscle function. The graphs that follow are all generated from skeletal muscle *in vitro,* but the information can be applied to both skeletal muscle and heart muscle *in vivo.*

Preload-Length Tension Curve

Figure IV-2-1 shows that resting skeletal muscle acts as a simple spring. As preload is added, the muscle stretches and develops a passive tension. The passive tension can be considered an internal force that opposes and equals the preload force.


Tension (grams)
5
4
3
2
1
0
A
B
C
1
2
3
4
5
6
7
Muscle Length (units)

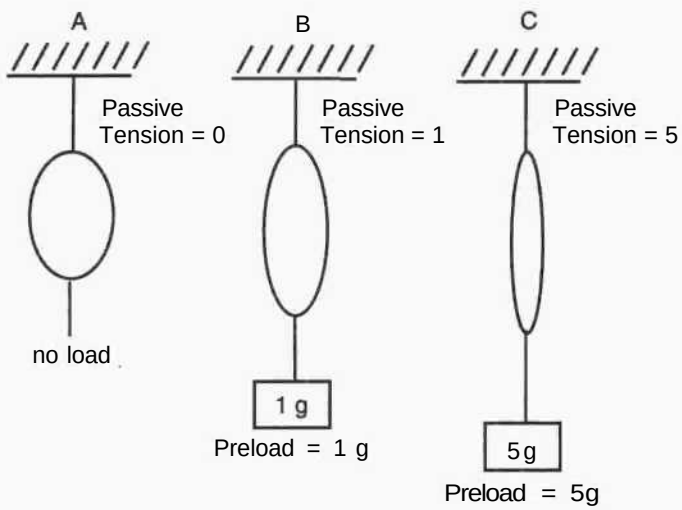

A
B
C
Passive Tension = 0
Passive Tension = 1
Passive Tension = 5
no load
1 g
Preload = 1 g
5g
Preload = 5g

Figure IV-2-1

ISOMETRIC TETANIC CONTRACTION OF THE ISOLATED SKELETAL MUSCLE

During an isometric contraction, the cross-bridge cycling will produce active tension, but the overall muscle length will not change.

The muscle does not shorten and lift the afterload because the afterload is greater than the total tension in the muscle during contraction.

Effect of Calcium Ion

In a tetanic isometric contraction, the intracellular environment is saturated with free calcium.

- In skeletal muscle, all of the free calcium is from calcium stored in the sarcoplasmic reticulum.
- Under these conditions, all the cross-bridges that can cycle with sites on the actin will be continuously cycling.

Active Tension Development

The active tension developed during a tetanic isometric contraction is proportional to the number of these cross-bridges that cycle.

- The more cross-bridges that cycle, the greater the developed active tension.

Total Tension

The preload creates a passive tension prior to contraction, and cross-bridge cycling during contraction adds an active tension component.

The total tension in the active muscle is the passive or preload tension plus the active tension.

The preceding is illustrated in Figure IV-2-2. The numbers presented for both passive and active tension are for illustrative purposes only.

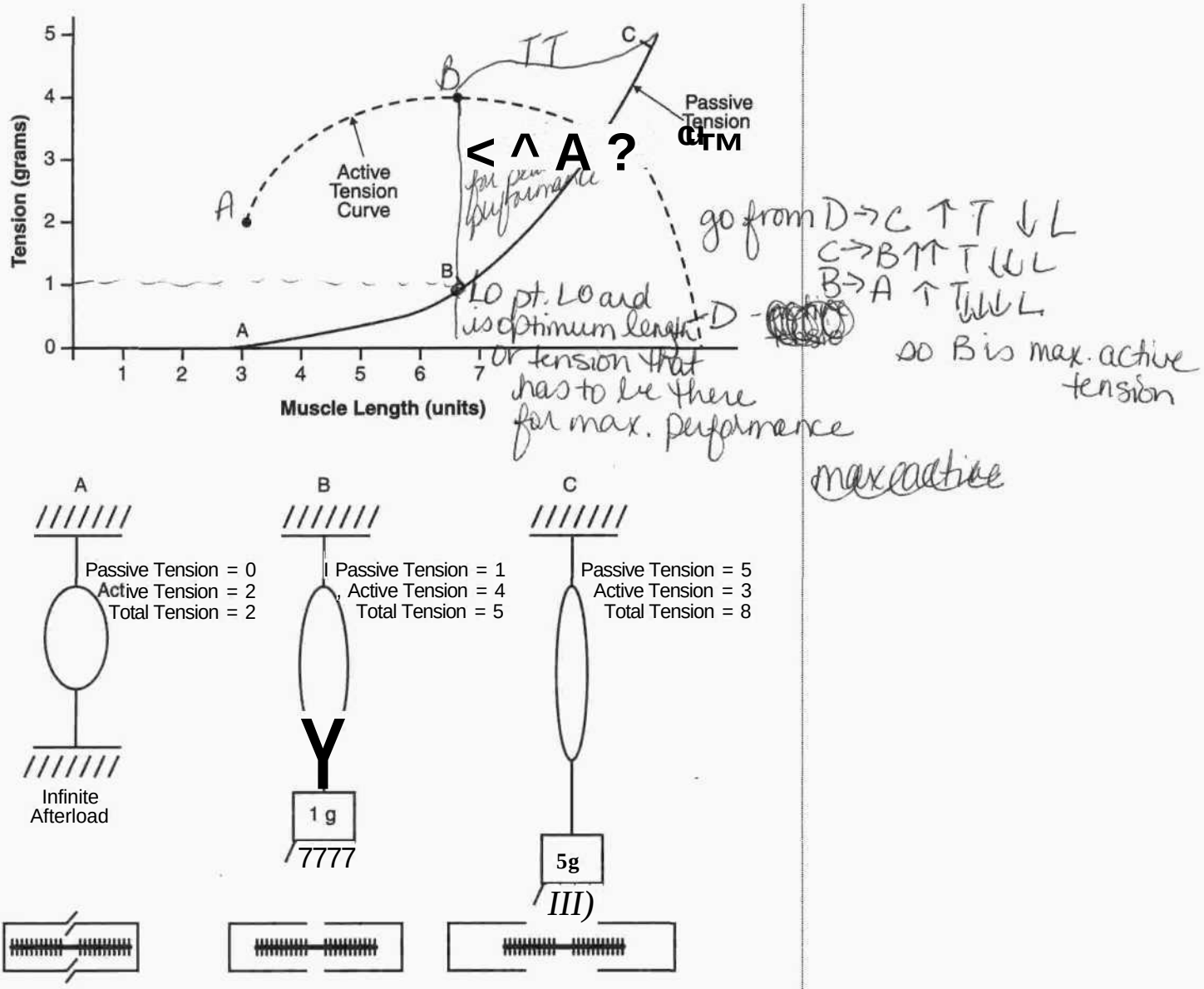

Tension (grams)
Muscle Length (units)
Active Tension Curve
Passive Tension
A
B
C
Infinite Afterload
Passive Tension = 0
Active Tension = 2
Total Tension = 2
Passive Tension = 1
Active Tension = 4
Total Tension = 5
Passive Tension = 5
Active Tension = 3
Total Tension = 8
1 g
5g

Figure IV-2-2

Muscle Length Versus Tensions

Figure IV-2-3 illustrates the passive, active, and total tension curves for isolated skeletal muscle. L_o designates the ideal prestretch length *in vivo.*

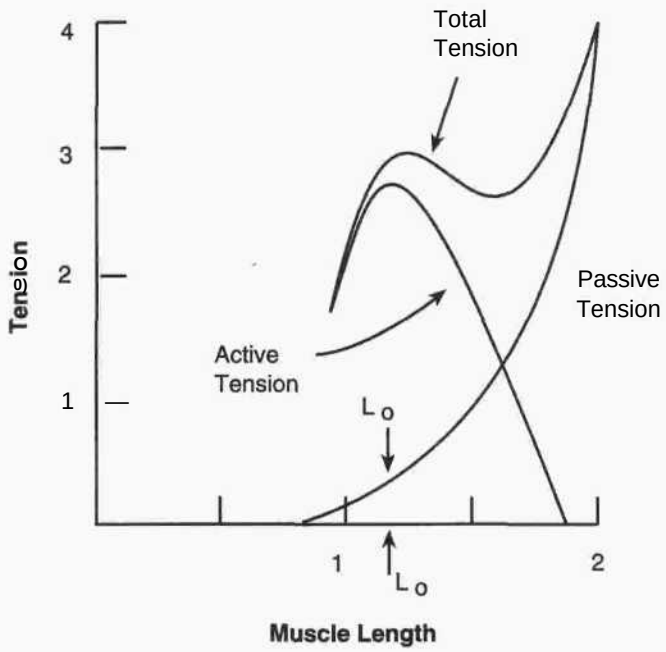


Figure IV-2-3

The passive curve is a function of the length of the relaxed muscle. The active tension curve (maximal isometric contraction) is a function of the number of cross-bridges that are capable of cross-linking with the actin. The total tension curve is simply the sum of the passive and the active curves.

Sarcomere Stretch Versus Active Tension

Figure IV-2-4 shows the active tension curve and the dependence of active tension on the overlap of the actin and myosin filaments.

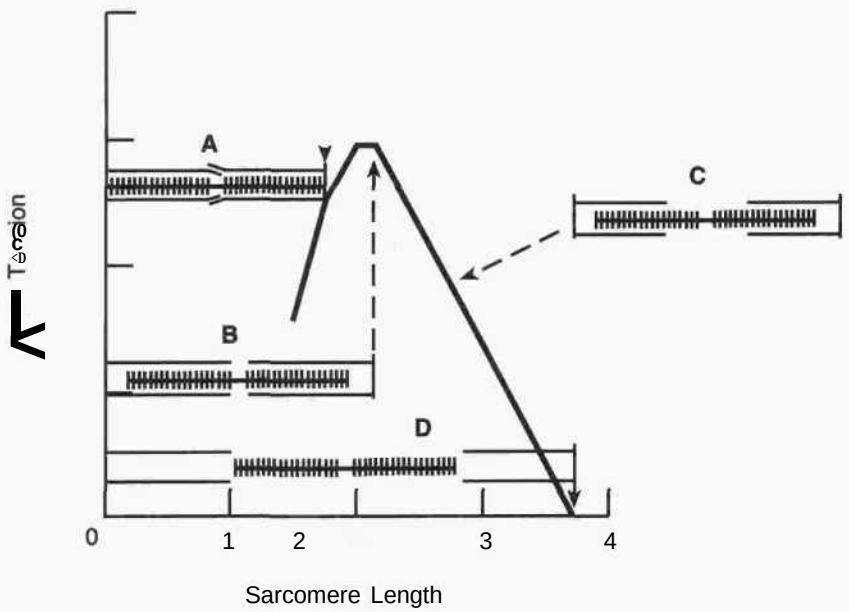


Figure iV-2-4

Sarcomere A: With no prestretch, the actin filaments obstruct one another, preventing some cross-bridge cycling during contraction.

Sarcomere B: The initial prestretch of the sarcomere produces the ideal relationship between the actin and myosin filaments so that if sufficient calcium is available, all the cross-bridges would cycle and a tetanic isometric contraction would produce the maximal tension.

- *In vivo* resting skeletal muscle is prestretched close to this ideal length, sometimes called L_o.

Sarcomere C: The preload overstretches the sarcomere, decreasing the overlap between the actin and myosin. Under these conditions, fewer cross-bridges are available.

Sarcomere D: The sarcomere has been stretched to the point that there is no overlap of actin and myosin filaments. This sarcomere cannot develop active tension or shorten following stimulation.

Isotonic Contractions

During contraction, the overall muscle length decreases, and the load is lifted or moved.

The muscle shortens and lifts the load because muscle (total) tension increases and eventually equals the load.

Active shortening occurs only when total tension equals the afterload.

HypotheticalExample

In vivo, skeletal muscle is prestretched close to L_o. In the following hypothetical *in vivo* situation, the passive tension at L_o is 100 g. The total force necessary to lift the afterload is 900 g. When contraction begins, the muscle must increase tension from 100 g to 900 g (by creating 800 g of active tension) before the load (afterload) can be lifted.

During the shortening phase of the isotonic contraction, the total tension in the muscle approximately equals the afterload.

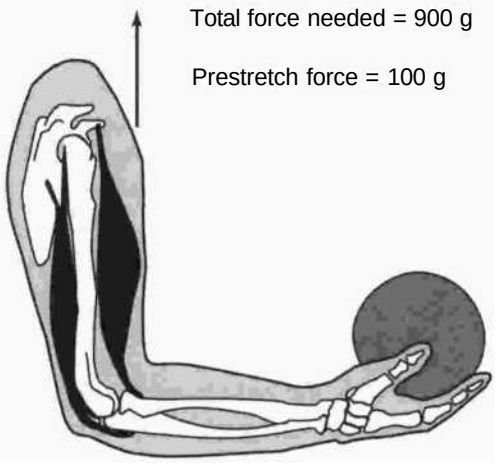


Figure IV-2-5

Most of the energy consumed during the preceding contraction was utilized in the development of active tension. This also applies to cardiac muscle. Cardiac ventricular muscle develops active tension during isovolumetric contraction. This is the most energy-demanding phase of the cardiac cycle. Very little energy is needed for the actual shortening phase.

Relationship Between Velocity and Load

Figure IV-2-6 shows the maximum velocity of shortening (Vmax) occurs when there is no afterload on the muscle. Increasing afterload decreases velocity, and when afterload exceeds the maximum force generated by the muscle, shortening will not occur (isometric contraction).

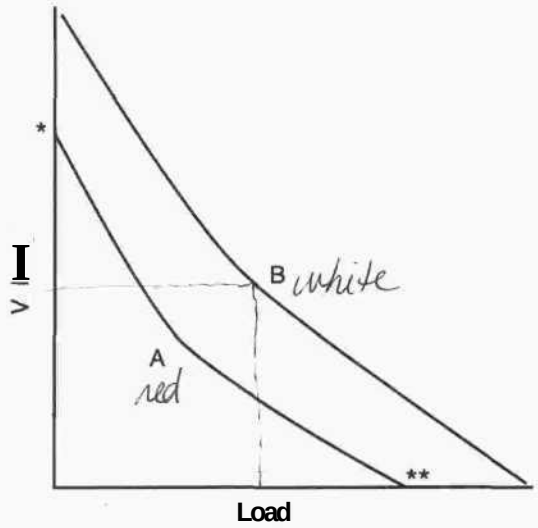


Figure IV-2-6

*Maximum velocity (Vmax) is determined by the muscle's ATPase activity. It is the ATPase activity that determines a fast versus a slow muscle.

**Maximum force generated by a muscle (or maximum load lifted by a muscle) is determined by muscle mass or, putting it another way, the number of motor units activated during contraction. The greater the muscle mass, the greater the maximum force generated.

Muscle A: A smaller, slower muscle (red muscle)

Muscle B: A larger, faster muscle (white muscle)

PROPERTIES OF WHITE VERSUS RED MUSCLE

White Muscle

Generally, large (powerful) muscle that is utilized short term, e.g., leg muscles of a sprinter, ocular muscles of the eye.

MajorCharacteristics

- Large mass per motor unit
- High ATPase activity (fast muscle)
- High capacity for anaerobic glycolysis
- No myoglobin

Red Muscle

Generally smaller (less powerful) muscle utilized long term (endurance muscle), e.g., postural muscle.

MajorCharacteristics

- Small mass per motor unit
- Lower ATPase activity (slower muscle)
- High capacity for aerobic metabolism (mitochondria), which is more efficient than anaerobic glycolysis
- Has myoglobin (imparts red color)

Table IV-2-L Histological Features of Skeletal, Cardiac, and Smooth Muscle

Skeletal	Cardiac	Smooth
Striated	Striated	Nonstriated
Actin and myosin form sarcomeres	Actin and myosin form sarcomeres	Actin and myosin not organized into sarcomeres
Sarcolemma lacks junctional complexes between fibers	Junctional complexes between fibers including Gap junctions	Gap junctions
Each fiber innervated	Electrical syncytium	Electrical syncytium
Troponin to bind calcium	Troponin to bind calcium	Calmodulin to bind calcium
High ATPase activity (fast muscle)	Intermediate ATPase activity	Low ATPase activity (slow muscle)
Extensive sarcoplasmic reticulum	Intermediate sarcoplasmic reticulum	Limited sarcoplasmic reticulum
T tubules form triadic contacts with reticulum at A-I junctions	T tubules form dyadic contact with reticulum near Z lines	Lack T tubules
Surface; membrane lacks calcium channels	Voltage-gated calcium channels	Voltage-gated calcium channels

two *tL* Ca^{2+} affects smooth mm.

Chapter Summary

Preload generates passive musclejension and prestretches the sarcomere.

The amount of sarcomere prestretch determines the maximum number of cycling cross-bridges and thus the maximum active tension.

Skeletal muscle *in vivo* is prestretched to L_o, a prelength where potentially every cross-bridge can cycle with actin and contribute active tension.

White muscle is generally large and fast (high ATPase), whereas red muscle is smaller and slower (low ATPase).

Skeletal muscle is fast (high ATPase), each fiber is innervated, and onlyjnternally stored calcium is utilizedjfoiLcontractJorjuThis is very differerrtjrom both cardiac and smooth muscle!

MUSCLE PHYSIOLOGY

Review Questions

Muscle Structure/Function

Directions: Select the ONE best answer.

1. Check each of the following statements about skeletal muscle contraction that is true.

   1. The major function of the T system (transverse tubules) is to store and release Ca^{2+}.
   2. The intracellular release of Ca^{2+} causes the formation of bonds between actin and myosin.
   3. The bonds between actin and myosin are maintained until the Ca^{2+} is sequestered.

   Which of the following best summarizes your conclusions?

   A. all of the above are true
   B. none of the above are true
   *-. statement 2 is true
   D. statement 3 is true
   E. statements 2 and 3 are true

2. In a series of experiments, it is noted that in a skeletal muscle fiber an intracellular concentration of Ca^{2+} of 10^{-6}-^{5} mol/L is the threshold value needed for inducing contraction. On this basis, one would expect a concentration of 10^{-5}-^{5} mol/L of Ca^{2+} to cause:

   Hfc a more forceful contraction.
   B. a less forceful contraction.
   C. a contraction of equal force.
   D. relaxation.

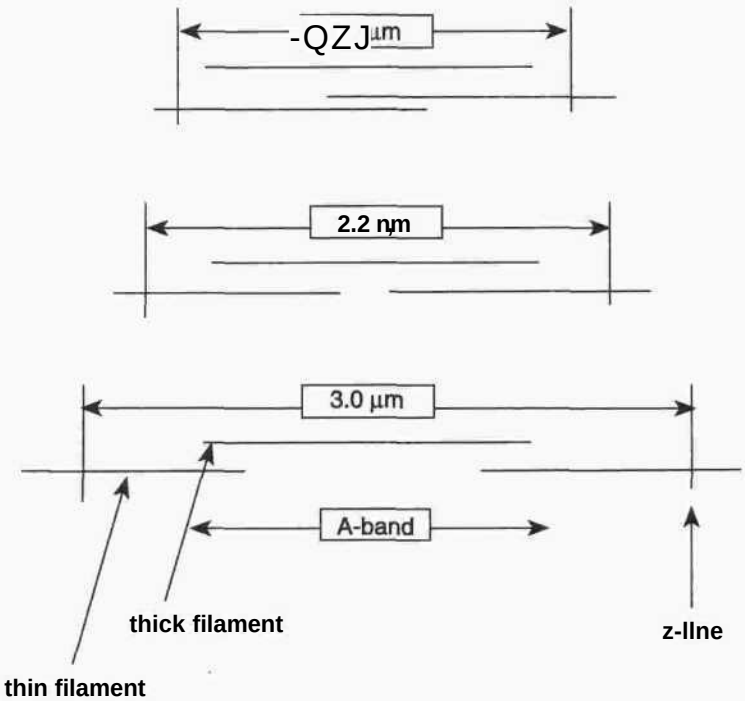
3. Skeletal and cardiac muscle, which are both striated, at resting length contain in each sarcomere an A band. This A band contains:

   A. essentially all the contractile protein myosin, but no actin.
   B. essentially all the contractile protein actin, but no myosin.
   i-G. essentially all the myosin, plus some actin.
   D. essentially all the actin, plus some myosin.
   E. troponin and tropomyosin, but no actin.

4. The rate at which Ca^{2+} is sequestered by the sarcoplasmic reticulum of skeletal muscle during a twitch is directly related to:

A. the rate of tension development
B. the rate of ATP hydrolysis by myosin.
C. both of the above.
D. the height of the action potential.
E. the rate of relaxation.

5. During the resting state, a single skeletal muscle sarcomere can exist at a number of lengths:



During an isometric contraction, the length at which it can exert its maximum force in response to stimulation is:

A. 1.7 μm
B. 2.2 μm
C. 3.0 μm
D. all of the above
E. both 2.2 and 3.0 μm

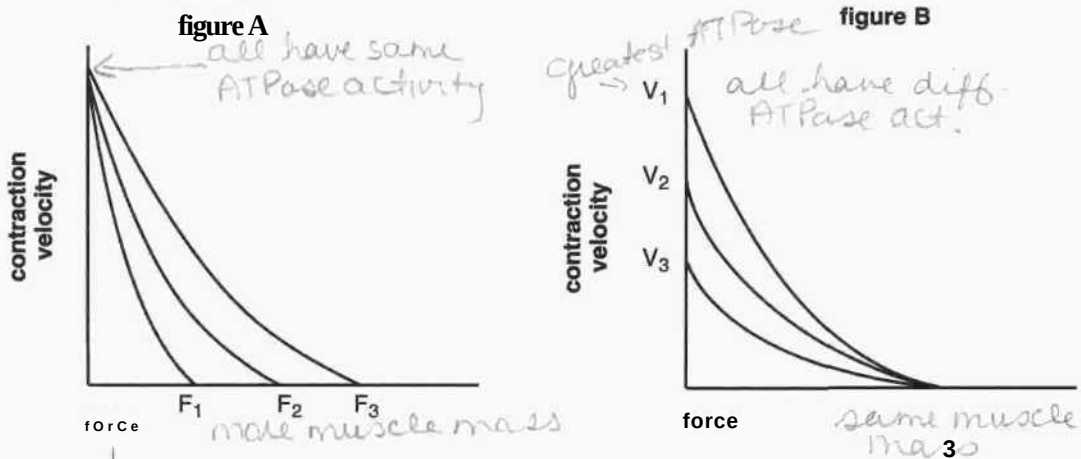
6. When skeletal muscle shortens in response to stimulation there is:

A. a decrease in the width of the I band
B. a decrease in the width of the A band
C. a decrease in the width of the A and I bands
D. an increase in the width of the H zone
E. all of the above occur

Skeletal Muscle Mechanics

Directions: Select the ONE best answer.

Questions 1 and 2

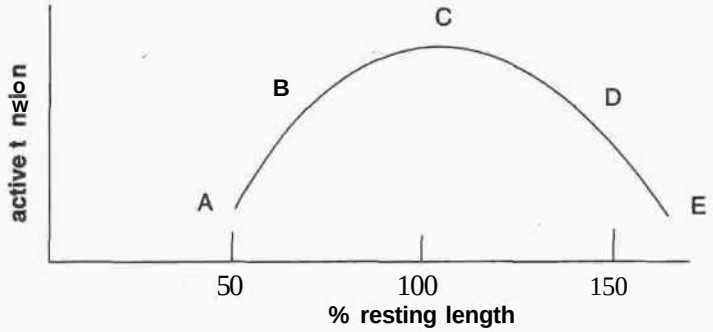


A. figure A
B. figure B
C. neither figure

1. Illustrates differences in the force-velocity relationship of skeletal muscle caused by changes in myosin ATPase activity.

2. Illustrates differences in the force-velocity relationship of skeletal muscle caused by changes in recruitment of additional motor units.

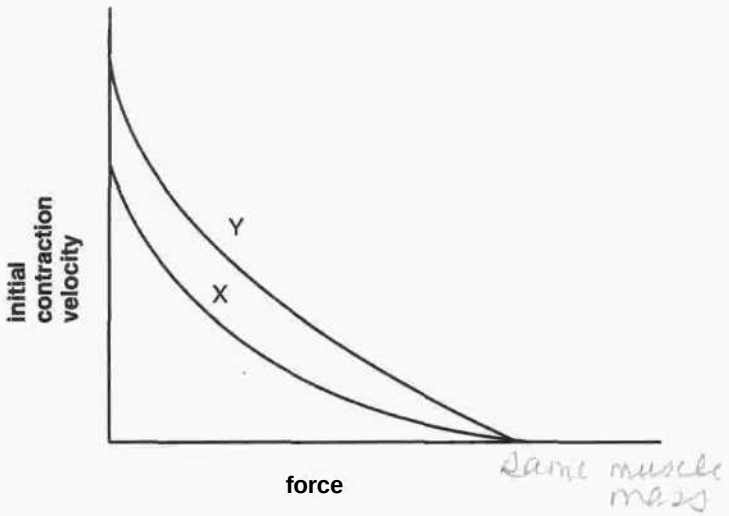
Question 3



The least ove is at greatest length of m.

3. The figure above depicts the isometric length-tension relationship of skeletal muscle. Identify the region where actin and myosin overlap is the least. [£f

Question 4



Same muscle mass

4. In the diagram above, the shift from curve X to curve Y could be produced by:

   A. changes in afterload
   B. changes in preload
   UZ. changes in myosin ATPase activity
   D. changes in number of active cross-bridges
   E. spatial summation of fibers

5. In an isometric contraction of a skeletal muscle, force of contraction cannot be altered by:

   A. changing the resting length of the muscle
   B. increasing stimulation frequency
   C. increasing the number of sarcomeres in parallel in the muscle
   D. increasing the number of sarcomeres in series in the muscle.

6. The slow twitch muscle fiber differs from the fast twitch fiber in that the former (check each correct answer):

   1. has a smaller number of muscle fibers in each motor unit
   2. has a higher concentration of myoglobin and mitochondria
   3. has a higher ATPase activity
   4. in a large limb serves as a reserve which can be recruited if there is a forceful contraction
   5. is more readily fatigued
   6. is part of a motor unit that consists mainly of red fibers

   Which one of the following best summarizes your conclusions?

   Statements:

   A. 1,2, and 3 are correct
   B. 1,2, and 6 are correct
   C. 2,3, and 4 are correct
   D. 3,4, and 5 are correct
   E. 4, 5, and 6 are correct

7. Which of the following characteristics of skeletal muscle make tetanic contraction possible?

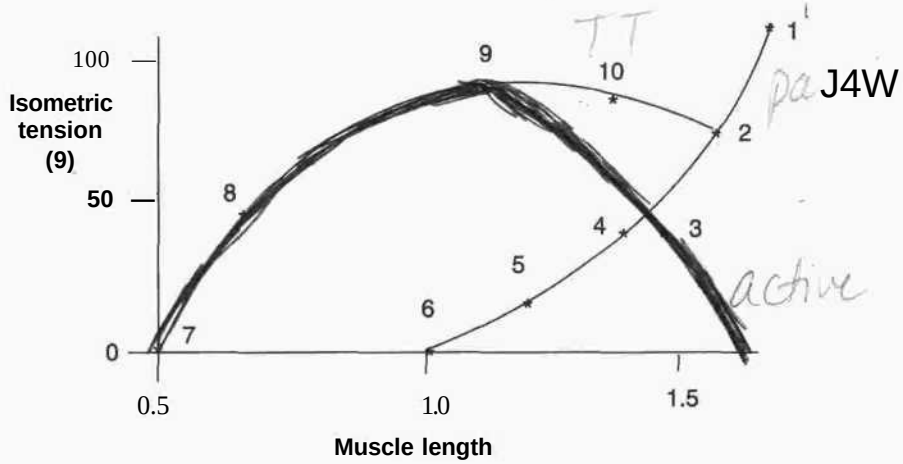
   A. The motor neurons to skeletal muscle have a short refractory period and are therefore capable of delivering a high frequency of stimuli to a muscle fiber.
   B. The cell membrane of the skeletal muscle fiber recovers its excitability well before the cell ceases its contraction.
   C. Both of the above are correct.
   D. The prolonged exposure of the muscle end plate to high concentrations of acetylcholine throughout the tetanus.
   E. The action potential of skeletal muscle outlasts the period of contraction.

8. All of the following will occur when an unstimulated muscle is stretched except:

   A. increased preload
   B. increased afterload
   C. increased muscle length
   D. increased passive tension

Questions 9-12

The following length-tension diagram was obtained on a muscle. Supramaximal tetanic stimuli were used to initiate a contraction at each muscle length studied.



9. Which point represents a preload of 40 g?

A. point 3
B. point 4
C. point 8
D. points 4 and 8
E. points 3,4, and 8

10. Maximal active tension in the diagram in question 9 is developed by skeletal muscle at point(s):

A. 1
B. 2
C. 4
D. 3 and 4
***E* 9**

11. Which point(s) in the diagram represent(s) no overlap between most of the muscle's thick and thin filaments? Point(s):

A. 2
B. 3
C. 6
D. 7
E. 6 and 7

12. If a muscle was at point 4 on the passive curve, what is the active tension generated during stimulation?

A. Less than 40 g
B. 40 to 60 g
C. 60 to 80 g
D. 80 to 100 g

13. If the gastrocnemius muscle is removed from the body, it will achieve a length:
    A. greater than it had in the body, because it is more relaxed
    B. shorter than it had in the body, because it is less relaxed
    C. shorter than it had in the body, because of its elastic characteristics
    D. the same as it had in the body

14. Which of the following best defines contraction?
    A. a series of chemical reactions that cause the muscle to pull
    B. a series of chemical reactions that cause the muscle to shorten
    C. a series of chemical reactions in which the muscle responds to stimulation
    D. shortening
    E. production of tension

15. Which of the following statements is true?
    A. a muscle at resting length exerts its maximum force during an isotonic contraction
    B. the maximum velocity of shortening during contraction occurs when there is no afterload
    C. the preload is the weight the muscle moves before it starts to relax
    D. in most forms of muscle contraction in an intact individual, the preload and afterload are equal

16. Skeletal muscle contraction:
    A. equals the duration of the action potential.
    B. equals the duration of the absolute refractory period.
    C. precedes the refractory period.
    D. ends immediately after the refractory period is over,
    E. none of the above are correct.

17. During an isometric contraction *in vivo:*
    A. the total tension in the muscle is generated from actin-myosin cross-bridges.
    B. intracellular free calcium is lower than under resting conditions.
    C. ATPase activity of the sarcoplasmic reticulum is inhibited,
    D. troponin-bound calcium is required to maintain active tension.
    E. the Na/K-ATPase pump is actively inhibited.

Muscle Physiology: Answers

Skeletal Muscle Structure/Function

1. **Ans C** The sarcoplasmic reticulum is the major intracellular storage and release site for calcium. The free calcium then attaches to troponin, causing the movement of tropomyosin and exposing the cross-bridge attachment sites on the actin. Thus, statement 2 is correct. However, the bonds are not maintained; rather, there is cycling of the cross-bridges. Cycling means the bonds form then break and continue this cycling during contraction. Every time a single cross-bridge goes through one cycle, 1 ATP is hydrolyzed.

2. **Ans** A A calcium concentration of $10^{-5.5}$ mol/L is greater than a concentration of $10^{-6.5}$ mol/L. More free calcium means more activated and cycling cross-bridges. The more cross-bridges that cycle, the greater the force of contraction.

3. **Ans** C The A band is the region of the thick or myosin filaments. Since at resting length there will be some overlap between the myosin and actin filaments, the A band will also contain some actin.

4. **Ans** E Sequestration means the movement of calcium back into the sarcoplasmic reticulum. This is an energy-dependent process that terminates contraction.

5. **Ans** B Maximum force during an isometric contraction is achieved when all cross-bridges are cycling. This can only be achieved when the system is saturated with calcium and there is the ideal overlap between actin and myosin. The figure with a sarcomere length of 2.2 μ demonstrates this ideal overlap. The first figure with a sarcomere length of 1.7 μ, shows an overlap of actin filaments. This would decrease the number of potential cycling cross-bridges and thus decrease the maximum achievable force during contraction. The bottom figure shows an overstretched sarcomere that has a decreased overlap between the actin and myosin. This also will decrease the number of potential cycling cross-bridges. Remember, when the sarcomere is stretched to the point where there is no overlap between actin and myosin, no cycling between the actin and myosin is possible. Under these conditions there will be no active tension following stimulation.

6. **Ans** A A band: The length of the myosin filaments. This length remains unchanged. I band: Actin without overlapped myosin. This length decreases with contraction. H zone: Myosin without overlapped actin. This length decreases with contraction.

Shortening during contraction results in the movement of the thin and thick filaments past one another and thus overlap between the actin and myosin increases.

Skeletal Muscle Mechanics

l.AnsB

2. **Ans A** These two graphs show the force-velocity relationship for isotonic contractions. The starting point for each curve on the y axis represents the maximum velocity of contraction, i.e., the velocity with no load. This parameter is determined by the muscle's ATPase activity. In figure A all three curves start at the same point on the Y axis, therefore they all have the same ATPase activity. In figure B the three curves start at different points on the y axis, thus they all have different ATPase activities. Muscle Vj has the greatest ATPase activity, therefore it is the fastest muscle, and V_3 has the least ATPase activity (slowest muscle).

The point where each curve crosses the x axis is the maximum force the muscle can generate during contraction. This is determined by the muscle mass or the number of motor units activated during contraction. In figure A the maximum force that can be generated increases from Fj through F_3, thus activated muscle mass also increases. In figure B all three curves end at the same point on the x axis, thus all three muscles have the same muscle mass. Also, with each curve the maximum velocity occurs when there is no load, and as load increases, velocity during shortening decreases. When the curve crosses the x axis, there is zero velocity, which means the muscle is unable to lift the load (isometric contraction).

3. **Ans** E This curve demonstrates the relationship between the maximum possible active tension during an isometric contraction and muscle length. The active tension achieved is determined by the number of cross-bridges cycling, which in turn is determined by the relationship between actin and myosin filaments. At point C, which represents the greatest achievable active tension from this muscle, there is the ideal overlap between the actin and myosin. This is the resting length of most skeletal muscles *in vivo*. When muscle length increases there is less overlap between the actin and myosin, fewer cross-bridges can cycle, and less active tension will develop. The least overlap is at the greatest muscle length; the far right in the graph. To the left of point C the decrease in muscle length destroys the relationship between the actin and myosin; actin filaments overlap and eventually the myosin hits the Z lines.

4. Ans C A shift from curve X to curve Y produces a higher intersection point on the y axis. This means a greater ATPase activity and a faster muscle, i.e., a greater velocity of shortening. Since the point on the x axis is the same, the two muscles can generate the same maximum force during contraction, i.e., they have the same muscle mass.

S.AnsD By altering resting length, overlap between the actin and myosin will change and this will affect the number of cross-bridges that can cycle during stimulation. Increasing the frequency of stimulation will increase the calcium released from the sarcoplasmic reticulum and this will increase the number of cross-bridges cycling. Increasing the number of sarcomeres in parallel is similar to activating additional motor units (motor units are connected in parallel). Adding sarcomeres in series does not increase the strength of contraction. An analogy would be that a longer rope is not a stronger rope.

6. AnsB A slow twitch is associated with a red endurance muscle. It does have a smaller number of muscle fibers and it is generally not as powerful as a white muscle. It has greater myoglobin and mitochondria because it works mainly aerobically. It has lower ATPase activity because it is a slower muscle. The muscles kept in reserve for a very forceful contraction are mainly the white larger motor units. The slower red muscle is our endurance muscle, which fatigues less readily than white fast muscle. As mentioned earlier slow muscle is red because of the presence of myoglobin.

7. AnsC Both statements A and B are correct. Tetanus in skeletal muscle is possible because multiple action potentials can be delivered before and during the mechanical event. Multiple action potentials will saturate the troponin with calcium, resulting in continuous cycling of all available cross-bridges. This is possible only because of the very short refractory period of the neuronal and skeletal muscle action potentials.

8. AnsB All of the variables will always change as indicated except afterload. A relaxed muscle is stretched by the application of preload. However, this does not necessarily indicate the afterload will be changed. Afterload is the load the muscle is trying to move during stimulation.

9. **AnsB**

10. **Ans E**

ll.AnsA

12. **Ans** B This length-tension graph depicts the three basic curves discussed in class. The curve that starts at point 6 and goes through point 1 is the passive or preload curve. The active tension curve starts at point 7, reaches a peak at point 9 and then declines and crosses the x axis as the dashed line. The line between points 9 and 2 represents the total tension developed by adding the passive and active tensions together. The point that represents a preload of 40 g is on the passive curve at point 4. If this point is taken across to the y axis, it represents a tension of 40 g.

Maximal active tension will be represented by the point at the peak of the active curve, point 9. This would be an active tension of about 75 to 80 g.

No overlap between actin and myosin means no active tension upon stimulation. This is represented by the point (muscle length) where the active tension curve crosses the x axis. This point is not labeled, but the same length is represented by the point on the preload curve directly above; point 2. If a muscle is at point 2 on the preload curve (or beyond it, like point 1), no active tension will be developed when the muscle is stimulated. Point 2 or 1 is a better answer than point 7 because there the loss of active tension was produced by destroying the geometric relationship between the actin and myosin.

If a relaxed muscle at point 4 on the passive curve is stimulated maximally, it will generate active tension, depicted by the point on the dashed curve directly above. This point on the y axis would represent a tension of approximately 50 g. The answer is not point 10; this represents the total tension in the muscle during stimulation (passive plus active)

13. **Ans** C Relaxed skeletal muscle *in vivo* is stretched close to the ideal passive length. Thus, if the muscle is removed from the body, preload will be eliminated and the muscle will shorten.

14. **Ans** A In this question you are looking for the best, not necessarily the perfect, definition. Answer A is reasonable. In both an isometric and an isotonic contraction the muscle is attempting to pull a load. Answer B is poor because there is no muscle shortening in an isometric contraction. In C, chemical reactions could be something not associated with contraction. Production of tension will occur with the application of preload, this is not contraction.

15. **Ans** B Afterload decreases the velocity of shortening. When there is no load, velocity will be maximal. During an isotonic contraction, force is determined by afterload. Tension in the muscle during the shortening phase will approximately equal the afterload. The greatest force is developed by a maximal stimulation during an

isometric contraction. In an intact individual the preload is constant in most cases. The afterload will vary and will represent the load the muscle is attempting to lift. If the muscle is trying to lift 100 lb. the afterload is 100 lb.

16. Ans E The action potential and the absolute refractory period are extremely short and are over for a significant time interval before mechanical contraction begins.

17. Ans D Calcium must remain bound to the troponin to maintain cross-bridge cycling. If the calcium becomes detached from troponin, the tropomyosin will cover the attachment site on the actin and cycling will terminate. During an isometric contraction cross-bridges will generate active tension. The total tension will be the sum of the active tension and any preload tension that was present before contraction began. Contraction is initiated by the release of calcium from the sarcoplasmic reticulum. During contraction the free calcium will always be higher than under resting conditions. Removal of the free calcium back to the sarcoplasmic reticulum produces relaxation.

SECTION V

Cardiac Muscle

Electrical Activity of the Heart

1

CHARACTERISTICS OF A RESTING VENTRICULAR MUSCLE CELL

Table V-l-1. Characteristics of a Resting Ventricular Muscle Cell (concentrations in mEq/L)

	Ion cone, out	Cone, in	Equil. pot	Permeability
K+	4	135	-94mV	high
Na+	145	10	+70 mV	low
Ca2+	2	10^{-4}	+132 mV	low

MEMBRANE CHANNELS

Ungated Potassium Channels

Always open and unless the membrane potential reaches the potassium equilibrium potential (—94 mV), a potassium flux (efflux) continues through these channels.

What the USMLE Requires You to Know

- The mechanisms in detail that produce a ventricular action potential
- The special characteristics of SA nodal cells
- Heart block

Voltage-Gated (-Dependent) Sodium Channels

Closed under resting conditions.

Membrane depolarization is the signal that causes these channels to quickly open and then close.

Because they open and close quickly, they are sometimes referred to as the *fast channels.*

These channels have the same characteristics as the voltage-gated sodium channels in the neuron axon.

Once closed, they will not respond to a second stimulus until the cell repolarizes.

Voltage-Gated Calcium Channels

Closed under resting conditions.

Depolarization is the signal that causes these channels to open, but they open more slowly than the sodium channels.

Consequently, they are sometimes called the *slow channels.*

Because they allow sodium as well as calcium to pass, the *slow calcium-sodium channel* is also appropriate terminology.

The calcium entering the cell through these channels will participate in contraction and will also be involved in the release of additional calcium from the sarcoplasmic reticulum.

If the fast channels fail to open, depolarization occurs via the entrance of calcium through these channels.

Voltage-Gated Potassium Channels

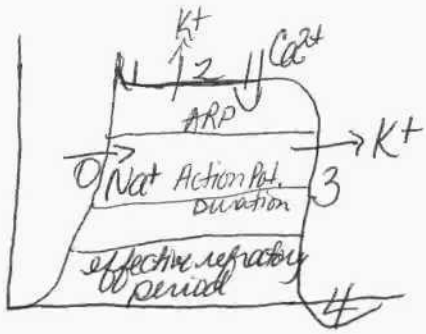
KOpen under resting conditions.

Depolarization is the signal to close these channels.

They will be closing during the depolarization phase and will be closed during the main part of the plateau phase.

They begin to reopen during the latter part of the plateau phase and continue to reopen during repolarization.

Thus, potassium conductance is exceptionally high under jxsting^conditigjis^ decreases during depolarization) is at *an* **the plateau phase, andincreasesbaxktowmHheMghresting** level duriiigprepolarization.



ACTION POTENTIAL OF A VENTRICULAR FIBER (FAST RESPONSE)

Phases

Figure V-l-1 shows the labeled phases of the ventricular action potential. On the same time scale are the conductance changes in sodium ($G^{\wedge}$, fast channels), calcium (Gca, slow channels) and potassium (G_K, voltage-gated channels).

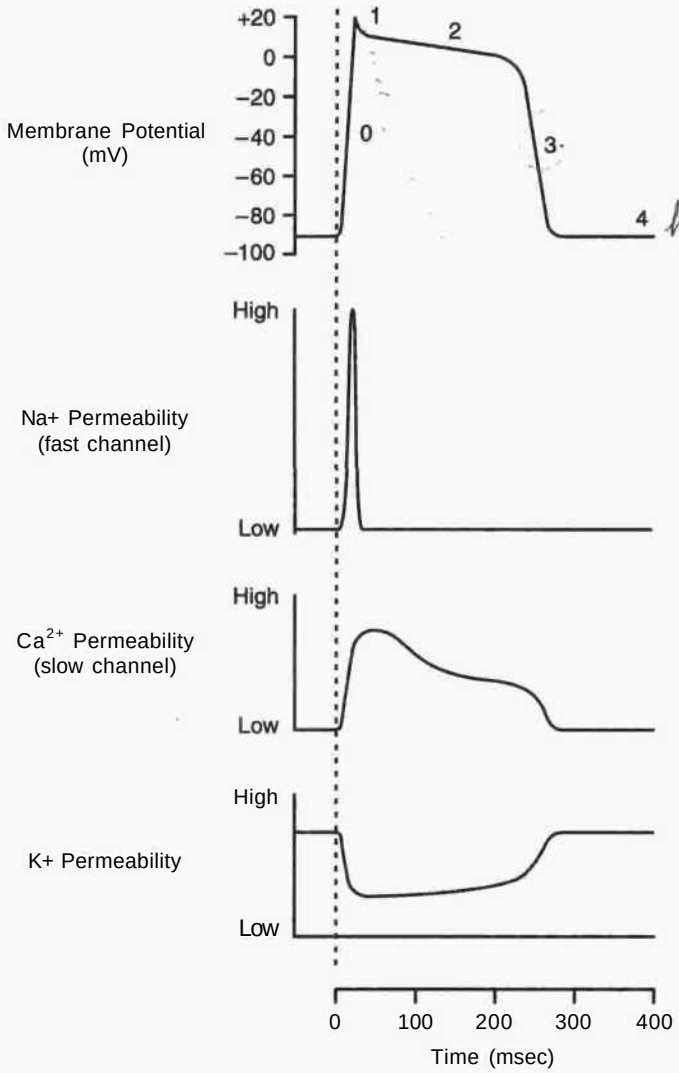


Figure V-1-1

Which of following phases max. conductance of K+? 4

In which of following phases the voltage K+ is fully closed? 2

hyperpolarization of K+

Arrhythmia - treated w/ K+ blockers. K+ blockers keeps Na+ inside cell and slows down action potential duration which slows down heart

Ionic Basis of the Action Potential

Phase 0

Fast channels open, IT $G^{\wedge}_{a}$.

Sodium influx then causes depolarization.

The channels open and close quickly, and they have closed by the time the main part of the plateau phase is entered.

Phase 1

This slight repolarization is due to a potassium current and the closing of the sodium channels.

Phase 2

Slow channels are open, G_{Ca} ft permitting a calcium influx.

Voltage-gated potassium channels are closed; G_K U- compared with resting membrane.

Potassium efflux continues through the ungated potassium channels.

If voltage-gated potassium channels did not close during depolarization, early repolarization would occur, preventing the full development of the plateau phase.

The development of the plateau phase is dependent on the closing of voltage-gated potassium channels.

Phase 3

Calcium or slow channels close, G_{Ca} JJ; this eliminates any influx through these channels.

Voltage-gated potassium channels are reopening, G_K It.

Because we are a long way from the potassium equilibrium potential and conductance to potassium is increasing, a large potassium efflux begins, and the cell quickly repolarizes.

If the voltage-gated potassium channels did not reopen, the cell would still repolarize, but more slowly, through the ungated potassium channels.

ELECTRICAL VERSUS MECHANICAL EVENTS

Figure V-1-2 shows that cardiac muscle cannot be tetajiized because the duration of the effective refractory periodls approximately equal to the duration of the mechanical event.

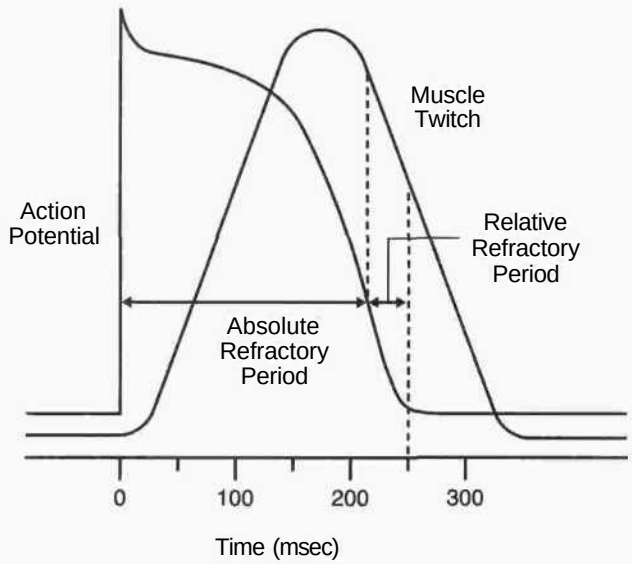
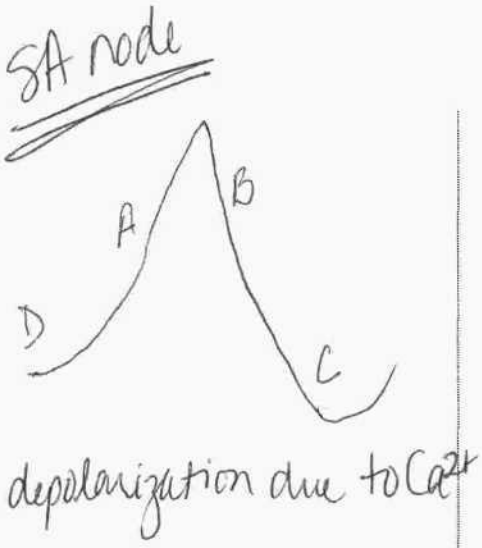


Figure V-1-2

ACTION POTENTIAL CHARACTERISTICS OF SPECIALIZED CELLS

General Features

The specialized cells of the heart consist of the cells of the sinoatrial (SA) node, atrioventricular (AV) node, and Purkinje fibers. These cells all possess an unstable phase 4.



Characteristics of SA Nodal Cells

Figure V-1-3 shows an action potential of an SA nodal cell.

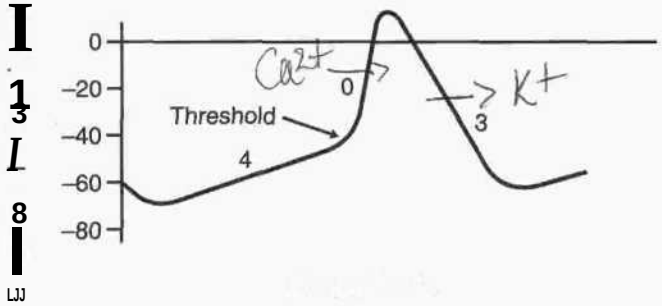


Figure V-1-3

General Properties

They all have a pacemaker potential or prepotential.

- Unlike regular contracting myocyte cells, there is not a stable membrane potential during phase 4; rather, there is a slow gradual depolarization toward threshold.
- Once threshold is reached, an action potential is generated.
- Although the concept is still somewhat controversial, it is generally held that phase 4 is associated with a decreasing potassium conductance, which increases excitability.

Phase 0

Phase 0 is mainly a slow channel or calcium spike rather than a fast channel or sodium spike.

Phase 3

As is the case with other action potentials, phase 3 is due to a rapid potassium efflux (Gj£ increases).

Effect of Sympathetics

The slope of the prepotential increases, threshold is reached sooner, and the intrinsic firing rate increases (via increased oaijjiutm conductance of nodal fibers).

Figure V-1-4 summarizes the effects of sympathetics on the SA nodal cells.

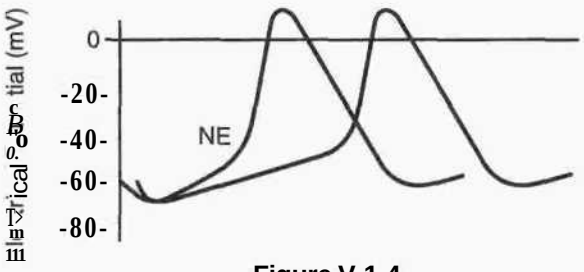


Figure V-1-4

EffectofParasympathetics

Hyperpoiarize the cell via increasing potassium conductance. Thus, it takes longer to reach threshold, and the intrinsic firing rate decreases.

There may also be a decrease in the slope of the prepotential.

Figure V-l-5 summarizes the effects of parasympathetics on the SA nodal cells.

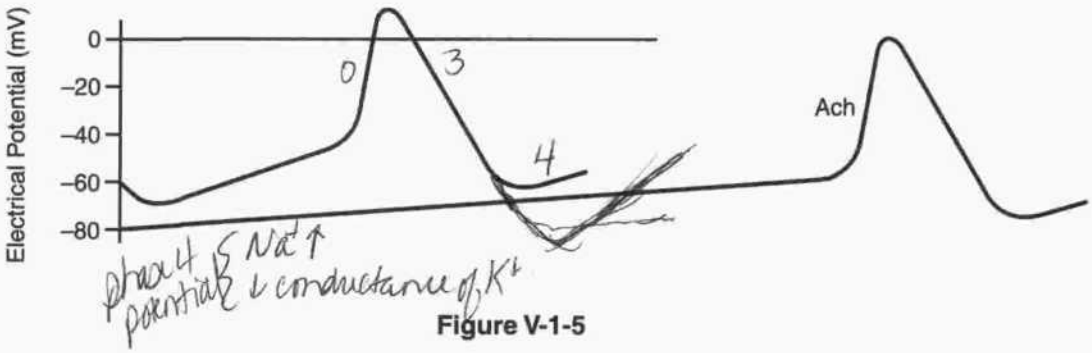


Figure V-1-5

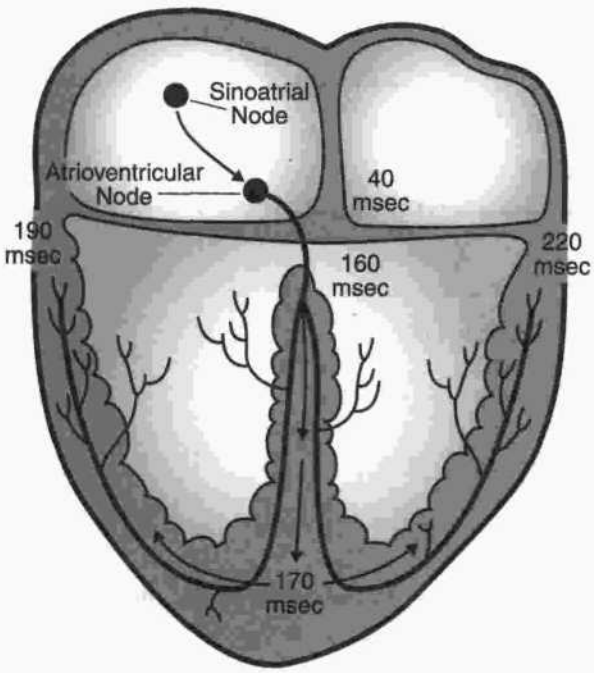
Conduction Pathways and Velocity of Conduction

Pathway

SA node => atrial muscle => AV node (delay) => Purkinje fibers => ventricular muscle

Velocity

Figure V-l-6 illustrates conduction times.



Fastest conducting fiber = Purkinje cell

Slowest conducting fiber = AV node

Figure V-1-6

Greatest automaticity: SA node

Automaticity

SA nodal cells: Highest intrinsic rate, primary pacemaker of the heart (100-120/min)

AV nodal cell: Second highest intrinsic rate, secondary pacemaker of the heart (40-60/min)

Purkinje cells: Slowest intrinsic rate (30-40/min)

ELECTROCARDIOGRAPHY

The Electrocardiogram

The normal pattern is demonstrated in Figure V-l-7.

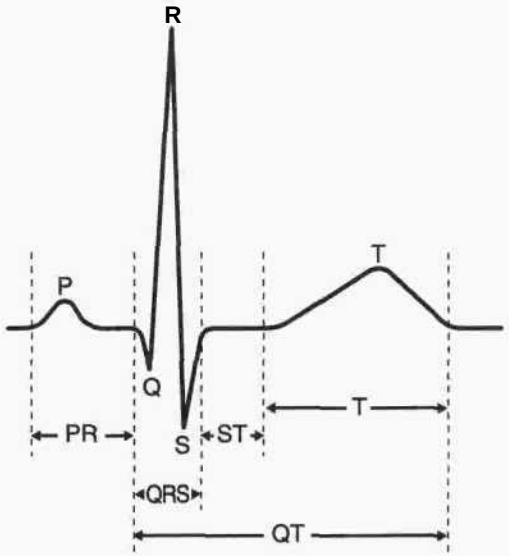


Figure V-1-7

- P wave: Atrial depolarization
- QRS complex: Ventricular depolarization
- T wave: Ventricular repolarization

PR interval: From the beginning of the P wave to the beginning of the QRS complex (120-210 msec); mostly due to conduction delay in the AV node

QT interval: From the beginning of the QRS complex to the end of the T wave

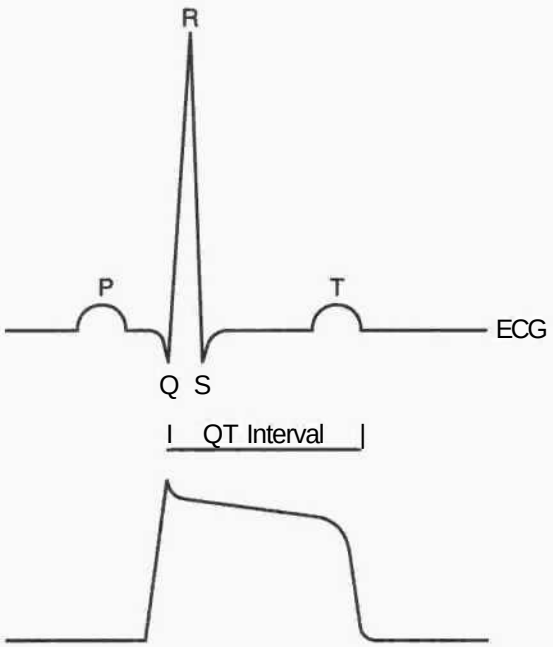


Figure V-1-8

CommonConventions

Paper speed: 25 mm/sec

Calibration: 1 mV = 1 cm pen deflection

A wave of depolarization approaching a positive electrode leads to an upward deflection of the pen.

Ventricular Depoiarization

Proceeds from endocardium to epicardium

Ventricular Repolarization

Proceeds from epicardium to endocardium

HEART BLOCK

Partial (First-Degree) Block

Slowed conduction through the AV node.

PR interval is increased (>220 msec).

Second-Degree Block

Some impulses are not transmitted through the AV node.

JkdoJ>itzJ_(Wenckebach): PR interval progressively lengthens.

MobilgJI: no measurable lengthening of the PR interval.

Figure V-l-9 shows second-degree heart block. This is characterized by some missing QRS complexes following P waves.

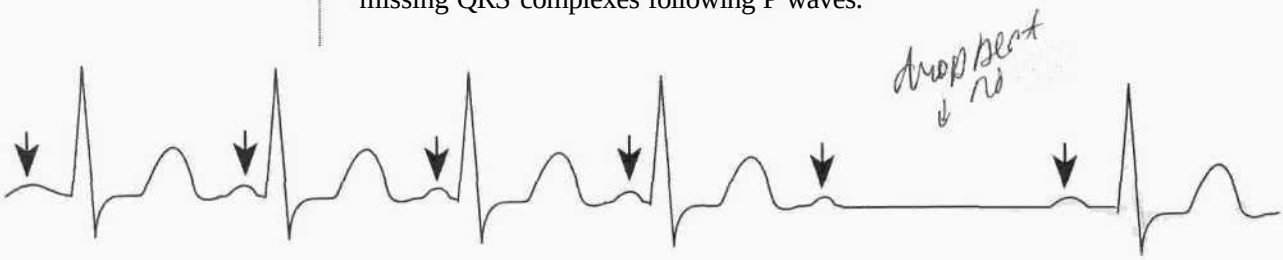


Figure V-1-9

Complete (Third-Degree) Block

No impulses are Conducted frnm thp qtria tr> vpntriclas.

Atria and ventricles beat independently.

The electrocardiogram is characterized as having no correlation between P waves and QRS complexes.

Because of differences in the intrinsic rates of pacemaker tissue, the frequency of P waves is greater than the frequency of QRS complexes.

Einthoven's Triangle

ConventionalArrangementofElectrodes

Figure V-l-10 demonstrates the conventional arrangement of electrodes for recording the electrocardiographic leads, and Einthoven's triangle.

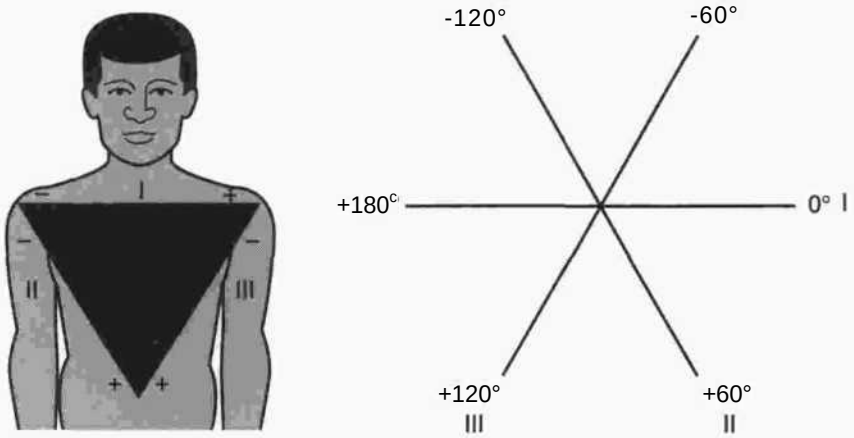


Figure V-1-10

Einthoven's Law: I + III = II

Mean Electrical Axis

The mean electrical axis of the ventricles describes the net direction of current movement during ventricular depolarization.

It is affected by a number of factors, including the position of the heart, heart mass, and conduction time.

It can be calculated by summing the depolarization during the QRS complex in any two leads.

The mean electrical axis is indicated in Figure V-1-11.

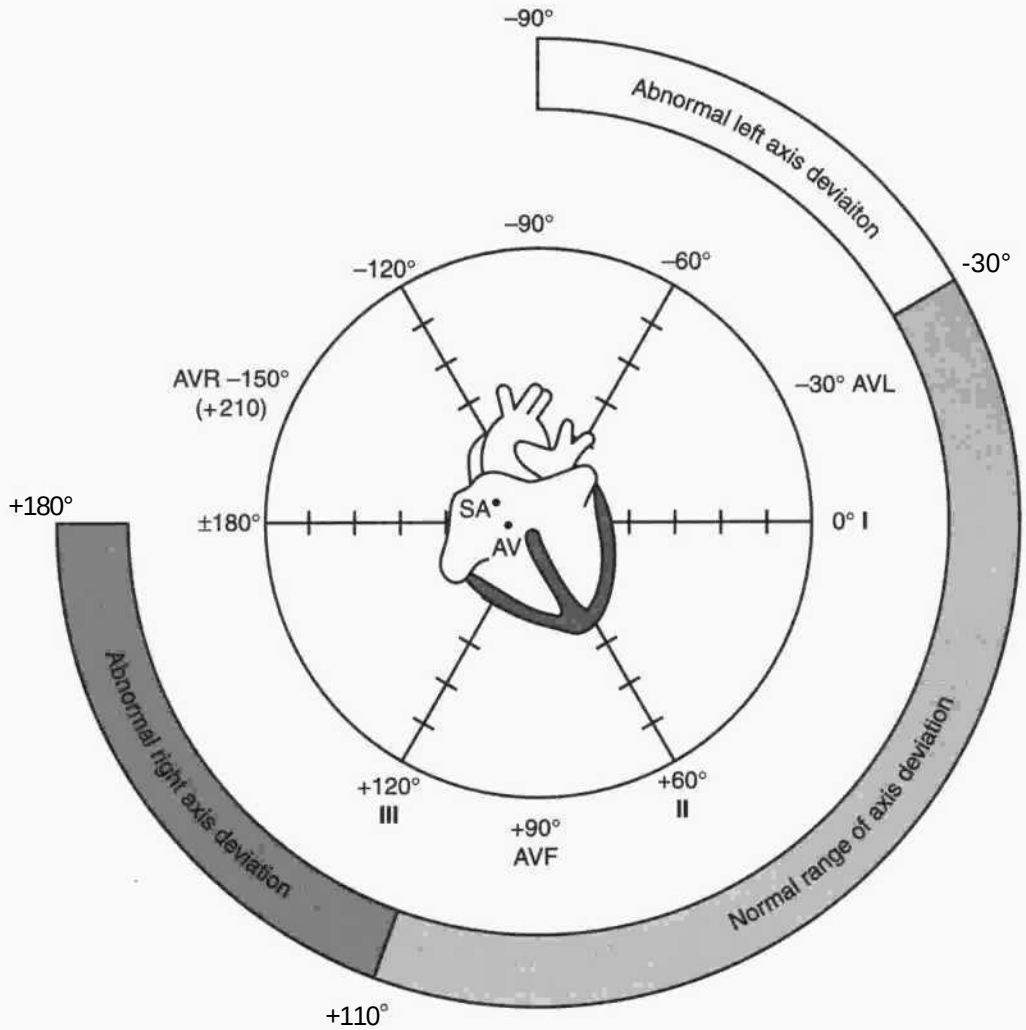

–90°
Abnormal left axis deviation
-30°
–90°
–120°
–60°
AVR –150°
(+210)
–30° AVL
+180°
±180°
SA
AV
0° I
+120°
III
+60°
II
+90°
AVF
Abnormal right axis deviation
Normal range of axis deviation
+110°

Figure V-1-11

Chapter Summary

Ventricular depolarization is due to a sodium influx through fast channels. These channels are the same as those that produce depolarization in a neuron and in skeletal muscle.

The plateau phase is established by a reduced potassium conductance that limits potassium efflux and by an influx of calcium through the slow channels.

Repolarization occurs rapidly because of a large increase in potassium conductance, beginning in the latter part of the plateau phase.

Cardiac muscle cannot be tetanized because of the long duration of the action potential.

Specialized cells in the heart are characterized by an unstable phase 4 membrane potential that gradually depolarizes to threshold.

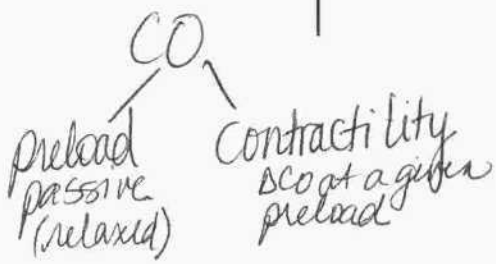
Phase 0 in an SA nodal cell is due mainly to an influx of calcium through slow channels.

In SA nodal cells, sympathetics increase the slope of the prepotential and thus the intrinsic rate, whereas parasympathetics hyperpolarize and decrease the intrinsic rate.

First-degree heart block is a slowed conduction through the AV node, second-degree heart block is the lack of transmission of some impulses through the AV node, and third-degree heart block is a total block at the AV node.

Heart Muscle Mechanics

2



SYSTOLIC PERFORMANCE OF THE VENTRICLE

General Features

Systolic performance actually means the overall force generated by the ventricular muscle during systole. This is determined by the number of cross-bridges cycling during contraction.

The greater the number of cross-bridges cycling, the greater the force of contraction.

The number of cross-bridges cycling is determined by two independent variables: the amount of preload on the muscle and the level of contractility.

These two factors are summed together to determine the overall force of ventricular contraction. Recent work has demonstrated that they are not completely independent, but the generalizations made here will apply to the physiological and clinical setting.

Preload

General Features

As in skeletal muscle, preload is the load on the muscle in the relaxed state.

More specifically, it is the load or prestretch on ventricular muscle at the end of diastole.

What the USMLE Requires You to Know

- Ventricular performance as determined by preload and contractility
- Afterload and its influence on ventricular ejection
- Control of heart rate
- The baroreceptor reflex
- The normal cardiac cycle
- The major characteristics of aortic stenosis and insufficiency and mitral stenosis and insufficiency
- The major features of a left ventricular pressure-volume loop and the changes in altered states
- The effect of exercise on the cardiovascular system

Preload on ventricular muscle is not measured directly; rather, indices are utilized.

The best indices of preload on ventricular muscle are those measured directly in the ventricles.

Indices of left ventricular preload:

- Left ventricular end-diastoHc~v61ume (LVEDV)
- Left ventricular end-diastolic pressure (LVEDP)

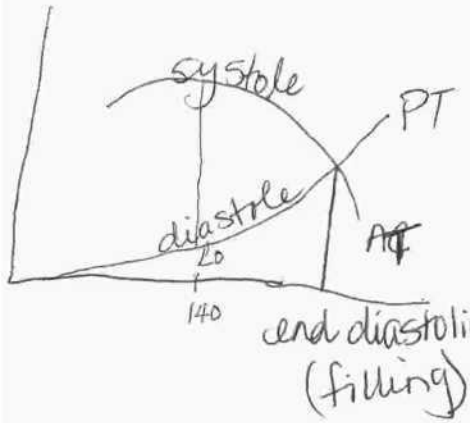
Less reliable indices of left ventricular preload are those measured in the venous system. The farther from the ventricle, the less reliable the index.

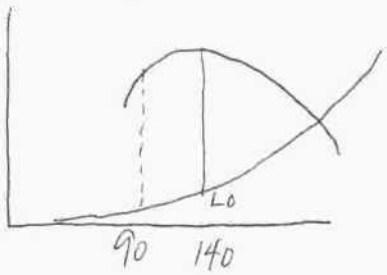
- Left atrial pressure
- Pulmonary venous pressure
- Pulmonary wedge pressure

Even though pulmonary wedge pressure, measured via a Swan-Ganz catheter, is the least reliable index of those listed, its easy measurement in the clinical situation makes it the one most often utilized.

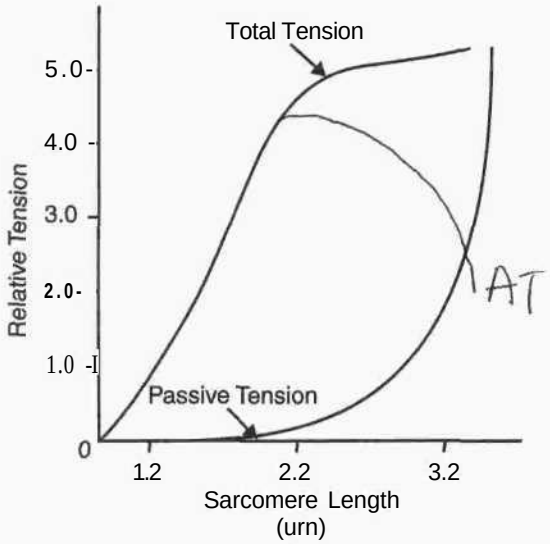
ThePreloadFactorinSystolicPerformance(Frank-Starling Mechanism)

The preload effect can be explained on the basis of a change in sarcomere length. This is illustrated in Figure V-2-1.





Length—Tension Relationship



Frank-Starling Mechanism

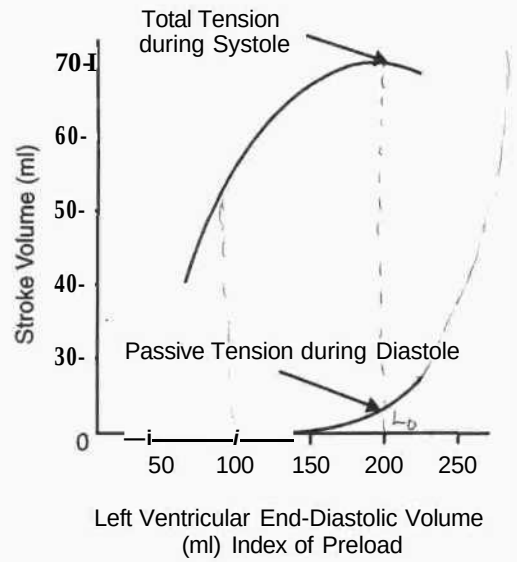


Figure V-2-1

The resting length of skeletal muscle *in vivo* is at a sarcomere length close to the optimum for maximal cross-bridge Unking between actin and myosin during contraction.

Heart muscle at the end of diastole is below this point. Thus, in a normal heart, increased preload increases sarcomere length toward the optimum actin-myosin overlap. This results in more cross-Unking and a more forceful contraction during systole.

Independence of Preload and Contractility

Figure V-2-2 and the accompanying description of the graph demonstrate the independence of the preload and contractility factors in acute situations.

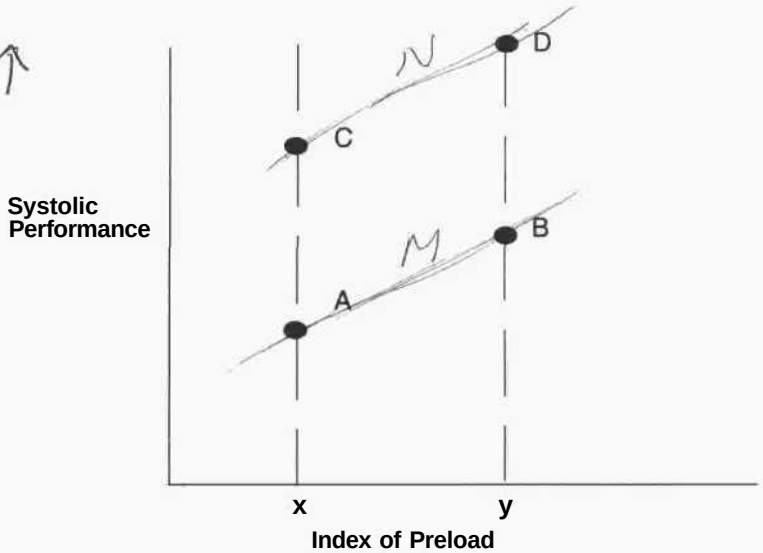


Figure V-2-2

Assume X represents a normal preload and point A the force generated at this preload under normal resting conditions.

If preload is increased to point Y, what is observed is an increased force of contraction during systole, point B.

Thus, we conclude that preload is one factor that determines the overall force of ventricular contraction.

Further, we can generalize, when preload is increased, there will be in most cases an increased force of contraction, whether the heart is normal or diseased.

If we return to our original preload X but in this case simply increase sympathetic activity to the ventricle, we also observe an increased force of contraction, point C, but at the same preload.

Thus, we must conclude that preload was not responsible for the increased performance and that, therefore, by default, it must have been an increase in contractility.

This is because there are two factors that determine the overall force of ventricular contraction: preload and contractility.

It is difficult to define *contractility* without using the word *preload.* For example, a change in contractility can be considered a change in performance at a given preload, or, if a change in performance cannot be explained on the basis of preload, there must have been a change in contractility.

If we increase preload to Y and also increase sympathetic activity, we obtain a very large increase in the force of contraction, point D.

In summary, based on the preceding description:

A => B increased performance due entirely to preload

A =* C increased performance due entirely to contractility

A ^ D increased performance due to an increase in both preload and contractility

The Contractility Factor in Systolic Performance (Inotropic State)

An acceptable definition of *contractility* would be a change in performance at a given preload. In other words, if a change in performance cannot be explained on the basis of preload, there must have been a change in contractility.

Stated another way, contractility is a change in the force of contraction at any given sarcomere length.

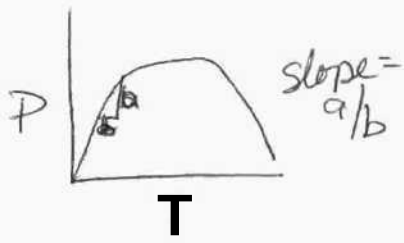
Acute changes in contractility are due to changes in the intracellular dynamics of calcium. Drugs that increase contractility usually provide more calcium and at a faster rate to the contractile machinery. More calcium increases the availability of cross-link sites on the actin, increasing cross-Unking and the force of contraction during systole.

Indices of Contractility

Increased ^*jdt* (change in pressure vs. change in time) = rate of pressure development during isovolumetric contraction. Contractility affects the rate at which the ventricular muscle develops active tension, which is expressed as pressure in the ventricle during isovolumetric contraction.

Increased ejection fraction (stroke volume/end-diastolic volume). Ejection fraction can now be estimated fairly easily by a noninvasive technique and is currently a common clinical index of contractility.

When contractility increases, there are changes in addition to an increased force of contraction. This is illustrated in Figure V-2-3. The solid line represents left ventricular pressure before and the dashed line after an increase in contractility. The numbers refer to the descriptions below the figure.



ejection fraction = Stroke vol. / EDV
(N = 66%)

EDV - ESV / EDV

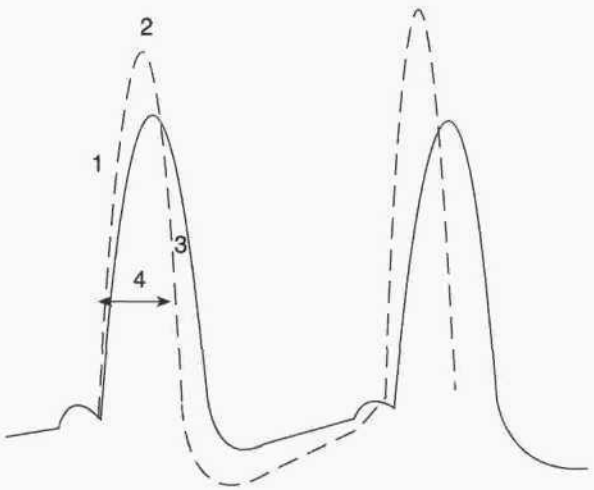


Figure V-2-3

The overall changes induced by increased contractility can be summarized as follows:

1. Increased *dp/dP*. increased slope, thus increased rate of pressure development
2. Increased peak left ventricular pressure due to a more forceful contraction
3. Increased rate of relaxation due to increased rate of calcium sequestration
4. Decreased systolic interval due to effects #1 and #3

Both an increased preload and an increased contractility will be accompanied by an increased peak left ventricular pressure, but only with an increase in contractility will there be a decrease in the systolic interval.

Whereas contractility affects systolic interval, heart rate determines diastolic interval.

Thus, increased sympathetic activity to the heart will produce the following:

Systolic interval decreased: contractility effect

Diastolic interval decreased: heart rate effect

*Cardiac**Function Curves***

Cardiac function curves are an excellent graphical depiction of the effects of preload versus contractility. In Figure V-2-4, the axes represent the following:

y axis: Index of systolic performance, e.g., stroke work, stroke volume, stroke power (cardiac output). All are indices of the force of ventricular contraction.

x axis: Index of ventricular preload, e.g., ventricular end-diastolic volume or pressure, atrial or venous pressure.

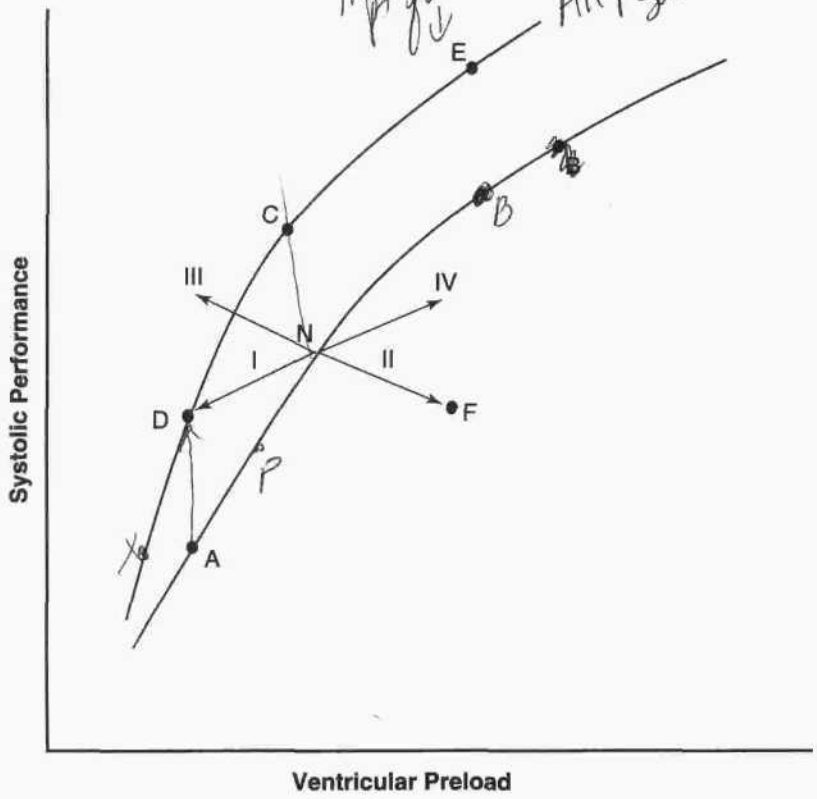


Figure V-2-4 Cardiac function curve

A cardiac function curve is generated by keeping contractility constant and following ventricular performance as preload increases. Thus:

All points on a ventricular function curve have the same contractility.

All curves will have an ascending limb, a peak point, and possibly a descending limb.

The pericardium normally prevents the large increases in preload necessary to reach the peak of a cardiac function curve.

Starting at N, which represents a normal, resting individual:

A = decreased performance due to a reduction in preload

B = increased performance due to an increased preload

Starting at N, point C represents an increased performance due almost entirely to increased contractility (close to the situation during exercise).

Any point above a ventricular function curve means increased contractility.

Any point below a ventricular function curve means decreased contractility.

Points C, D, and E represent different levels of performance due to changes in preload only; all three points have the same contractility.

Vector I: consequences of a loss in preload, e.g., hemorrhage.

Performance decreases because of a loss in preload.

The increased contractility partially compensates for the loss of preload.

When there is a loss of either preload or contractility that compromises performance, the other factor usually increases to return performance toward normal. However, the compensatory mechanism is usually incomplete.

Vector II: consequences of a loss in contractility, e.g., congestive heart failure.

Performance decreases because of a loss in contractility.

The increased preload partially compensates for the loss of contractility.

Vector III: consequences of an acute increase in contractility.

Performance increases.

Preload decreases.

Vector IV: consequences of an acute increase in preload, e.g., volume loading the individual.

Performance increases.

Contractility decreases.

Afterload

As in skeletal muscle, afterload is the load on the muscle during contraction.

With left ventricular muscle, it represents the force that the muscle must generate to eject the blood into the aorta.

↓ Contractility → systolic failure
↳ depends on amt. of Ca^{2+}

Acceptable indices of afterload on the left ventricle are the following:

Mean aortic pressure

Hypertension: increased afterload

Hypotension: decreased afterload

Peak left ventricular pressure

The Influence of Afterload on Ventricular Ejection

The ability of the heart to eject a stroke volume depends on preload and contractility.

How large a stroke volume is actually ejected also depends on afterload.

- An acute increase in afterload reduces the volume of blood ejected.
- The blood not ejected remains in the left ventricle and increases preload in the next cycle.
- The increased preload and increased force of contraction restore stroke volume.
- Although it is more complex than outlined here, a chronic change in afterload is not necessarily accompanied by a change in preload.

Chronic exposure of the ventricle to an increased afterload (e.g., hypertension) causes it to hypertrophy. Hypertrophy increases the force of contraction at a given preload and helps maintain stroke volume.

Ventricular Volumes

End-diastolic volume (EDV): Volume of blood in the ventricle at the end of diastole

End-systolic volume (ESV): Volume of blood in the ventricle at the end of systole

Stroke volume (SV): Volume of blood ejected by the ventricle per beat

Yo ? ip - /oo

SV « EDV - ESV

End-diastolic reserve volume (EDRV): Difference between the EDV and the maximal ventricular volume

Residual volume (RV): Volume of blood in the ventricle after maximal contraction

End-systolic reserve volume (ESRV): Difference between the ESV and RV

Ventricular Volumes During a Cardiac Cycle

The ventricular volumes generated during a cardiac cycle are indicated in Figure V-2-5.

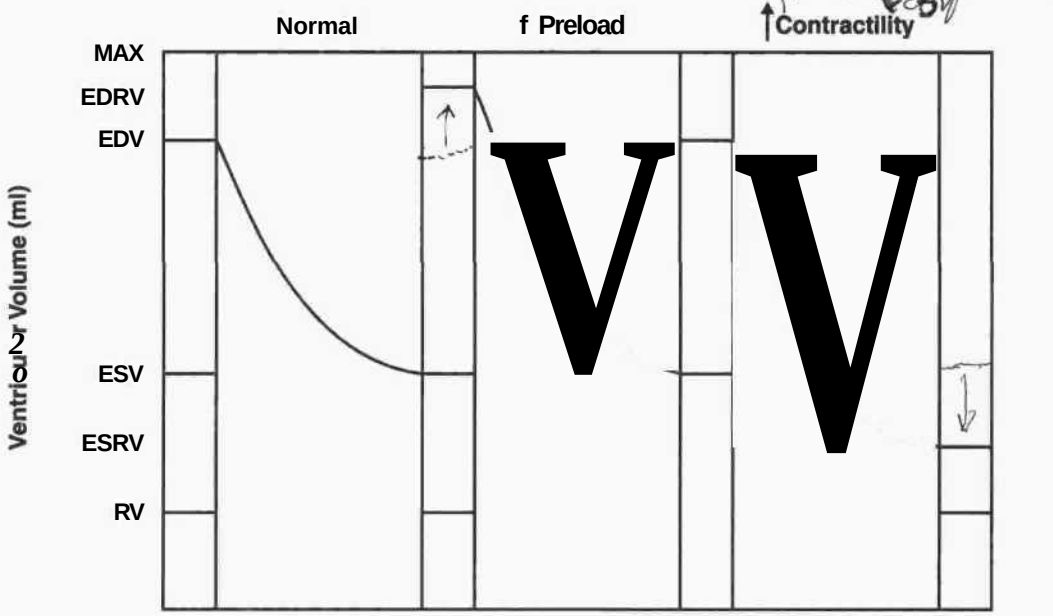


Figure V-2-5

Preload: The increase in stroke volume that occurs as a result of an increase in EDV is at the expense of the EDRV.

Contractility: The increase in stroke volume that occurs as a result of an increase in contractility is at the expense of the ESRV.

Control of Heart Rate

Intrinsic heart rate in the human is approximately 110 beats/min.

Neural Influences

Parasympathetic nerves: Right vagus predominates at SA node; left vagus at AV node slows AV conduction time.

Sympathetic nerves: Stimulation causes tachycardia; additional effect on contractility augments increase in cardiac output

(^Bainbridge Reflex)

Receptors: stretch receptors in the right atrium

Afferents: Vagus

Efferents: Vagus

Mechanism: Stretch of the right atrium leads to an increase in heart rate

Respiratory Arrhythmia

Tachycardia associated with increase in venous return to the right heart during inspiration is responsible for respiratory arrhythmia.

Responsible for the initial increase in heart rate during exercise as muscle pump increases venous return.

The Baroreceptor Reflex and the Control of Blood Pressure

Baroreceptor reflex: short-term regulation of blood pressure

Renin-angiotensin-aldosterone system: long-term regulation of blood pressure

Figure V-2-6 illustrates the main features of the baroreceptor reflex.

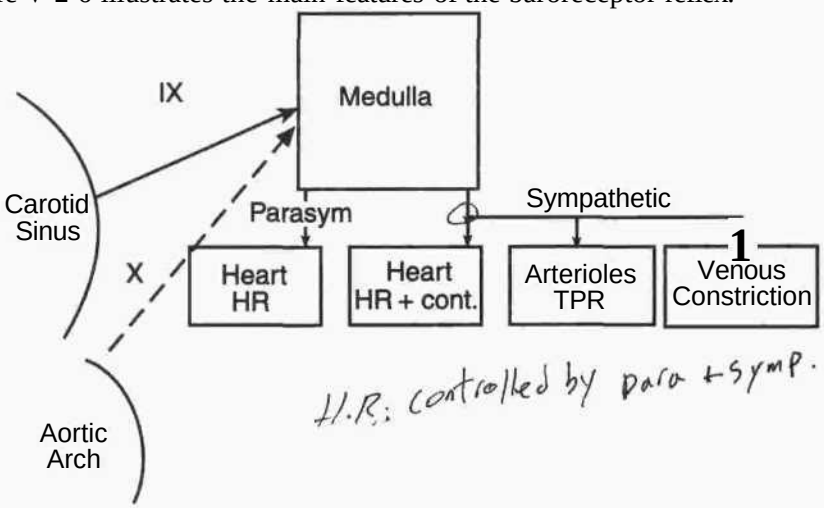


Figure V-2-6

MAP = CO X TPR

A lowered blood pressure (MAP) leads to a rise in cardiac output (CO) and total peripheral resistance (TPR1.

A rise in blood pressure leads to a decrease in cardiac output and TPR.

The main receptors of the system are located in the carotid sinus. Here the receptors monitor the stretch of the vessel wall as an index of arterial blood pressure. The afferents are always active, with impulses traveling centrally. This is necessary if both increases and decreases in blood pressure are to be detected. The medulla interprets only the afferent activity as an index of blood pressure. A rise in afferent activity signals an increase in blood pressure, and a loss of afferent activity signals a decrease in blood pressure.

The output is via the parasympathetic and sympathetic systems to change both cardiac output and TPR in a direction to return blood pressure toward the indexed set point.

Table V-2-1 summarizes these reflex changes for specific maneuvers.

Table V-2-1. Reflex Changes for Specific Maneuvers

Condition	Aff. Activity	Para.	Sym.	BP	HR
BP increase	⇈	⇅	ft	↓	↓
BP decrease	⇈	ft	⇅	t	t
Carotid occlusion	ft	ft	⇅	⇅	⇈
Carotid massage	⇈	⇃	ft	⇓	9
Cut afferents	ft	ft	⇅	⇅	⇅
Lying to stand	ft	ft	⇅	1T toward normal	⇂
Orthostatic hypotension	4	⇊	⇅	⇈ toward normal	⇅
Fluid loss	I	⇊	⇂	⇈ toward normal	⇅
Volume load	⇑	⇅	9	ft toward normal	⇓
Weightlessness	⇅	⇂	H	ft toward normal	⇓

Cardiac Cycle

Normal Cardiac Cycle

Figure V-2-7 illustrates the most important features of the cardiac cycle.

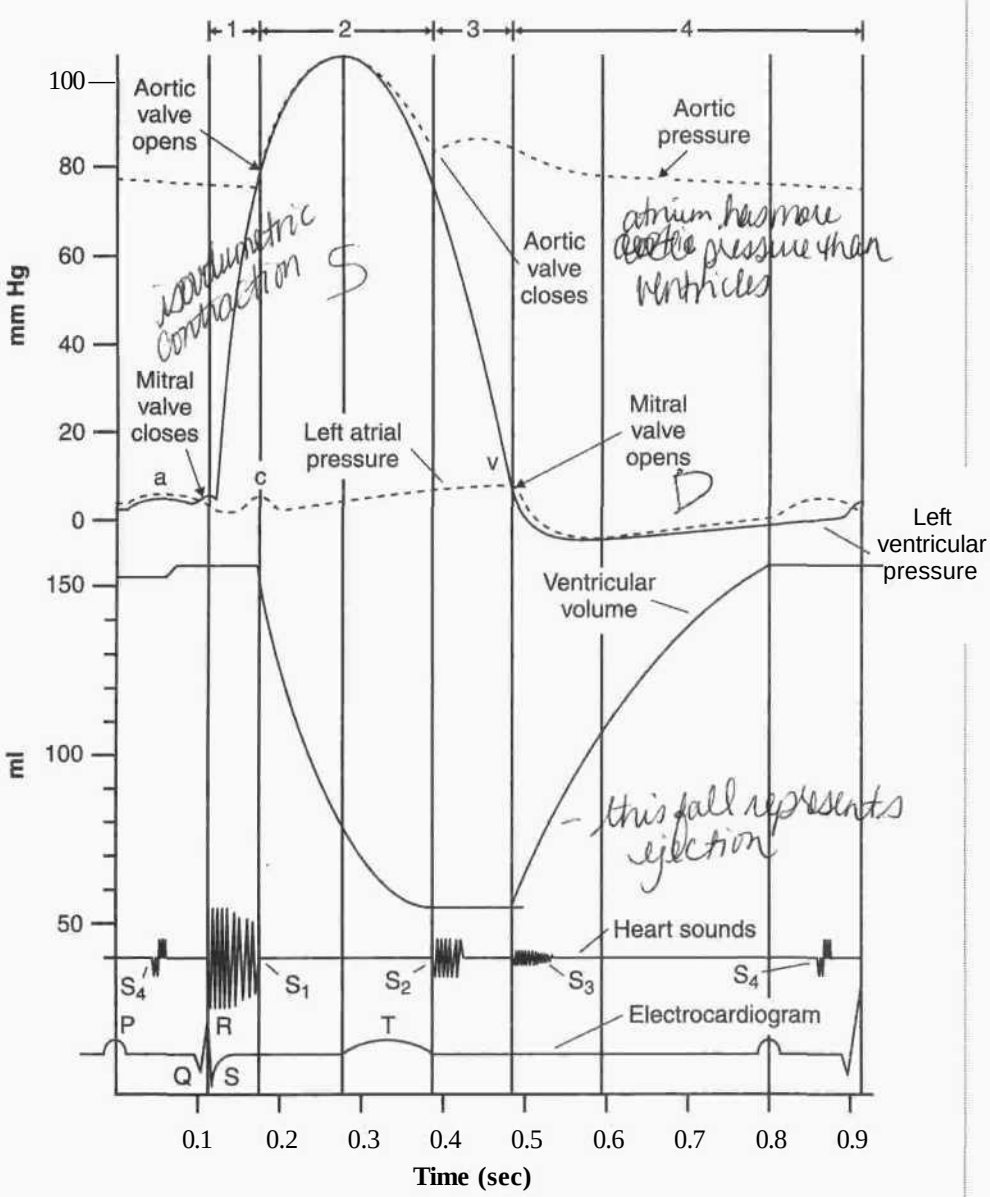


Figure V-2-7

The following describes the most important aspects of Figure V-2-7:

=* QRS => contraction of ventricle => rise in ventricular pressure above atrial => final closure of mitral valve

It is always a pressure difference that causes the valves to open and close.

Closure of the mitral valve terminates the ventricular filling phase and begins isovolumetric contraction.

Isovolumetric Contraction
No change in ventricular volume, and both valves (mitral, aortic) closed. Ventricular pressure is increasing, and volume is equivalent to end-diastolic volume.

Opening of the aortic valve terminates isovolumetric contraction and begins the ejection phase.

Ejection Phase
Ventricular volume decreasing, but most rapidly in early stages. Ventricular and aortic pressures increase initially but decrease later in phase.

Closure of the aortic valve terminates the ejection phase and begins isovolumetric relaxation.

Isovolumetric Relaxation
No change in ventricular volume, and both valves (mitral, aortic) closed. Ventricular pressure is decreasing, and volume is equivalent to end-systolic volume.

Opening of the mitral valve terminates isovolumetric relaxation and begins the filling **phase.**

Filling Phase
Ventricular volume increasing but most rapidly in initial stages. Final increase in ventricular volume is due to atrial contraction.

Heart Sounds

Systolic:

First (SI) due to closure of AV valves

Second (S2) due to closure of aortic and pulmonic valves

Diastolic: third, fourth—during ventricular filling

Valves on the right side of the heart open first but close last. A delayed closing of the pulmonic valves, as occurs during inspiration, can cause splitting of the second heart sound.

Venous ***Pulse***

Figure V-2-8 provides an example of a normal jugular venous pulse tracing. The jugular pulse is generated by changes on the right side of the heart. Pressures shown on the previous page represent those from the left heart.

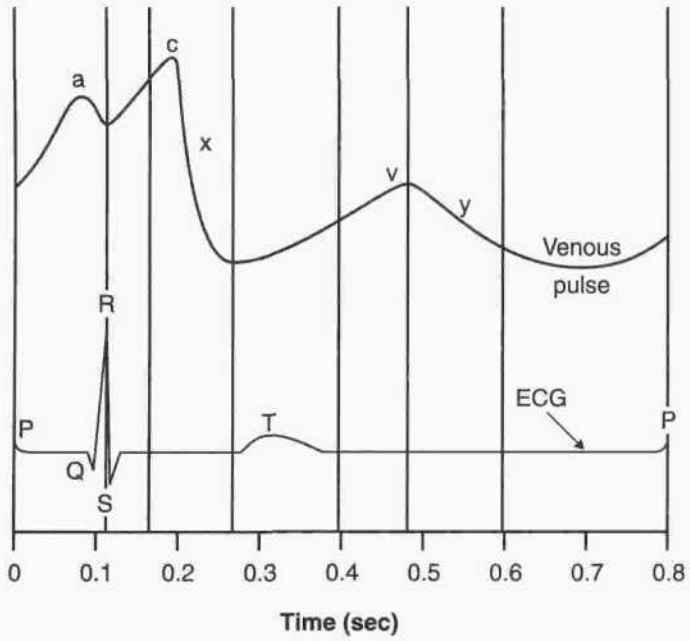


Figure V-2-8

a wave: The highest deflection and produced by the contraction of the right atrium.

c wave: Mainly due to the bulging of the tricuspid valve into the atrium (rise in right atrial pressure); occurs near the beginning of ventricular ejection.

v wave: Terminates when the tricuspid valve opens. The wave is due to the rise in right atrial pressure that develops as the right atrium fills with blood.

a wave due to contraction of rt. atrium
v wave rt. atrial filling
c wave: bulging of tricuspid valve during rt. ventricular contraction

1. Vent Press - ↑
2. yes gradient - OMMC stenosis
murmur should be in systole

VALVULAR PROBLEMS

Aortic Stenosis

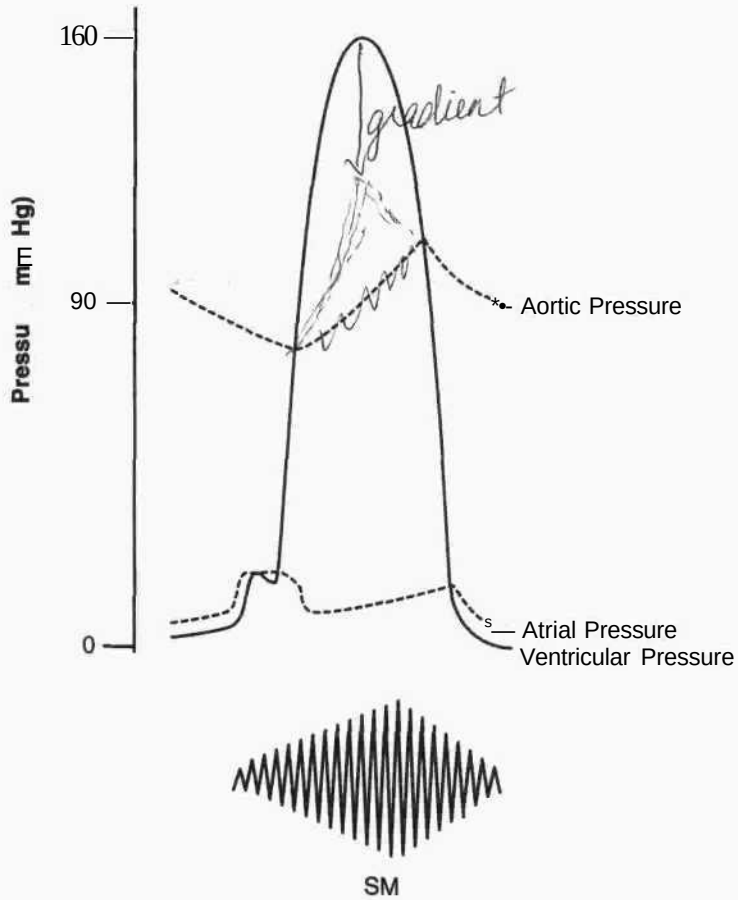


Figure V-2-9

Narrow orifice slows the rate at which SV is ejected. The aortic valve acts as a major resistance in series.

Ventricular systolic pressure increases (increased afterload) to overcome the increased resistance of the aortic valve.

Mean aortic pressure is maintained in the normal range.

There is a pressure gradient between the left ventricle and aorta during ejection.

Systolic murmur (SM).

Concentric hypertrophy.

Aortic Insufficiency

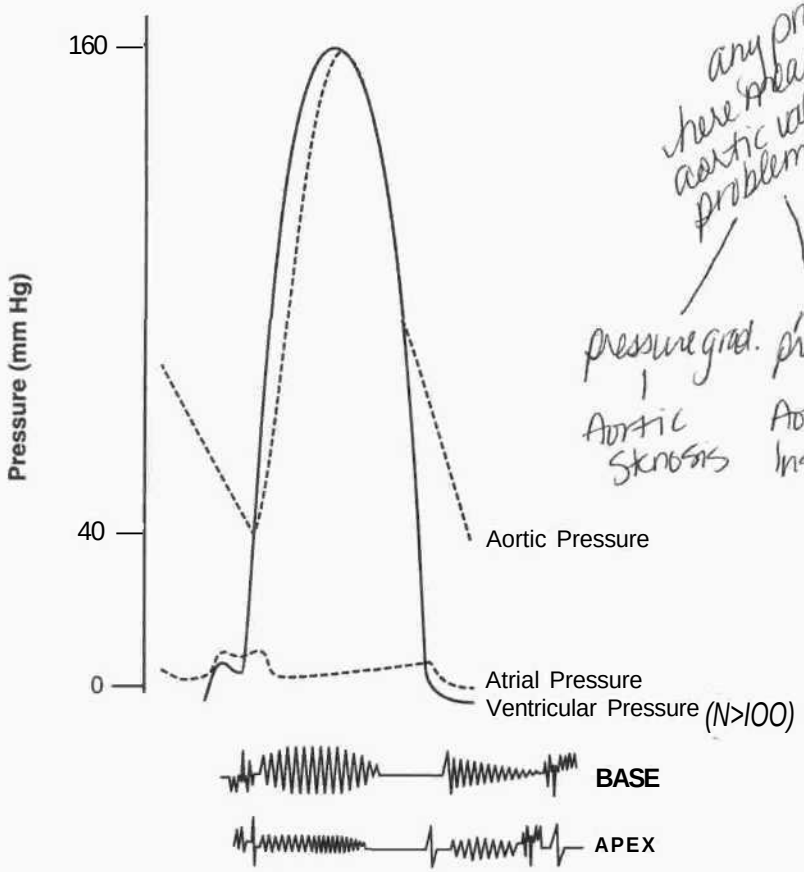


Figure V-2-10

The aortic valve does not close properly at the beginning of diastole. As a result, during diastole there is retrograde flow from the aorta into the ventricle. The amount of blood regurgitated into the left ventricle during diastole may be as much as 60-70% of the amount ejected during systole.

Increased ventricular end-diastolic pressure (increased preload)

Increased ventricular and aortic systolic pressures

Decreased aortic diastolic pressure

Increased aortic pulse pressure

Diastolic murmur

Eccentric hypertrophy

Mitral Stenosis

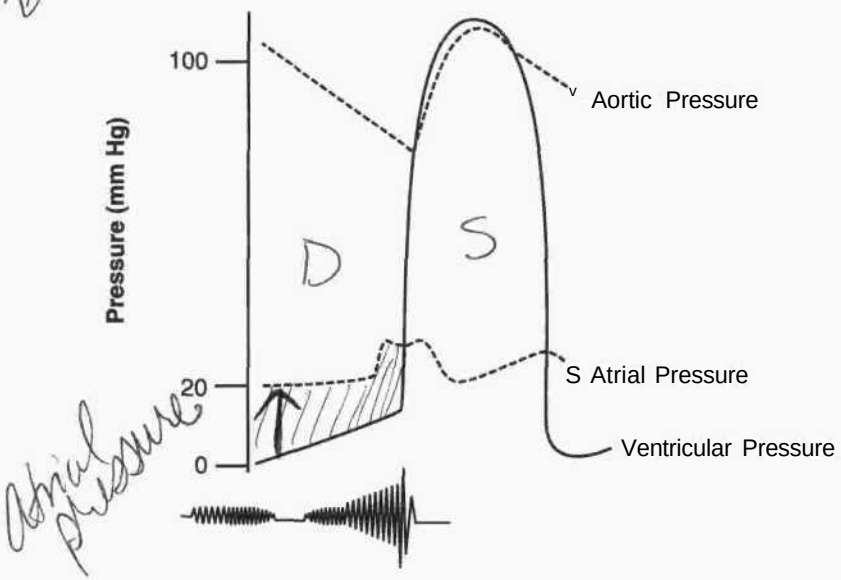


Figure V-2-11

A narrow mitral valve impairs emptying of the left atrium (LA) into the left ventricle (LV) during diastole. This creates a pressure gradient between the atrium and ventricle during filling.

Pressure and volume can be dramatically elevated in the left atrium, with little change or a decrease in the left ventricle.

Diastolic murmurs are present.

Mitral Insufficiency

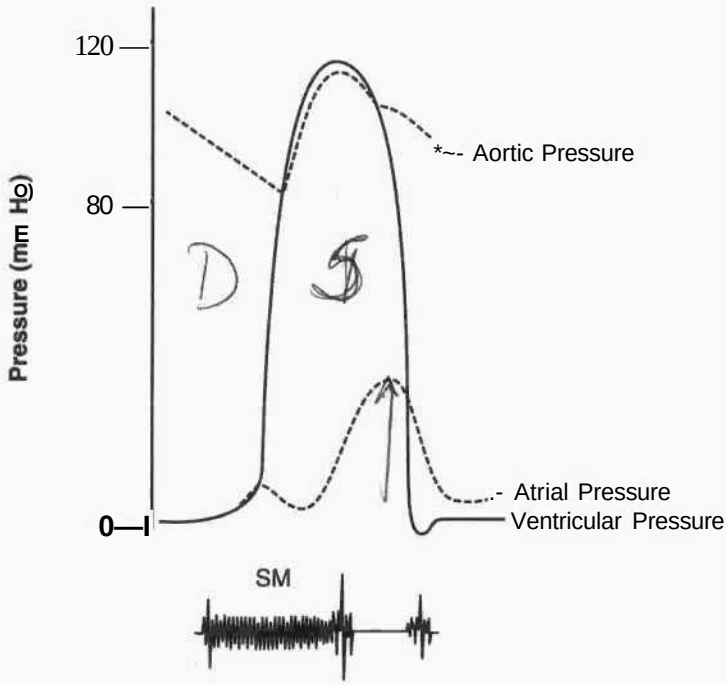


Figure V-2-12

An incompetent mitral valve allows blood to regurgitate from the LV to the LA throughout ventricular systole.

Atrial volumes and pressures are increased.

Ventricular volumes and pressures are increased during diastole, but there is no pressure gradient between the atrium and ventricle.

Systolic murmur (SM).

1. no ↑ or ↓ vent. press.
2. atrial press. - ↑ in systole
3.

PRESSURE-VOLUME LOOPS

Figure V-2-13 shows the major features of a left ventricular pressure-volume loop.

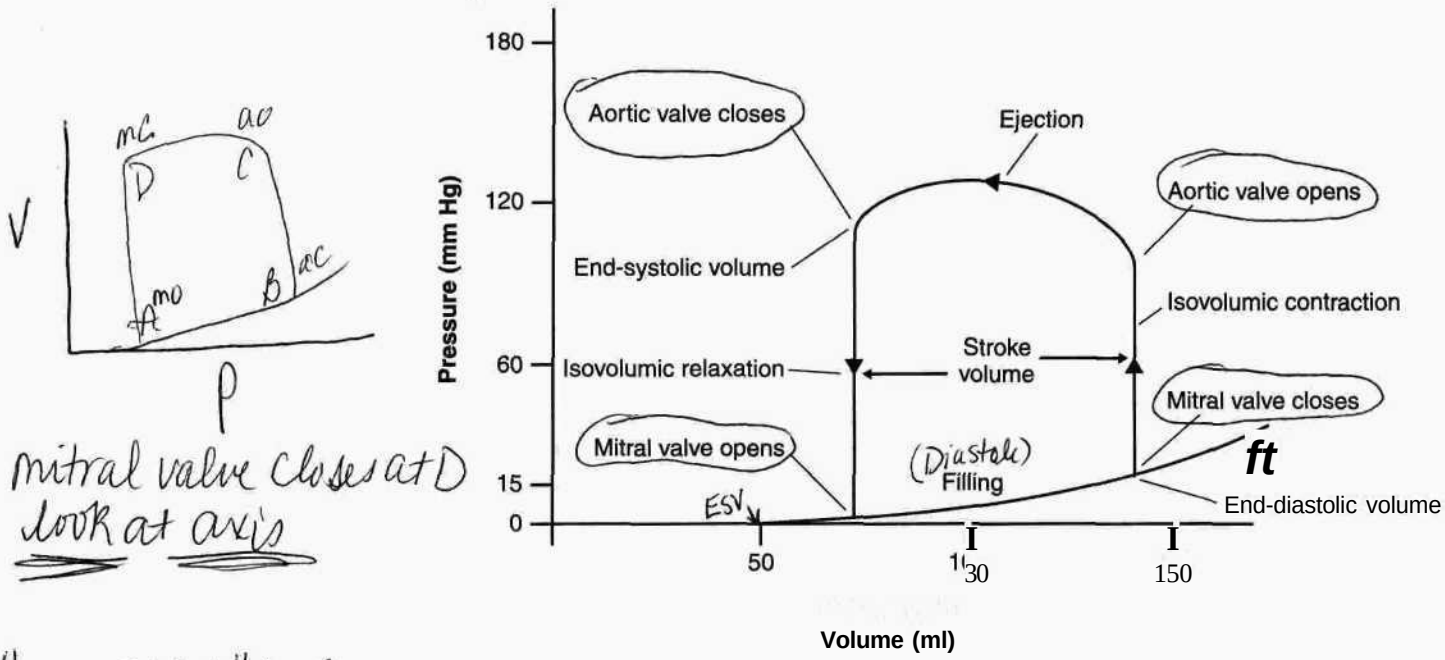


Figure V-2-13

Most of the energy consumption occurs during isovolumetric contraction.

Most of the work is performed during the ejection phase.

Mechanically Altered States

Aortic insufficiency

Increased preload, increased ventricular pressure

Heart failure (decreased contractility)

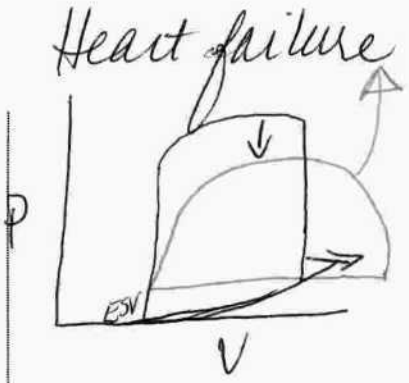
Decreased ventricular systolic pressure, increased preload, loop shifts to the right

Essential hypertension (aortic stenosis)

Increased ventricular systolic pressure

Increased contractility

Increased ventricular systolic pressure, decreased preload, loop shifts to the left



Exercise

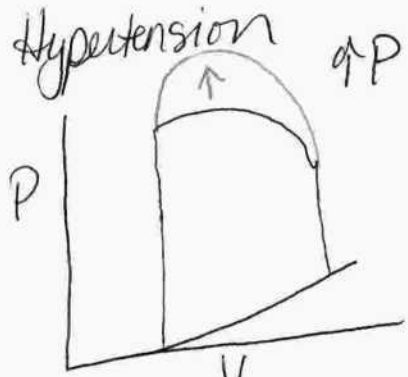
Increased ventricular pressure

Preload unchanged except in heavy exercise, when it can increase

Decreased end-systolic volume due to increased ejection fraction

BASIC ALTERATIONS DURING EXERCISE

The following assumes the person is in a steady state, performing moderate exercise at sea level.



Pulmonary Circuit

Blood flow (cardiac output)	large increase
Pulmonary arterial pressure	slight increase
Pulmonary vascular resistance	large decrease
Pulmonary blood volume	increase
Number of perfused capillaries	increase
Capillary surface area	increase, which means increased rate of gas exchange

Systemic Circuit

Arterial System

PO_2: no significant change, hemoglobin still fully saturated.

PCO_2: no significant change, increase in ventilation proportional to increase in metabolism.

pH: no change or a decrease due mainly to the production of lactic acid.

Mean arterial pressure: slight increase.

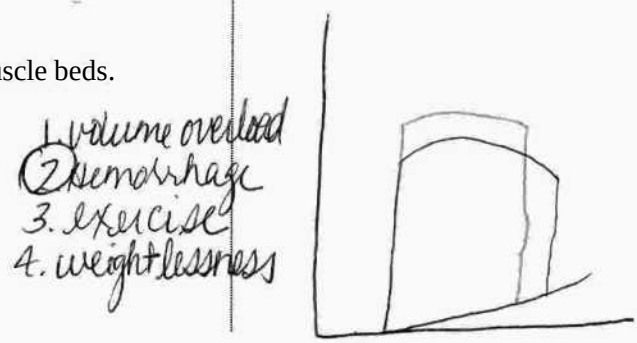
Blood flow: large increase.

Vascular resistance (TPR): large decrease, dilation of skeletal muscle beds.

Ita.lt*.

PO_2: decrease.

PCO_2: increase.



Regional Circulations

ExercisingSkeletalMuscle

Blood flow increases.

Vascular resistance decreases.

Capillary pressure increases.

Capillary filtration increases.

Lymph flow increases.

Venous PO_2 decreases and can reach extremely low levels.

Extraction of oxygen increases.

CutaneousBloodFlow

Initial decrease, then an increase to dissipate heat.

CoronaryBloodFlow

Increase due to increase in volume work of the heart.

CerebralBloodFlow

No significant change (arterial CO_2 remains unchanged).

RenalandGIBloodFlow

Any change would be a decrease. This is more likely in the splanchnic circuit.

Heart

Exercise produces an increase in the volume work of the heart that is mainly carried out by an increase in heart rate rather than an increase in stroke volume.

In light and moderate exercise, there may be no increase in preload. Preload does increase in heavy exercise.

Physical Conditioning

Regular exercise will raise maximal oxygen consumption ($\dot{V}0_2max$) by:

L Increasing the ability to deliver oxygen to the active muscles. It does this by increasing the cardiac output (CO).

The resting conditioned heart has a lower heart rate but a greater stroke volume (SV) than does the resting unconditioned heart.

During exercise, there is an increase in stroke volume, as much as 35% above resting levels.

However, the maximal heart rate remains similar to that of untrained individuals.

2. Regular exercise also increases the ability of muscles to utilize oxygen. There are:

An increased number of arterioles, which decrease minimal resistance during exercise.

An increased capillary density, which increases the surface area and decreases diffusion distance.

An increased number of oxidative enzymes in the mitochondria.

Chapter Summary

Ventricular performance is determined by the amount of preload and the level of contractility.

Acutely, the preload effect is determined by sarcomere length, and contractility by the availability of calcium.

The best indices of preload are ventricular end-diastolic volume and pressure, and indices of contractility include the rate of pressure development during isovolumetric contraction and ejection fraction.

Both preload and contractility alter the force of ventricular contraction, but only contractility will have a significant effect on systolic interval.

A loss of preload or contractility will produce an increase in the other factor, which functions to minimize the loss in ventricular performance.

The baroreceptor reflex alters parasympathetic and sympathetic outflow to minimize acute changes in blood pressure.

Aortic stenosis increases afterload and produces a pressure gradient between the ventricle and aorta during ejection.

Aortic insufficiency increases preload and produces a retrograde flow from the aorta into the ventricle during isovolumetric relaxation.

Mitral stenosis increases left atrial volume and pressure, but ventricular volumes and pressures are normal or reduced.

Mitral insufficiency increases volumes and pressures in the atrium and ventricle.

Physical conditioning increases $V0_2max$ by increasing the delivery and the utilization of oxygen by the active muscles.

CARDIAC MUSCLE

Heart's Electrical Activity: Review Questions

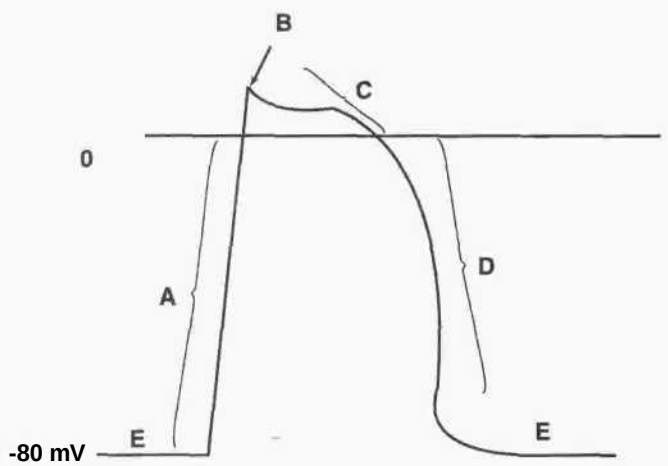
Questions 1-2. Select ALL the correct answers.

1. Which of the following structures are commonly seen in both skeletal and cardiac muscle?
   A. Gap junctions
   B. Sarcoplasmic reticulum
   C. Somatic innervation (neuromuscular junction)
   D. Troponin

2. Which of the following changes would be expected to make the membrane potential of a muscle cell more positive than normal (resting cell)?
   A. Increased conductance to calcium
   B. Increased conductance to potassium
   C. Decreased conductance to potassium
   D. Decreased conductance to sodium

DIRECTIONS for questions 3-6: Select the ONE best answer.

Questions 3-4



Correlate the ionic mechanism to the appropriate phase (labeled A-E)

3. High Na^+ conductance

4. High Ca^{2+} conductance

Questions 5-6

A. Cardiac muscle
B. Skeletal muscle
C. Both
D. Neither

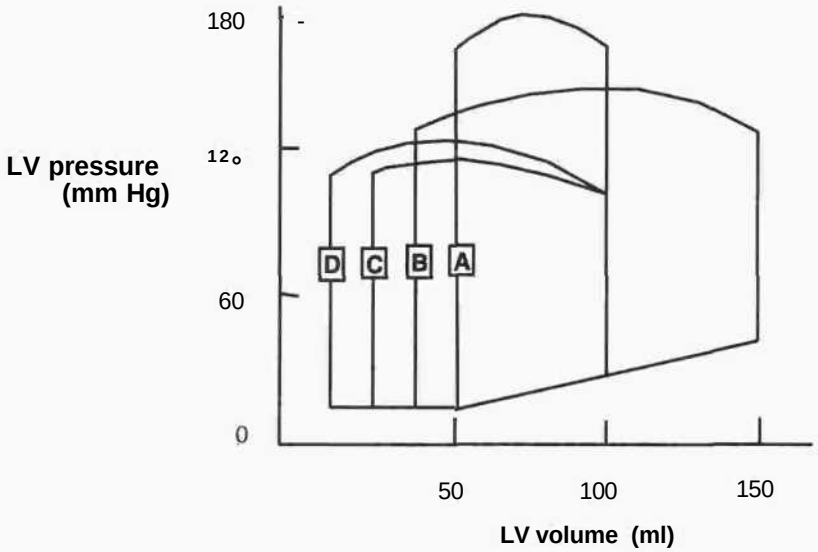
5. Force of contraction relatively insensitive to extracellular Ca^{2+}

6. Developed tension increases with increased free intracellular Ca^{2+}

Pumping Action of the Heart: Review Questions

DIRECTIONS for Questions 1-9: Select the ONE best answer.

Questions 1-2



The diagram above depicts four pressure-volume loops of the left ventricle (labeled A-D), illustrating different functional states. Loop D illustrates the control state.

1. Which pressure-volume loop best describes the response to a sudden increase in afterload?

2. Which pressure-volume loop best describes the response to a negative inotropic agent?

Questions 3-4

The following data were obtained from an individual:

temperature = 98°F
pulse rate = 200 beats/min
respiration = 30/min
mean arterial blood pressure = 85 mm Hg
right atrial pressure = 1 mm Hg
oxygen consumption = 20,000 ml/10 min
pulmonary artery oxygen content =10 ml/100 ml blood
aortic oxygen content = 20 ml/100 ml blood
coronary sinus blood oxygen content = 5 ml/100 ml blood
end diastolic volume = 120 ml
end systolic volume = 20 ml
body surface area = 0.47 m^2

3. The cardiac output of this person is:

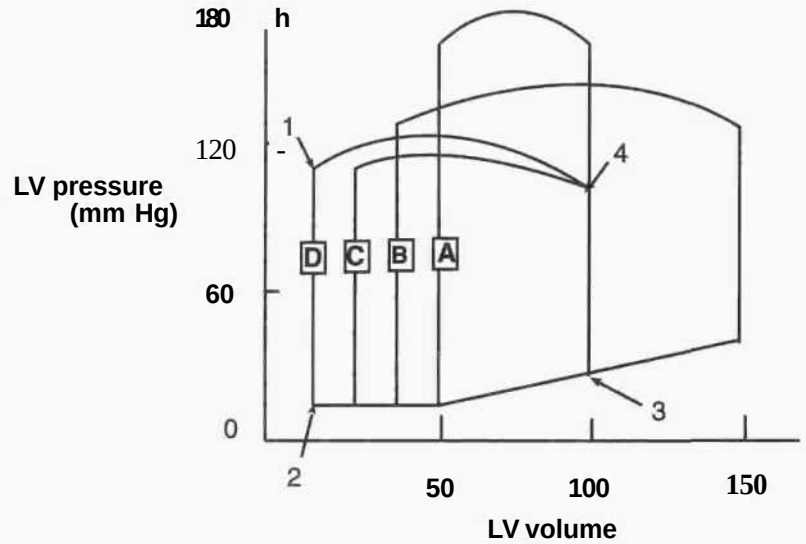
   For CO use the Fick principle
   or
   CO = HR X SV

   A. 2L/min
   B. lOL/min
   C. 20L/min
   D. 25L/min
   E. 30L/min

4. The ejection fraction of this person is:
   EF = stroke volume/end-diastolic volume

   A. 0.40
   B. 0.60
   C. 0.80
   D. 0.95
   E. 1.00

Question 5-6



The diagram above depicts four loops (labeled A-D) illustrating pressure-volume relationships of a left ventricle in different functional states. "D" = control loop.

5. Which P-V loop best describes the condition of aortic insufficiency?
   A. loop A
   B. loopB
   C. loop C
   D. loopD

6. Which of the four parts, labeled 1-4, in loop D coincides with the opening of the mitral valve?
   A. point 1
   B. point 2
   C. point 3
   D. point 4

Question 7

The following data were collected from an individual in a supine position:

temperature = 98°F
pulse rate = 83 beats/min
respiration = 15/min
blood pressure = 125/75 mm Hg
oxygen consumption = 1200 ml/12 min
pulmonary artery oxygen content = 16 ml/100 ml blood
aortic oxygen content = 20 ml/100 ml blood
coronary blood flow to left ventricle = 100 ml/min
coronary sinus blood oxygen content = 5 ml/100 ml blood
body surface area = 8.3 m^2

7. The stroke volume of this individual is approximately:
   A. 30 ml
   B. 60 ml
   C. 70 ml
   D. 80 ml
   E. 90 ml

8. In aortic stenosis:
   A. the peak left intraventricular pressure is lower than systolic arterial blood pressure
   B. the peak intraventricular pressure is equal to the systolic arterial blood pressure
   C. The peak left intraventricular pressure is usually higher than the systolic arterial blood pressure
   D. both the peak left intraventricular pressure and systolic arterial blood pressure are higher than normal (> 120 mm Hg)
   E. both the peak left intraventricular pressure and systolic arterial blood pressure are lower than normal

9. In mitral stenosis:
   A. both the left atrial pressure and the left ventricular pressure are higher than normal
   B. the left atrial pressure is higher than normal whereas the left ventricular pressure is equal to or less than normal
   C. the left atrial pressure is normal and the left ventricular pressure is higher than normal
   D. both the left atrial pressure and the left ventricular pressure are lower than normal

Questions 10-14. Select all the correct answers.

10. Which of the following changes in the ventricles can be due to the effects of epinephrine?
    A. increased *dpldt* during isovolumetric contraction
    B. increased peak intraventricular pressure
    C. increased rate of relaxation of the myocardium
    D. increased rate of firing of the Punkinje fibers

11. The production of the second heart sound is due to the closure of the:
    A. mitral valve
    B. aortic valve
    C. tricuspid valve
    D. pulmonic valve

12. The dicrotic notch of the aortic blood pressure curve:
    A. is produced by the contraction of the left ventricle
    B. signals the beginning of the isovolumetric relaxation phase
    C. associates with the third heart sound
    D. signals the closure of the aortic valve

13. Increased volume work of the left ventricle occurs in:
    A. aortic stenosis
    B. anemia
    C. interatrial septal defect
    D. hyperthyroidism

14. Which of the following changes in cardiac function can be related to the effects of norepinephrine?
    A. increased contractility
    B. increased rate of phase 4 depolarization of the sinoatrial node
    C. increased intraventricular pressure
    D. increased force of contraction associated with increased end-diastolic volume

In each of the foUowing patients choose one of the following problems that best fits the data provided.

A. Aortic insufficiency
B. Aortic stenosis
C. Mitral insufficiency
D. Mitral stenosis

Normal values (mm Hg)		
	systolic	**diastolic**
LV	120	<10
RV	25	**<10**

PATIENT 1

A 58-year-old man was evaluated for recurrent episodes of congestive heart failure over the previous 3 months that did not respond to digitalis.

Physical Examination: Vital signs: pulse 115; respirations 26; blood pressure 100/50.
Cardiac: prominent systolic murmur.

Laboratory Findings: ECG: sinus tachycardia; left atrial enlargement; left ventricular hypertrophy.
Cardiac Catheterization: left ventricle 140/11.5, right ventricle 28/6.5

PATIENT 2

A 60-year-old man had mild dyspnea, worsening on exertion. Following examination, mild chest pain developed and the manifestations of acute pulmonary edema occurred.

Physical Examination: Vital signs: pulse 100, respirations 30, blood pressure 110/60. General moderate respiratory distress. Neck: no jugular venous distension.
Chest: rales over lower 1/3 of lung fields.
Cardiac: diastolic murmur noted.
Extremities: no edema
Cardiac Catheterization: left ventricle 110/6, right ventricle 32/8

PATIENT 3

A 37-year-old man with a known heart murmur since the age of 22 complained of dyspnea on exertion.

Physical Examination: Vital signs: pulse 86, respirations 22, blood pressure 152/51.
Chest: clear.
Cardiac: diastolic murmur radiating down left sternal border.
Laboratory Findings: left ventricular hypertrophy
Cardiac Catheterization: left ventricle 151/14, right ventricle 29/8

PATIENT 4

A 58-year-old man complained of intermittent dyspnea. He suddenly developed pulmonary edema and was treated with diuretics. The pulmonary edema recurred 2 days later and was again treated with diuretics.

Physical Examination: Vital signs: pulse 92, respirations 32, blood pressure 96/62.
General respiratory distress.
Neck: no jugular venous distention.
Chest: rales over lower lung fields.
Cardiac: systolic murmur
Cardiac Catheterization: left ventricle 98/16, right ventricle 29/7

Blood Pressure Regulation: Review Questions

Questions 1-2

Select all the correct answers.

1. A patient suffers a blood loss over a period of 20 minutes. At the end of this period, his arterial pressure has changed from 100 to 70 mm Hg and his heart rate from 70 to 140/min. His hematocrit is 36% and his skin is cold. Which of the following conditions would **not** be expected to occur in this situation?

   A. A decreased capillary hydrostatic pressure
   B. A decreased interstitial fluid volume
   C. An increased plasma colloid osmotic pressure
   D. An increased total systemic resistance

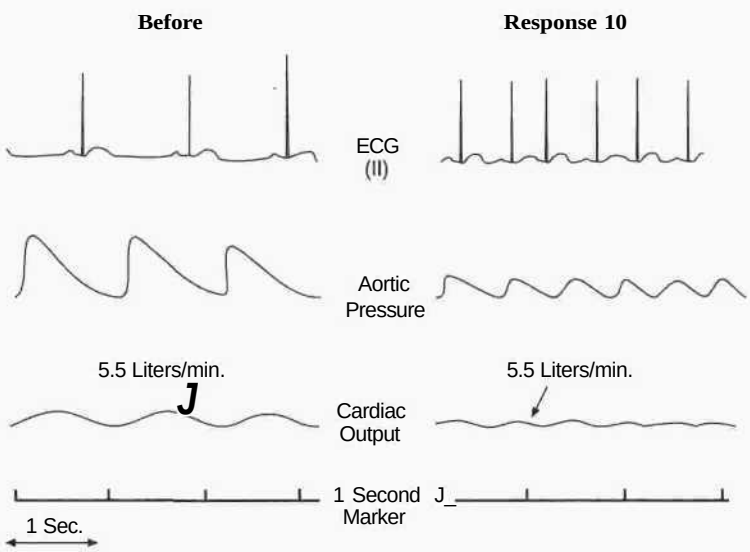
2. Some other responses to the hemorrhage discussed in question 1 include (check each correct answer):

   A. A decreased glomerular filtration rate
   B. A decrease in venous tone
   C. Sodium retention
   D. A decreased secretion of antidiuretic hormone (ADH)
   E. An increased production of angiotensin II (A-II)

Question 3

Select the ONE best answer.

3. The following record demonstrates an individual's response to drug X:



On the basis of these data you could conclude that drug X produced:

A. An increased pulse pressure
B. An increased peripheral resistance
C. A decreased arterial pressure due to venous dilation
D. An increased systolic pressure
E. A reflex increase in heart rate

Question 4

Select the ONE best answer.

4. Check each of the following changes produced by a decrease in the carotid sinus pressure from 90 mm Hg to 70 mm Hg:

   1. A decrease in the frequency of impulses moving centrally in the glossopharyngeal nerve
   2. A reflex stimulation of cardiac sympathetic neurons
   3. A reflex stimulation of cholinergic postganglionic sympathetic neurons

   Which one of the following best summarizes your conclusions?

   A. Statement 1 is correct
   B. Statement 2 is correct
   C. Statements 1 and 2 are correct
   D. Statements 2 and 3 are correct
   E. Statements 1,2, and 3 are correct

Question 5

Select all the correct answers.

5. The total systemic peripheral resistance is increased in response to (check each correct statement):

   A. A decreased blood volume (i.e., hemorrhage)
   B. Changing from a reclining to a standing position
   C. Hypertension produced from overtransfusion
   D. Lifting a heavy load
   E. Strenuous running

DIRECTIONS: Choose the answer that reflects a major change occurring with each of the following situations.

Questions 6-9

A. Increased left ventricular stroke volume.
B. Increased right ventricular stroke volume.
C. Decreased left ventricular stroke volume.
D. Decreased right ventricular stroke volume.
E. Both A and B are correct.

6. Aortic insufficiency

7. The beat that follows a sudden increase in pulmonary arterial pressure

8. Patent ductus arteriosus

9. During exercise

Questions 10-11

Choose A if the following statement is true or B if it is false.

10. The peak systolic wall tension of the left ventricle increases when the arterial blood pressure suddenly increases.

11. The function of the baroreceptor reflex is such that an increased arterial blood pressure leads to decreased vagal parasympathetic activity.

Questions 12-13

Select the ONE best answer.

12. Aortic insufficiency:
    A. increases aortic pulse and diastolic pressure
    B. increases pulse pressure and decreases diastolic pressure
    C. decreases aortic pulse and diastolic pressure
    D. is similar to vasoconstriction in that it decreases pulse pressure and increases diastolic pressure
    E. is similar to vasodilation in that it decreases pulse pressure and increases diastolic pressure

13. Venous return to the right heart is normally increased by:
    A. increased minute ventilation
    B. increased venous tone
    C. increased cardiac sympathetic tone
    D. all of the above
    E. none of the above

14. Write in Column I each of the appropriate matches from Column II (F, G, H, etc.). Each item in Column II can be used once or more than once. The numbers in parentheses represent the number of appropriate matches for the items in Column I.

Column I (Mechanisms)

1._____warming the blood to the hypothalamus of the brain causes a reflex vasodilation in this circulation (1)

2._____a 30% decrease in the total blood volume does NOT cause a reflex vasoconstriction in this part of the systemic circulation (2)

3._____resistance to flow increases in response to a local decrease in Po_2 (1)

4._____resistance to flow decreases during running even when body temperature remains constant (3)

5._____contains high- and low-pressure capillaries that are in series with each other (1)

6._____contains only low-pressure capillaries (1)

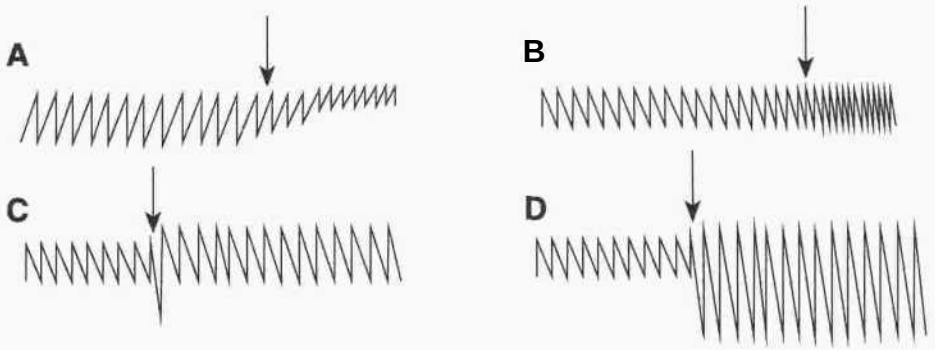
7._____its veins have the lowest concentration of oxygen found in the body (1)

8._____its veins have the highest concentration of oxygen found in the systemic circulation **(1)**

Column II (Systems)

F. cerebral circulation
G. coronary circulation
H. cutaneous circulation
I. gastrocnemius muscle
J. renal circulation
K. pulmonary

15. The following records were obtained from a patient with a decentralized heart (i.e., an individual who has received a heart transplant). In each of these records the aortic pressure was recorded at a constant paper speed and amplification.



Identify in questions 1 through 4 in which record (A through D) each of the indicated changes occurred. The arrow points to where the change began.

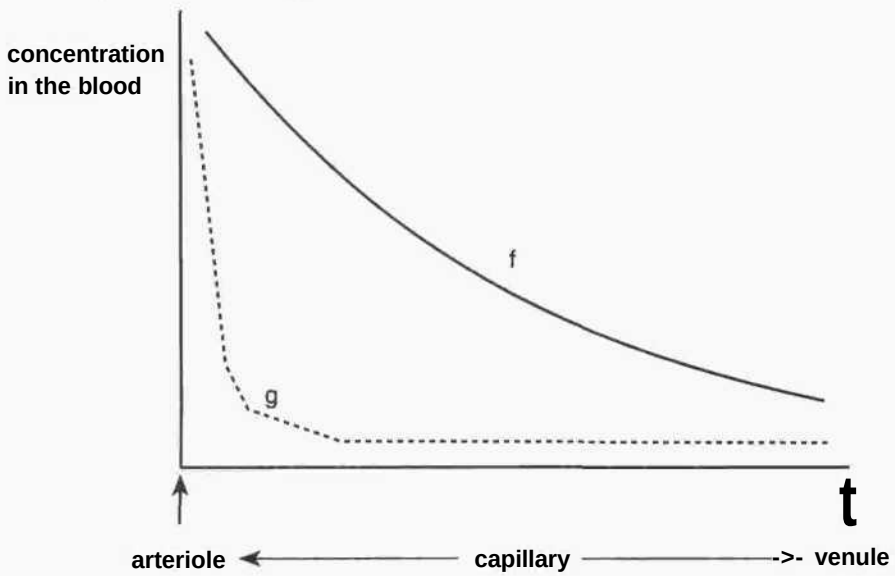
1._____an increased left ventricular stroke volume

2._____an increased heart rate

3._____an increased total systemic resistance

4._____aortic insufficiency

16. In a healthy individual two substances, f and g, are found to have a lower concentration on the venular side of a capillary than the arteriolar side. Their concentration in the blood changes as they pass through the capillary in the following manner.



What valid conclusions can you make from this figure?

(Wait for pulmonary if there is a problem understanding terms)

A. substance f is blood flow-limited (i.e., perfusion-limited)
B. substance g is perfusion-Umited
C. both A and B are correct

Electrical Activity of the Heart: Answers

1. AnsB, D All muscle has sarcoplasmic reticulum, therefore it is present in both skeletal and heart muscle. Troponin, which binds calcium, is also present in both muscle types. There is nothing resembling gap junctions in skeletal muscle. Gap junctions (intercalated discs) are regions of low electrical resistance that permit action potentials to be transmitted cell to cell. Each skeletal muscle cell must be innervated in order to function.

2. **Ans** A, C Increased conductance to calcium would cause an influx of calcium and membrane depolarization. This is the main mechanism of depolarization in the pacemaker cells, which have the slow but not the fast voltage-gated channels. Decreased conductance to potassium means the potassium that is pumped into the cell cannot diffuse out as readily. The accumulation of these positive potassium charges inside the cell would slowly depolarize the cell. Increased conductance to potassium would accelerate the resting efflux of potassium and hyperpolarize the cell (make cell more negative). It would take an increase conductance to sodium and the subsequent influx to make the cell more positive.

3. **Ans** A Assuming this is a fast cell (regular contracting heart muscle cell), then the fast (sodium) channels will be open in A.

4. **Ans** C The slow voltage-gated channels, because they are slow to open, peak in the plateau phase.

5. **Ans** B Extracellular calcium does not participate, to any great extent, in the contraction of a skeletal muscle cell. On the other hand, in heart muscle, extracellular calcium enters through the slow channels during the plateau phase of the action potential and actively participates in the contractile mechanism.

6. AnsC The more free intracellular calcium, the more troponin-bound calcium and the greater the force of contraction up to the point where the system becomes saturated with calcium. This applies to both skeletal and cardiac muscle.

Pumping Action of the Heart: Answers

1. **Ans** A In all of these questions remember, it is the best answer that is to be selected. Some of the details you might expect to see will not be included in the loops. The obvious change to expect with an increase in afterload is an increased pressure generated by the ventricle during systole. The only loop that demonstrates this effect over the control loop D is loop A. Here systolic pressure rises to about 180 mm Hg.

2. **Ans** C A negative inotropic agent would decrease the force of contraction and thus a decrease in ventricular systolic pressure would ensue. The only loop that shows this effect is loop C. The increase in preload that likely would occur is not demonstrated, but the best answer is still loop C.

3. **Ans** C This calculation, as stated, can be performed two ways.

Fick principle:

$$\mathbf{CO} = \frac{\text{oxygen consumption}}{\text{pulmonary A-V } O_2 \text{ difference}}$$

$$= \frac{2{,}000 \text{ ml/min}}{0.2 \text{ ml/ml} - 0.1 \text{ ml/ml}} = 20{,}000 \text{ ml/min or } 20 \text{ L/min}$$

0.2 ml/ml = pulmonary venous blood which is the same as systemic arterial
0.1 ml/ml = pulmonary arterial blood

CO = HRXSV
= 200beats/min X 100 ml
= 20,000 ml/min

SV = EDV-ESV
= 120 ml - 20 ml = 100 ml

4.AnsC ejection fraction = stroke volume/end-diastolic volume
= 100 ml/120 ml = 0.833; best answer 0.8

5.AnsB Aortic insufficiency is characterized with a large increase in preload and usually a slight increase in ventricular systolic pressure (increased preload increases force of contraction). The only loop that shows an increased preload is loop B which must be the best answer.

6.AnsB The mitral valve opens at the beginning of ventricular filling or, putting it another way, at the end of isovolumetric relaxation. This represents point 2 on the figure.

7. Ans A This represents another calculation using the Fick principle to obtain cardiac output and then dividing by heart rate to obtain stroke volume.

$$CO = \frac{\text{oxygen consumption}}{\text{pulmonary A-V O2 difference}}$$

$$= \frac{100 \text{ ml/min}}{0.2 \text{ ml/ml} - 0.16 \text{ ml/ml}} = 2500 \text{ ml/min}$$

stroke volume = 2500/83 = 30 ml

8. **Ans** C In aortic stenosis the aortic valve does not open properly during systole, and because it acts as a resistance, pressure decreases across the valve. In most cases the ventricular pressure development increases to compensate for the aortic valve resistance, and the loss of pressure across the valve means aortic systolic pressure will be less than ventricular systolic pressure.

9. **Ans** B With mitral stenosis the valve does not open properly during ventricular filling, and flow from the atrium to the ventricle is restricted. Consequently blood is retained in the left atrium, and atrial pressure and volume increase. Ventricular volumes and pressures if anything will decrease.

10. **Ans** A, B, C, D Epinephrine will increase the contractility of the myocardium and heart rate. A, B, and C are all changes associated with an increase in contractility. These were all discussed in class and can be explained on the basis of changes in calcium dynamics. When heart rate increases, all cells in the heart will be firing at a higher rate, this includes the Purkinje cells.

11. **Ans** B,D The second heart sound occurs at the end of systole and is the combination of the closing of the aortic and pulmonic valves.

12. **Ans** B, D The dicrotic notch occurs at the end of ventricular systole and is produced by changes induced by the close of the aortic valve. It also marks the beginning of isovolumetric relaxation of the ventricle.

13. **Ans** B, D Increased volume work of the ventricle means an increase in volume pumped (cardiac output) without a significant change in afterload (usually blood pressure). Increased pressure work means a significant increase in afterload. In anemia, cardiac output increases because of the decreased viscosity and the decreased oxygen content of the systemic arterial blood. More blood must be pumped to supply the same amount of oxygen to the tissues per unit time. In hyperthyroidism body metabolism is elevated and thus an increase in cardiac output is necessary for the increased oxygen demands. Aortic stenosis would be increased pressure work of the heart, and an intra-atrial septal defect would be an increase in volume work of the right ventricle (flow through the septal defect is usually left to right).

14. **Ans A,B,C** Norepinephrine will increase contractility and heart rate. C will occur because of the increased contractility. B is the source of the increased heart rate. The sympathetics increase the rate of depolarization of the pacemaker potential (phase 4 depolarization) and in doing so the cell reaches threshold sooner. An increase in the force of contraction associated with an increase in end-diastolic volume is the preload effect. Contractility actually decreases preload because of the increased ejection fraction induced.

Cardiovascular Patient Cases: Answers

In the data provided the presence of a systolic versus a diastolic murmur will help limit the possibilities from 4 to 2. In a stenotic valve a murmur will occur when the valve is normally open and with an incompetent valve a murmur will occur when the valve is normally closed.

	Mitral	Aortic
systolic	insuff.	stenosis
diastolic	stenosis	insuff.

Patient 1 **Ans** B The presence of the systolic murmur means that it must be either mitral insufficiency or aortic stenosis. Both cases represent the possibility of left atrial and left ventricular enlargement. The definitive measurement is the pressure gradient across the aortic valve during systole. Left ventricular systolic pressure is 140 whereas aortic systolic pressure is 100 mm Hg. This value alone defines the problem as aortic stenosis.

Patient 2 **Ans** D The presence of the diastolic murmur probably means mitral stenosis or aortic insufficiency. Aortic insufficiency is characterized by a large increase in preload, but here left ventricular diastolic pressure is normal. The data are consistent with mitral stenosis. The rise in left atrial pressure has been transmitted into the pulmonary circuit, producing edema and congestion.

Patient 3 **Ans** A The diastolic murmur probably indicates either mitral stenosis or aortic insufficiency. With mitral stenosis the ventricle cannot fill adequately, and you would expect ventricular volume to be normal or below normal. Left ventricular hypertrophy indicates an enlarged ventricle, and the elevated left ventricular diastolic pressure demonstrates a rise in preload. This is all consistent with aortic insufficiency.

Patient 4 **Ans** C The systolic murmur probably indicates either aortic stenosis or mitral insufficiency. There is no large pressure gradient across the aortic valve during systole, therefore it cannot be

aortic stenosis. The data are consistent with mitral insufficiency, a rise in left ventricular diastolic pressure, and elevated left atrial pressures transmitted back to the pulmonary circuit, producing some congestion.

Blood Pressure Regulation: Answers

1. **AnsC** The loss of blood volume would decrease cardiac output, and blood pressure would drop. To compensate there would be a peripheral vasoconstriction to raise TPR. A peripheral constriction will decrease capillary pressure and promote the reabsorption of fluid from the interstitium. If anything this would dilute plasma proteins and decrease plasma colloid osmotic pressure.

2. **Ans** A, C, E Because of the decreased blood pressure and increased peripheral vasoconstriction, which would usually include the kidney, there would be decreased glomerular filtration and increased sodium retention. A drop in blood pressure means increased secretion of ADH and fluid retention. A drop in blood pressure and increased sympathetic activity is a stimulus to release renin, which then causes a rise in A-II. The increased sympathetic activity would if anything increase venous tone to add blood to the circulating volume as a compensation for hemorrhage.

3. Ans E The data shown demonstrate the following:

ECG—increased heart rate

aortic pressure—decreases

cardiac output— no change

Therefore based on our hemodynamic equation that applies to the systemic circuit

MAP = CO X TPR

↓ same ?

The conclusion is that the decreased blood pressure must be caused by a decrease in TPRll.

Ans A The data show a decrease in pulse pressure (systolic - diastolic).

Ans B We already concluded that the drug caused a decrease in TPR.

Ans C If there was a dilation of veins, more blood would pool there and.cardiac output would decrease. But cardiac output was unchanged.

Ans D Aortic systolic pressure decreased.

Ans E The decrease in blood pressure, via the carotid sinus, caused a reflex increase in heart rate.

4. Ans C A drop in blood pressure means less stretch on the carotid sinus receptors and therefore decreased afferent activity. A decrease in afferent activity is interpreted by the CNS as a drop in blood pressure; thus, sympathetic outflow should increase and parasympathetic outflow should decrease.

5. **Ans** A, B, D Hemorrhage will decrease cardiac output and blood pressure. To compensate, increased sympathetic activity will raise TPR. Standing up is similar to A. The gravity effect on the dependent veins increases their blood volume, which decreases circulating blood volume and blood pressure. Again, the response is increased sympathetic activity and an increase in TPR. If one becomes hypertensive, e.g., because of an overtransfusion of blood, the natural response is to vasodilate to return blood pressure toward normal. Lifting a heavy load causes one to initiate the Valsalva maneuver, which produces high abdominal pressures. This compresses the aorta and temporarily raises TPR. Strenuous running, on the other hand, causes a dilation in the exercising muscle, and TPR is decreased.

6. Ans A Aortic insufficiency is characterized by a large increase in preload on the left ventricle. By the Frank-Starling mechanism there will be an increased force of contraction and an increased stroke volume.

7. **Ans** D A sudden increase in pulmonary pressure means an increase in afterload on the right ventricle. In the systole following the increased pulmonary pressure, the ventricle will not empty to the same extent (SV decreases), and end-systolic volume will increase. This will subsequently cause an increase in preload and force of ventricular contraction to return stroke volume toward normal. Additional events are complex and not well understood.

8. Ans A In the newborn the flow will be from the aorta (fully oxygenated blood) into the pulmonary artery. This blood will return to the left ventricle, producing a volume overload on this chamber.

9. Ans E During exercise there is a general increase in cardiac output; thus, there will be an increase (although it is slight because of the increased heart rate) in the stroke volume of both ventricles.

10. Ans A (True) Wall tension will be determined mainly by the diameter of the ventricle and ventricular pressure during systole (wall thickness is a component that we will ignore). The larger the diameter and the greater the pressure, the greater the wall tension (T °= Pr). Thus, under these conditions wall tension should increase.

11. **Ans** B (False) An increased blood pressure produces increased afferent firing of carotid sinus receptors. The CNS would then attempt to lower blood pressure, and one change would be an increase in parasympathetic outflow.

12. **Ans** B In AI the large increase in preload causes a large stroke volume, and aortic systolic pressure can be slightly elevated over normal. However, during diastole, because the aorta is not only perfusing peripheral tissues but flowing back into the ventricle, aortic diastolic pressure is dramatically reduced. The difference between systolic and diastolic pressure is great; therefore, pulse pressure is increased.

13. **Ans** D Negative intrathoracic pressures promote venous return, and the increased cycling of this pressure when ventilation is increased is a further aid to venous return. Increased venous tone increases circulating blood volume and thus cardiac output. Finally, increased sympathetic tone to the heart will increase contractility and heart rate and thus increase the output of the heart. Cardiac output is the same as venous return.

14. **Matching**

1. **Ans H** The cutaneous circulation is involved in heat exchange with the environment in order to regulate body temperature. Vasodilation occurs when heat loss is required, and vasoconstriction, when heat needs to be conserved. This is mediated by decreasing and increasing sympathetic adrenergic activity. Warming the hypothalamus, where our thermostat resides, signals too much body heat, and cutaneous vasodilation is the response to dissipate that heat.

2. **Ans** F, G Reflex vasoconstriction will not affect systemic circulations that autoregulate. The cerebral and coronary are the two circuits that strongly autoregulate.

3. **Ans** K In the systemic circuit a decrease in PO_2 will, if anything, cause a vasodilation. However, unique to the pulmonary circuit is the phenomenon of hypoxic vasoconstriction. This is initiated whenever the alveolar PO_2 decreases. The result, which is not well understood, is a local vasoconstriction. This will decrease blood flow to that region of the lung.

4. **Ans** G, I, K, (H) During exercise cardiac output and thus the work of the heart increase. Since coronary flow increases with any increase in the pumping action of the heart, it will increase during exercise. Vasodilatory metabolites will increase flow in the exercising muscle. Pulmonary flow is cardiac output, which increases during exercise. The cutaneous circulation at the beginning of exercise

can constrict. But as heat builds up and need to dissipate that heat increases, there will be an appropriate cutaneous dilation.

5. **Ans** J — In the renal circulation the glomerular and the peritubular capillaries are connected in series. The glomerular capillaries are high-pressure, filtering capillaries, and downstream the peritubular capillaries are low-pressure, reabsorbing capillaries.

6. **Ans** K — The pulmonary circulation in general is a low-pressure circuit, and this applies to the capillary bed. The low pressure prevents significant filtration from the capillaries and keeps the alveoli dry (relatively).

7. **Ans** G — Even under resting conditions oxygen extraction is almost maximal in the coronary circuit. Maximal extraction means a low venous O_2. If exercise was specified then I would also be a correct answer.

8. **Ans** J — The kidney receives 20-25% of cardiac output and is overperfused in terms of supplying oxygen and nutrients. The high flow is to maintain adequate filtration. A tissue that is overperfused will have relatively high venous levels of oxygen.

15. **Ans** 1.-C, 2.-B, 3.-A, 4-D — These are difficult questions to deal with. In answer A, blood pressure increases, but diastolic increases more than systolic. Peripheral resistance affects diastolic more than systolic. Since there is a greater change in diastolic pressure, the likely origin is a change in TPR. An increased output of the heart will also increase blood pressure (here stroke volume); however, in this case systolic and diastolic will be more uniformly affected. The only reasonable answer is C. In B the pulsations are getting closer together, which means an increased heart rate. D demonstrates a slight increase in systolic pressure but a large decrease in diastolic pressure. The large drop in diastolic is characteristic of aortic insufficiency.

16. Ans B — The graph demonstrates that the concentration substances f and g are decreasing as they pass through the capillary. Presumably diffusion is occurring to the interstitium. The curve of f shows a slow decline throughout the length of the capillary, indicating it never equilibrates with the interstitium. If the substance does not equilibrate with the interstitium, it is referred to as "diffusion limited" (see respiratory section). Substance g, on the other hand, diffuses quickly, then the concentration plateaus. The fact that no change occurs in its concentration in the latter part of the capillary indicates it has equilibrated with the interstitium. If it equilibrates, it is referred to as a "perfusion-limited" situation. This is explained more thoroughly in the respiratory section.

SECTION VI

Respiration

Lung Mechanics

1

What is vol. of newborn child. Total lung vol.

LUNG VOLUMES AND THEIR MEASUREMENT

Figure VI-1-1 represents graphically the major lung volumes and capacities.

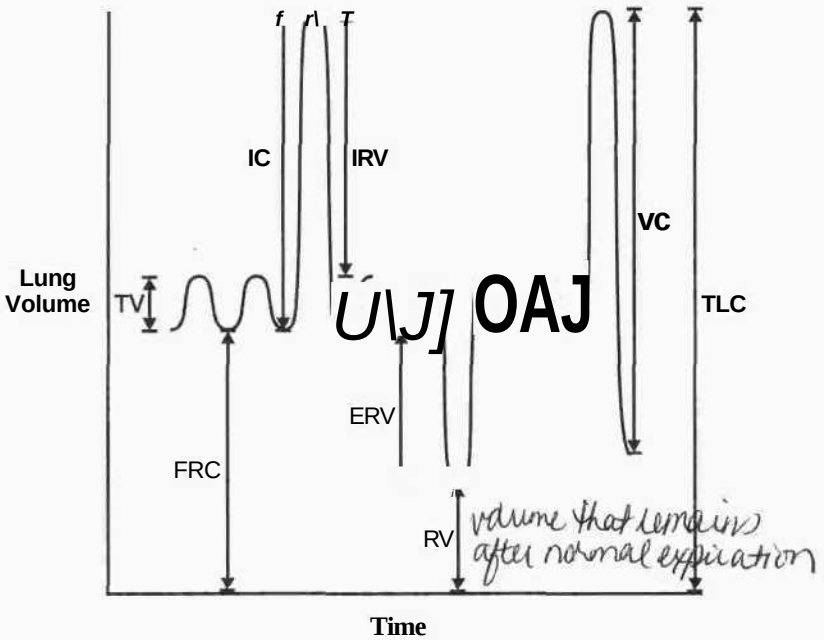


Figure VI-1-1

What the USMLE Requires You to Know

- The major lung volumes and capacities
- Dead space
- Total versus alveolar ventilation
- Mechanics of normal restful breathing
- Positive-pressure respiration
- Lung compliance and the consequences of a change in compliance
- **Lung** recoil as a function of tissue and surface tension forces
- The functions of surfactant and the consequences of a deficiency
- Determinants of airway resistance
- Obstructive versus a restrictive pattern

Which of following vol. can't be measured in normal spirometer? FRC, RV

Pt. M\ Am. 6 expired at 4 am., uneventful What would be this lung vol.?

Resp. rate 45 b/min. rapid and shallow. What acid/base change would you expect? Answer: acidosis

11b = 1ml

Which of following gases is not expected to be in conducting zone at end of respiration?

a. O_2
(b) CO_2 – b/c during inspiration you breath atmospheric air one found at expiration b/c of body metabolism
c. N
d. H
e. H_2O vapor

Alveolar ventilation

500 × 15 = 7500

500 − 150 = 350ml
dead space

350 × 15 = 5250 ml/min

Tidal volume (TV): The amount of air that enters or leaves the lung system in a single respiratory cycle (500 ml). There is a slight difference between inspired volume and expired volume, and by convention TV is usually considered the expired volume. The largest possible tidal volume would equal vital capacity.

Functional residual capacity (FRC): Volume of gas in the lungs at the end of a passive expiration or with the glottis open and all respiratory muscles relaxed. This is also considered to be the neutral or equilibrium point for the respiratory system (2700 ml).

Inspiratory capacity (IC): Maximal volume of gas that can be inspired from FRC (4000 ml).

Inspiratory reserve volume (IRV): The additional amount of air that can be taken into the lung system after a normal inspiration (3500 ml).

Expiratory reserve volume (ERV): The additional volume that can be expired after a normal expiration (1500 ml).

Residual volume (RV): The amount of air in the lung system that remains after a maximal expiration (1200 ml) (amount of air that can never be expelled from the lungs).

Vital capacity (VC): Maximal volume that can be expired after a maximal inspiration (5500 ml) (TLC - RV).

Total lung capacity (TLC): The amount of air in the lung system after a maximal inspiration (6700 ml).

Most volumes and capacities can be measured by using a spirometer, but residual volume and any capacity containing residual volume cannot be measured with a spirometer. TLC, FRC, and RV cannot be measured using simple spirometry.

VENTILATION

Total Ventilation

Total ventilation is also referred to as minute volume or minute ventilation. It is the total volume of air moved in or out (usually measured as the volume expired) of the respiratory system per minute.

$\dot{V}E = VT \times f$

$\dot{V}E$ = total ventilation

VT = tidal volume

f = respiratory rate

Normal resting values would be: VT = 500 ml f = 15

500 ml X 15/min = 7500 ml/min

Dead Space

Regions of the respiratory system that contain air but are not exchanging O_2 and CO_2 with blood are considered dead space.

Anatomical Dead Space

Airway regions that, because of inherent structure, are not capable of O_2 and CO_2 exchange with the blood. Anatomical dead space includes the conducting zone, which ends at the level of the terminal bronchioles. All the alveoli are considered to comprise the respiratory zone. Significant gas exchange (O_2 and CO_2) with the blood occurs only in the alveoli.

The size of the anatomical dead space in ml is approximately equal to a person's weight in pounds. Thus a 150-lb. individual has an anatomical dead space of 150 ml. This is a small volume when compared with the respiratory zone, which contains several liters of air.

Composition of the Anatomical Dead Space and the Respiratory Zone

The respiratory zone is a very constant environment Under resting conditions, rhythmic ventilation introduces a small volume into a much larger respiratory zone. Thus, the partial pressure of gases in the alveolar compartment changes very little during normal rhythmic ventilation.

Composition at the End of Expiration (Before Inspiration)

At the end of an expiration, the anatomical dead space is filled with air that originated in the alveoli or respiratory zone. Thus, the composition of the air in the entire respiratory system is the same at this static point in the respiratory cycle. This also means that a sample of expired gas taken near the end of expiration is representative of the respiratory zone. This situation is illustrated in Figure VI-1-2.

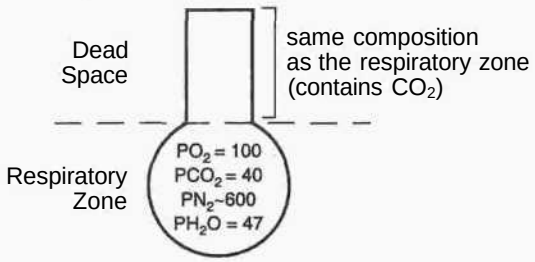


Figure VI-1-2

Composition at the End of Inspiration (Before Expiration)

The first 150 ml of any inspiration fills the dead space with room air, but none of that room air reaches the respiratory zone. This can be considered dead space ventilation. Beyond 150 ml, room air is added to the respiratory zone. This also

means that after the first 150 ml through the remainder of inspiration, the dead space contains humidified room air. This is illustrated in Figure VI-1-3.

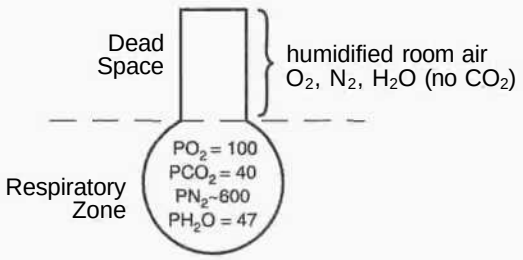


Figure VI-1-3

Alveolar Dead Space

Alveoli containing air but without blood flow in the surrounding capillaries.

Physiological Dead Space

This is the total dead space in the lung system. This region is the anatomical dead space plus alveolar dead space.

Alveolar Ventilation

Alveolar ventilation represents the room air delivered to the respiratory zone per minute. An important point here is to realize that the first 150 ml of each inspiration does not contribute to alveolar ventilation. However, every additional ml beyond 150 does contribute to alveolar ventilation.

$\dot{V}A = (VT\text{-}VD)f$

$\dot{V}A$ = alveolar ventilation
VT = tidal volume
VD = dead space
f = respiratory rate

= (500 ml - 150 ml) 15 = 5250 ml/min

The alveolar ventilation per inspiration is 350 ml.

Increases in the Depth of Breathing

There will be equal increases in total and alveolar ventilation.

If the depth of breathing increases from a depth of 500 ml to a depth of 700 ml, the increase in total and alveolar ventilation would be 200 ml.

Increases in the Rate of Breathing

There will be a greater increase in total than in alveolar ventilation.

For every additional inspiration with a tidal volume of 500 ml, total ventilation would increase 500 ml, but alveolar ventilation would increase by only 350 ml (assuming dead space is 150 ml).

V_A = has to do w/ depth of breathing
V_T = has to do w/ rate

Depth	Rate
$\uparrow O_2$	$\uparrow CO_2$
$\uparrow pH$	$\downarrow pH$

Problem
Given the following:

	Tidal Volume	Rate
Person A	600 ml	10/min
Person B	300 ml	20/min

Which person has the greater alveolar ventilation?

Answer: person A

The point of this question is that person B has rapid, shallow breathing. As such, this person has a large component of dead space ventilation (first 150 ml of each inspiration). Even though total ventilation may be close to normal, alveolar ventilation is depressed. Therefore, the individual would be considered to be hypoventilating.

In rapid, shallow breathing, total ventilation may be above normal, but alveolar ventilation may be below normal

INTRODUCTION TO LUNG MECHANICS

Muscles of Respiration

Inspiration - O.cHu«protest

The major muscle of inspiration is the diaphragm. Contraction of the diaphragm enlarges the vertical dimensions of the chest. Also utilized are the muscles of the chest wall. Contraction of these muscles causes the ribs to rise and thus increases the anterior-posterior dimensions of the chest.

Expiration -pCLS&v^ ptvuxw

Under resting conditions, expiration is normally a passive process; i.e., it is due to the relaxation of the muscles of inspiration. When it is active, the muscles of the abdominal wall can be considered the main muscles of expiration. The contraction forces the diaphragm up into the chest.

Included would be: external oblique, **rectoabdominal,** internal oblique, and transverse abdominal muscles.

Forces Acting on the Lung System

Units of Pressure

In respiratory physiology, they are usually given as cm H_2O.

$1\ cm\ H_2O = 0.74\ mm\ Hg\ (1\ mm\ Hg = 1.36\ cm\ H_2O)$

Lung Recoil and Intrapleural Pressure

Understanding lung mechanics mainly involves understanding the two main forces acting on the lung: lung recoil and intrapleural pressure.

Lung Recoil - (jjfl . se the lun j-

Represents forces that develop in the wallw the lung as the lung expands.

In a given situation, recoil changes only when lung volume changes.

As the lung enlarges, recoil increases; as the lung gets smaller, recoil decreases.

Recoil, as a force, always acts to collapse the lung.

Intrapleural Pressure exPands lunfc

Represents the pressure in the thin film of fluid between the lung and the chest wall.

Subatmospheric pressures (-) act as a force to expand the lung, and positive pressures (+) act as a force to collapse the lung.

During normal restful breathing, intrapleural pressure is always subatmospheric (or negative) and thus acts as a force to expand the lung.

When intrapleural pressure is a greater force than lung recoil, the lungs expand.

When the recoil force is greater than that created by intrapleural pressure, lung volume will be decreasing.

When the force of recoil and intrapleural pressure are equal and opposite, a static state exists, and lung size will be constant.

MECHANICS UNDER RESTING CONDITIONS

Before Inspiration

The glottis is open, and all respiratory muscles relaxed (FRC). This is the neutral or equilibrium point of the respiratory system (Figure VI-1-4). At FRC, the chest wall is under a slight tension directed outward. Intrapleural pressure is negative at FRC because the inward elastic recoil of the lungs is opposed by the outward-directed recoil of the chest wall. The intrapleural force and recoil force are equal

and opposite, and because no air is flowing through the open glottis, alveolar pressure must be zero. By convention, the atmospheric pressure is set to equal zero.

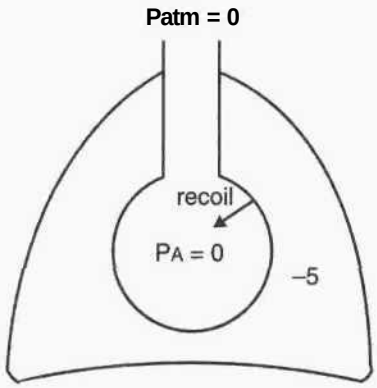


Figure VI-1-4

intrapleural pressure = -5 cm H_2O

recoil force = 5

alveolar pressure = 0

During Inspiration

1. Inspiration is induced by the contraction of the diaphragm, which is the main muscle of inspiration, along with some accessory muscles that expand the chest wall. The net result of contracting these muscles is to decrease (make more negative) intrapleural pressure.

   The greater the contraction, the greater the change in intrapleural pressure and the larger the force trying to expand the lung.

2. The expansion of the lung causes thegases in the alveolijo expand, creating ashghtly negative alveolar pressure. This causes air to flow into the lung.

Figure VI-1-5 illustrates the situation at some point during inspiration.

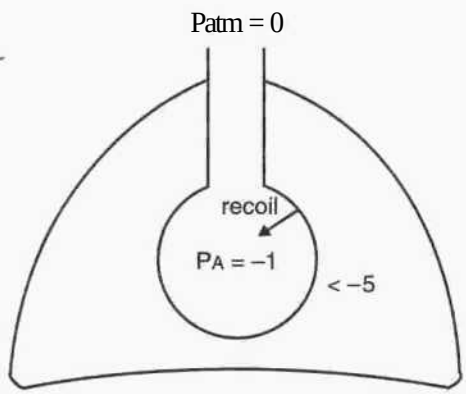


Figure VI-1-5

intrapleural pressure <-5 cm H2O

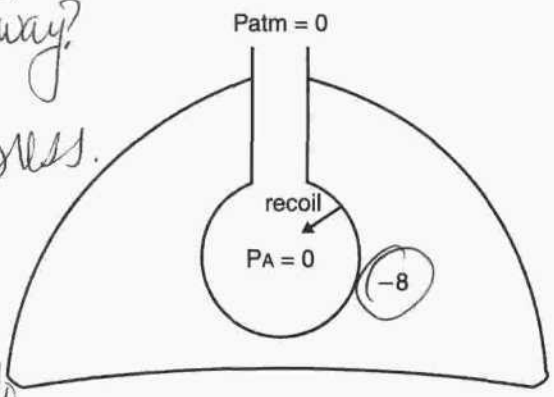
recoil force >5

alveolar pressure = -1 cm H2O

End of Inspiration

1. The lung expands until the recoil force increases to equal intrapleural pressure. Once the forces are again equal and opposite, the lung is at its new larger volume.
2. The inflowing air returns alveolar pressure toward zero, and when it reaches zero, air flow stops. Under resting conditions, about 500 ml of air flows into the lung system in order to return alveolar pressure back to zero.

Figure VI-1-6 illustrates the situation at the end of a normal inspiration.



intrapleural pressure = -8 cm H_2O

recoil force = 8

alveolar pressure = 0

Figure VI-1-6

Expiration

1. Expiration under resting conditions is produced simply by the relaxation of the muscles of inspiration.
2. The relaxation of the diaphragm and accessory muscles of inspiration increases (makes more positive) intrapleural pressure, which returns to -5 cm H_2O.
3. Lung deflation begins and continues until the recoil force decreases to again equal intrapleural pressure. Once this occurs, the lung system is back to FRC.
4. Deflation of the lung compresses the gases in the alveoli, creating a slightly positive alveolar pressure. This causes air to flow out of the lungs.
5. The outflowing air returns alveolar pressure toward zero, and when it reaches zero, airflow stops.

Intrapleural Pressure During a Normal Respiratory Cycle

The intrapleural pressure during a normal respiratory cycle is illustrated in Figure VI-1-7.

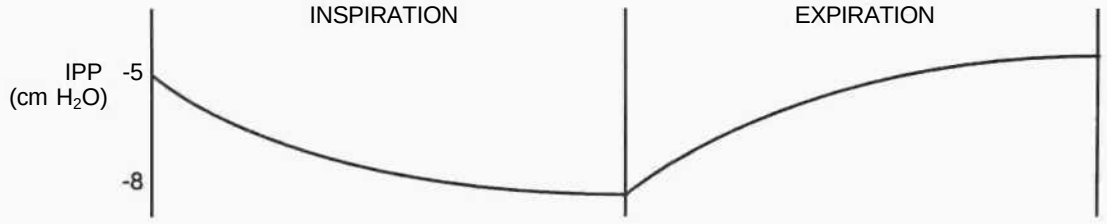


Figure VI-1-7

Intraalveolar Pressure During a Normal Respiratory Cycle

The intraalveolar pressure during a normal respiratory cycle is illustrated in Figure VI-1-8. By convention, total atmospheric pressure = 0.

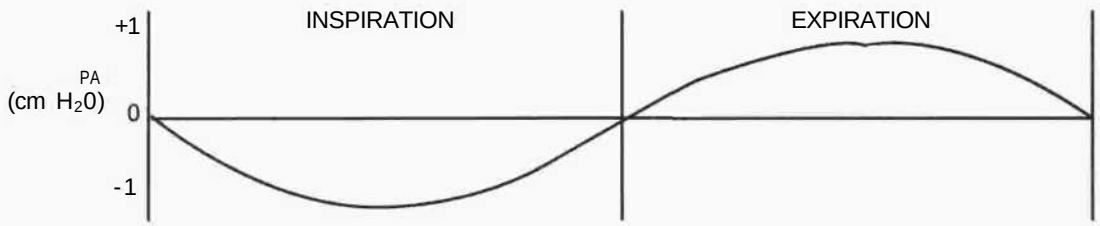


Figure VI-1-8. Intraaveolar Pressure

Pneumothorax

The following changes would occur with the development of a simple pneumothorax:

Intrapleural pressure increases from a mean at -5 cm H_2O to equal atmospheric pressure.

Lung recoil decreases to zero as the lung collapses.

Chest wall expands. At FRC, the chest wall is under a slight tension directed outward. It is this tendency for the chest wall to spring out and the opposed force of recoil that creates the intrapleural pressure of -5 cm H_2O.

Positive-Pressure Respiration

Assisted Control Mode Ventilation (ACMV)

Inspiratory cycle initiated by patient or automatically if no signal is detected within a specified time window.

Positive End-Expiratory Pressure (PEEP)

By not allowing intraalveolar pressure to return to zero at the end of expiration, the lung will be kept at a larger volume. This will decrease the tendency to develop regional atelectasis.

These factors are illustrated in Figure VI-1-9.

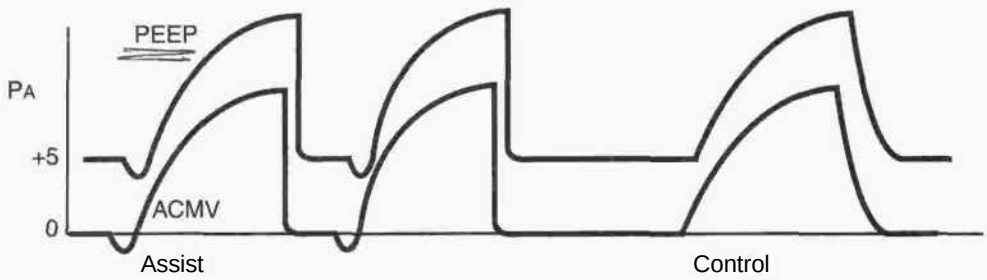


Figure VI-1-9. Positive-Pressure Respiration

Continuous Positive Airway Pressure (CPAP)

Not a true support-mode ventilation. Breathing is spontaneous but via a circuit that is pressurized.

This is illustrated in Figure VI-1-10.

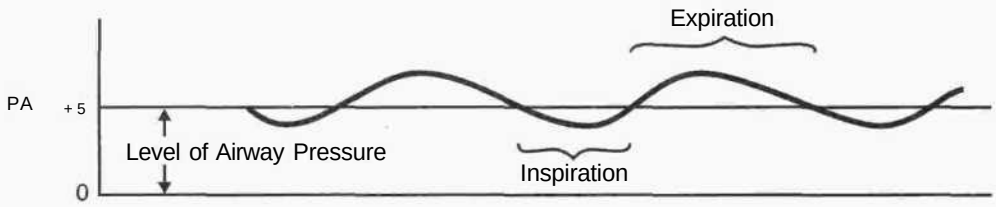
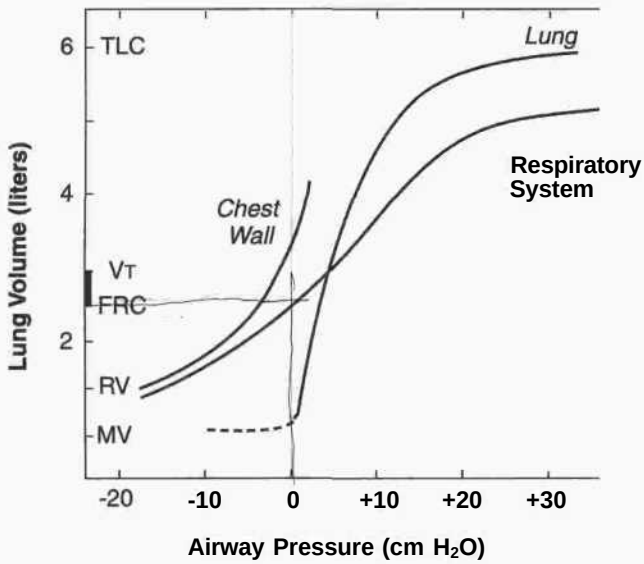


Figure VI-1-10

The diagram below (Figure VI-1-11), although not easily duplicated on human subjects, is often used to describe the independent properties of the lung and the chest wall. It can also be used to determine the FRC.



What is FRC?
FRC = 2.5L
Complete.

Figure VI-1-11. Functional Residual Capacity

Note that the compliance (see below) of the entire respiratory system is less than that of either the lung or the chest wall alone.

As stated earlier, the FRC represents the volume of air in the lungs at the end of a passive expiration. With the respiratory muscles relaxed, it is that moment in the respiratory cycle when the elastic recoil of the lungs is exactly balanced by the outward pull of the chest wall—or, as the diagram above is meant to show, when the force required to stretch the lungs is equal to the force required to compress the chest wall (MV = minimal volume).

Lung Compliance

Figure VI-1-12 represents a static isolated lung inflation curve.

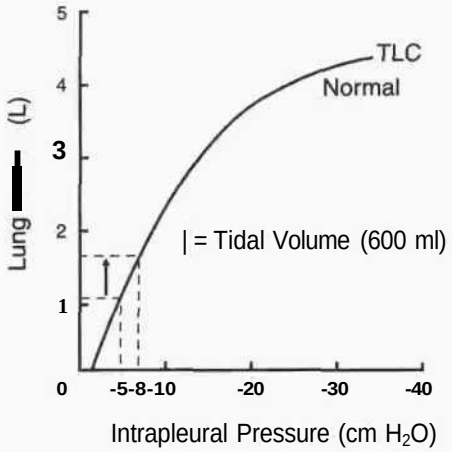


Figure VI-1-12. **Lung Inflation Curve**

Lung compliance is the change in lung volume (tidal volume) divided by the change in surrounding pressure. This is stated in the following formula:

$$\text{Compliance} = \frac{\Delta V}{\Delta P}$$

Problem

Tidal volume = 0.6 liters

Intrapleural pressure before inspiration = -5 cm H_2O

Intrapleural pressure after inspiration = -8 cm H_2O

$$\text{Lung compliance} = \frac{0.6 \text{ liters}}{3 \text{ cm } H_2O} = 0.200 \text{ liters/cm } H_2O$$

The preceding calculation simply means that for every 1 cm H2O surrounding pressure changes, 200 ml of air flows in or out of the respiratory system. It flows into the system if surrounding pressure becomes more negative (e.g., -5 to -6 cm H_2O) or out of the system if surrounding pressure becomes more positive (e.g., -5 to -4 cm H_2O).

Increased compliance means more air will flow for a given change in pressure.

Reduced compliance means less air will flow for a given change in pressure.

In the preceding curve, although the slope is changing during inflation, its value at any point is the lung's compliance. It is the relationship between the change in lung volume (tidal volume) and the change in intrapleural or surrounding pressure.

The steeper the line, the more compliant the lungs. Restful breathing works on the steepest, most compliant part of the curve. With a deep inspiration, the lung will move toward the flatter part of the curve, and thus it will have reduced compliance. At total lung capacity, lung compliance is reduced compared with FRC.

Problem

Given that the compliance of an individual's lung is 0.5 L/cm H_2O and mean intrapleural pressure is -7 cm H_2O, what is the volume of exhaled gas if intrapleural pressure rose to -5 cm H_2O?

Answer: 1 liter

$C = \Delta V / \Delta P$

$500 = \frac{\Delta V}{(-7)-(-5)}$

$500 = \frac{\Delta V}{2}$

$\Delta V = 1000$

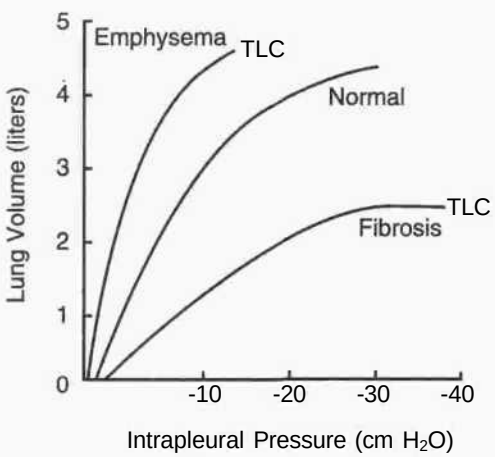
Problem

Given that the compliance of an individual's lung is 0.5 L/cm H_2O and intrapleural pressure is -10 cm H_2O. What is the new intrapleural pressure if this person exhaled 1.0 L?

Answer: -8 cm H_2O

In summary: Compliance is an index of the effort required to expand the lungs (to overcome recoil). It does not relate to airway resistance. Also, the compliance will change as the lungs are inflated because the curve is not a straight line. Very compliant lungs (easy to inflate) have low recoil. Stiff lungs (difficult to inflate) have a large recoil force.

Figure VI-1-13 shows states in which lung compliance changes.



1. emphysema = A
2. saline filled lung = A
3. aging = A
4. fibrosis = B
5. RDS = B
6. atelectasis = C

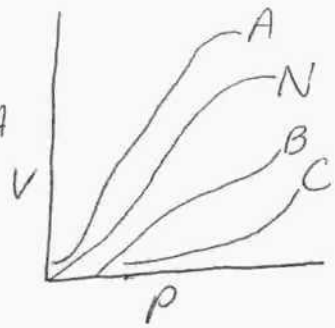


Figure VI-1-13. Lung Compliance

Increased lung compliance also occurs with aging and with a saline-filled lung.

Components of Lung Recoil

Lung recoil has two components:

1. The tissue itself, more specifically, the collagen and elastic fibers of the lung.

   The larger the lung, the greater the stretch of the tissue and the greater the recoil force.

2. The surface tension forces in the fluid lining the alveoli. Surface tension forces are created whenever there is a liquid-air interface.

   Surface tension forces tend to reduce the area of the surface and generate a pressure. In the alveoli, they act to collapse the alveoli; therefore, these forces contribute to lung recoil.

   Surface tension forces are the greatest component of lung recoil.

   The relationship between the surface tension and the pressure inside a bubble is given by the law of Laplace.

Laplace law - pressure is inversely related to radius

$$P = \frac{T}{r}$$

P = pressure

T = tension

r = radius

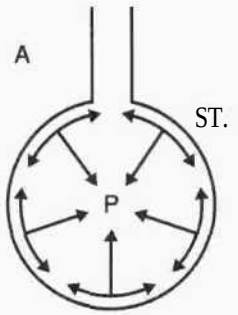


Figure VI-1-14

The major point of this relationship is simply that if wall tension is the same in two bubbles but their size differs, the smaller bubble will have the greater pressure.

Although the situation is more complex in the lung, it follows that small alveoli tend to be unstable. They have a great tendency to empty into larger alveoli and collapse (creating regions of atelectasis). This is illustrated in Figure VI-1-15. Collapsed alveoli are difficult to reinflate.

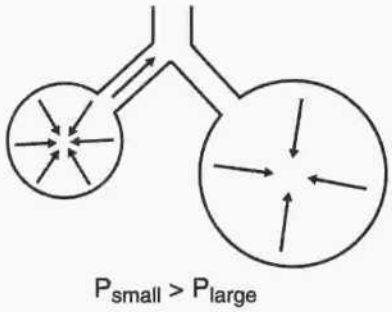


Figure VI-1-15

It is also possible to estimate the theoretical contribution of surface tension forces to lung recoil. Assuming the lung was lined by a simple electrolyte solution, estimates indicate that lung recoil should be so great that lungs theoretically should not be able to inflate. This overestimate is due to the fact that in the fluid lining a normal lung there is a compound called surfactant.

Surfactant has three main functions:

1. It lowers surface tension forces in the alveoli. In other words, surfactant lowers lung recoil and increases compliance. With surfactant, there is a greater change in lung volume for a given change in intrapleural pressure,
2. It lowers surface tension forces more in small alveoli than in large alveoli. This promotes stability among alveoli of different sizes by decreasing the tendency of small alveoli to collapse (decreases the tendency to develop atelectasis).
3. It reduces capillary filtration forces and thus the tendency to develop pulmonary edema. A negative intrathoracic pressure is a force promoting capillary filtration. Low recoil means an intrapleural pressure closer to atmospheric and thus a low force promoting capillary filtration.

Respiratory Distress Syndrome (RDS)

A deficiency of surfactant can develop, particularly in premature infants. This causes RDS.

Lung washings from infants with RDS have a very high surface tension, which shows little variation with area.

Premature birth and maternal diabetes are risk factors.

A lecithin/sphingomyelin ratio (L/S) of 2.0 or greater indicates lung maturity and a minimal risk for RDS.

A gestational age of 34 weeks divides those with increased incidence and mortality from those relatively free of the disorder.

Curve A in Figure VI-1-16 represents respiratory distress syndrome. The curve is shifted to the right, and it is a flatter curve (lung stiffer).

The symptoms include:

1. Increased lung recoil and decreased lung compliance.

   At a given lung volume, intrapleural pressure will be more negative.

   A greater change in intrapleural pressure is required to inflate the lungs.

2. Atelectasis.

   There is a greater tendency for small alveoli to collapse. Once collapse occurs, it is difficult to reinflate these alveoli.

   This is illustrated in curve B in Figure VI-1-16. Here a very negative intrapleural pressure (inspiratory effort) is required to reinflate the alveoli.

3. Pulmonary edema.

   Because a deficiency of surfactant increases recoil, a more negative intrathoracic pressure is required to maintain a given lung volume.

   Very negative intrapleural pressures represent a large force promoting capillary filtration.

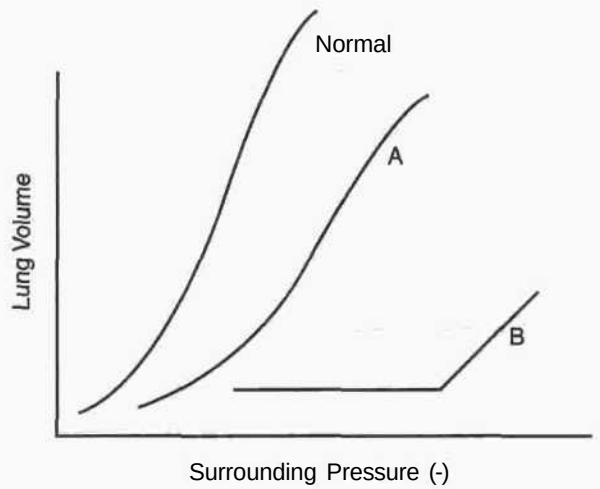


Figure VM-16

Airway Resistance

Radius of an Airway

$$\text{Resistance} = \frac{1}{\text{radius}^4}$$

In the branching airway system of the lungs, it is the first and second bronchi that represent most of the airway resistance.

Parasympathetic nerve stimulation produces bronchoconstriction.

Circulating catecholamines produce bronchodilation.

MECHANICAL EFFECT OF LUNG VOLUME

Figure VI-1-17 demonstrates the mechanical effect of lung volume.

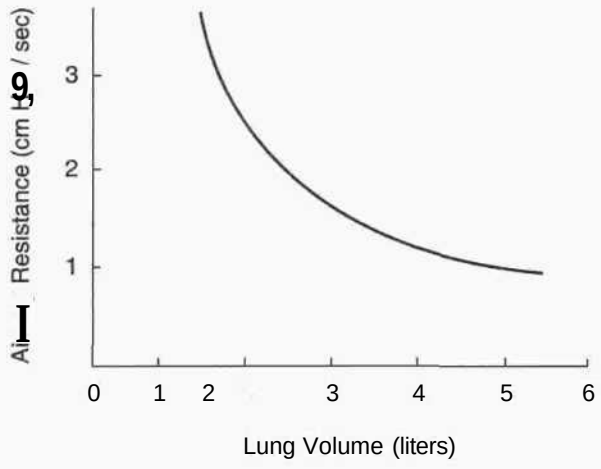


Figure VI-1-17. Airway Resistance

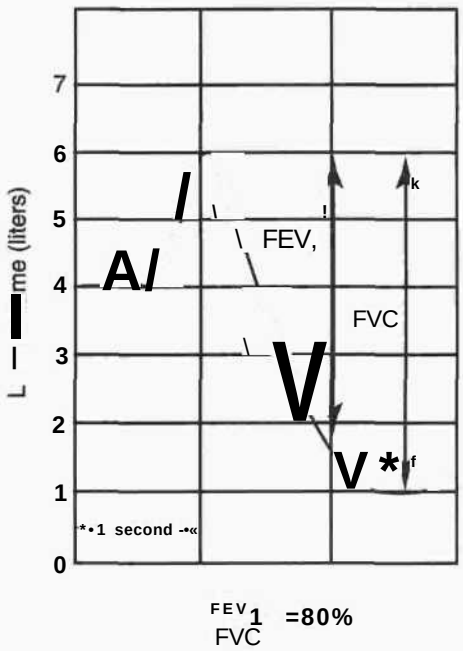
During inspiration, intrapleural pressure is decreasing, which produces greater transverse stretch throughout the airways. Consequently, airway resistance is decreasing during this maneuver.

The more negative the intrapleural pressure, the lower the resistance of the airways.

PULMONARY FUNCTION TESTING: *tfAAJLntnf-j St bit* only labels obstruction restriction
OBSTRUCTIVE VERSUS RESTRICTIVE PATTERNS

Vital Capacity (VC)

The VC is the maximum volume of air that an individual can move in a single breath. The most useful assessment of the VC is to breathe as quickly and forcefully as possible, i.e., a "timed" or forced vital capacity (FVC). During the FVC maneuver, the volume of air exhaled in the first second is called the forced expiratory volume in 1 sec (FEVi). This is illustrated in Figure VI-1-18.



$$\frac{FEV_1}{FVC} = 80\%$$

Figure VI-1-18. Vital Capacity

Normal people can exhale only 80% of their VC in 1 second because, during a forced expiration, intrapleural pressure becomes positive and the airways are compressed. Compression of the airways limits expiratory flow rates. This compression is called "dynamic compression of the airways." Maximum expiratory flow rates are "effort independent" (Figure VI-1-19).

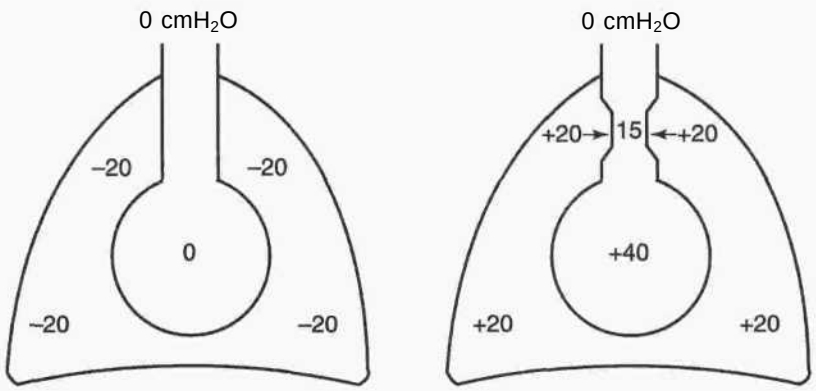


Figure VI-1-19.

The following figures (Figures VI-1-20 andVI-1-21) demonstrate a standard pulmonary function test, the measurement of FVC, which will demonstrate the presence of an obstructive versus a restrictive pattern. In this test, the subject is first requested to perform a maximal inspiration. At total lung capacity (TLC), the subject expires as quickly as possible to residual volume (RV).

Obstructive Pulmonary Disease

Obstructive disease is characterized by an increase in airway resistance that is measured as a decrease in expiratory flow rates.

Examples are chronic bronchitis, asthma, and emphysema.

Obstructive Pattern

Total lung capacity (TLC) is normal or larger than normal, but during a maximal forced expiration from TLC, a smaller than normal volume is slowly expired.

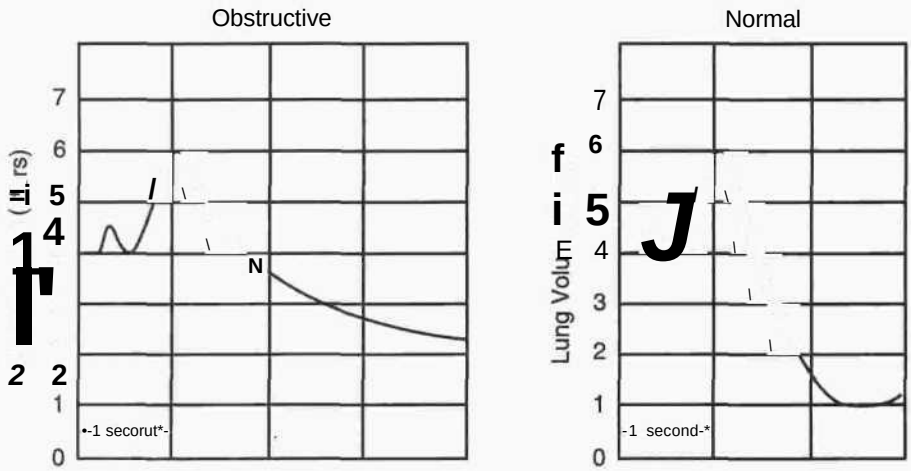


Figure VI-1-20

Restrictive Pulmonary Disease

Restrictive pulmonary disease is characterized by an increase in recoil, which is measured as a decrease in all lung volumes.

Restrictive Pattern

TLC is smaller than normal, but during a maximal forced expiration from TLC, the smaller volume is expired quickly and more completely than in a normal pattern.

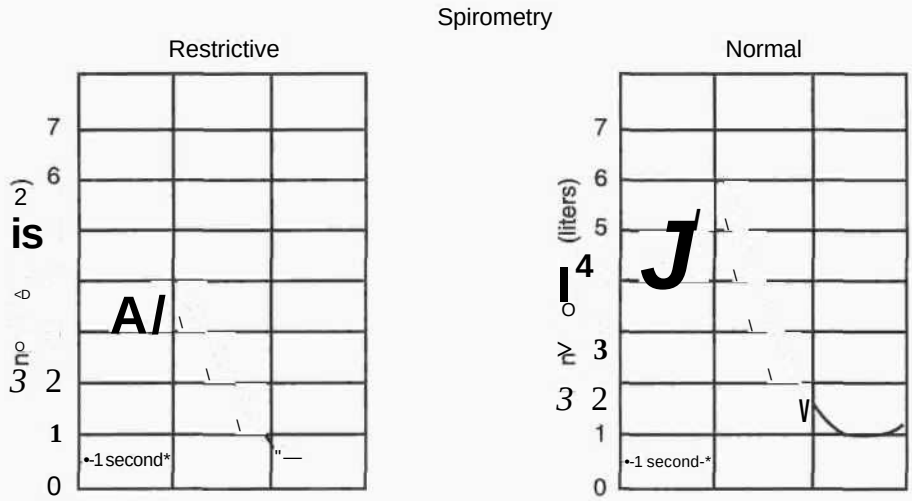


Figure VI-1-21

FEVj = forced expired volume during the first second, usually measured in liters.

Table VI-1-1. Summary of Obstructive versus Restrictive Pattern

Variable	Obstructive Pattern e.g., Emphysema	Restrictive Pattern e.g., Fibrosis
Total lung capacity	⇈	⇓
FEV!	⇓	⇑
Forced vital capacity	⇓	⇅
?FEV,/FVC	⇈	1T or normal
Peak flow	⇩	⇓
Functional residual capacity	⇑	⇓
Residual volume	⇑	⇓

obst. FEV, ⇊ / FVC ↓

rest. FEV, ↓ / FVC ⇊

↑ this is why FEV,/FVC is larger in restrictive dis. than in obst.

Forced vital capacity always decreases when puhnonary function is compromised.

A decrease in FEVj/FVC ratio is evidence of an obstructive rather than a restrictive pattern.

FLOW-VOLUME LOOPS

The instantaneous relationship between flow (liters/sec) and lung volume is useful in determining whether obstructive or restrictive lung disease is present. In the loop shown in Figure VI-1 -22, expiration starts at total lung capacity and continues to residual volume.

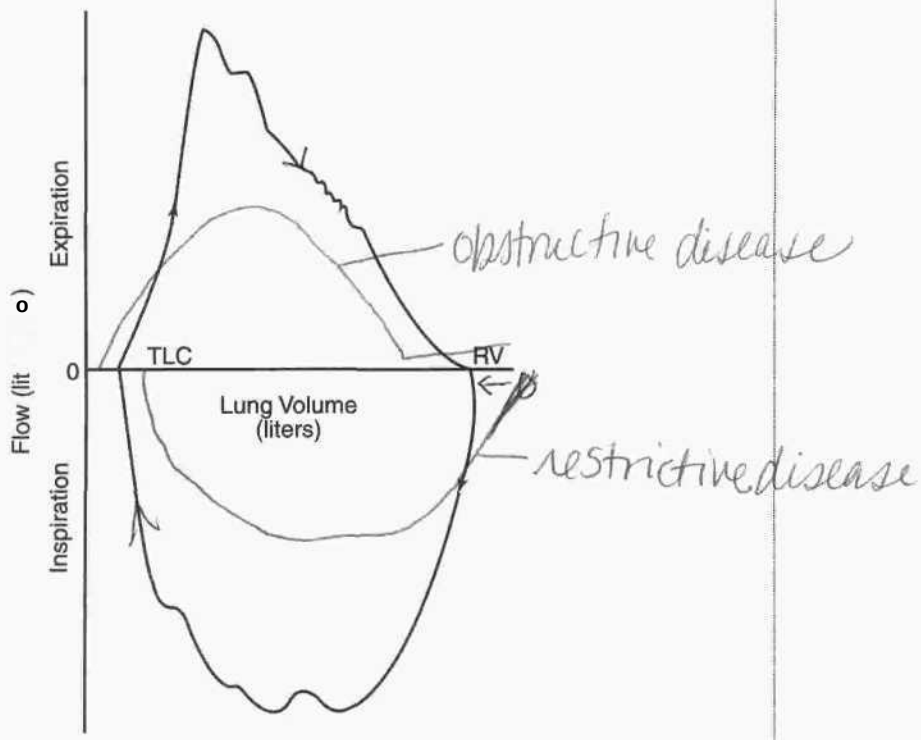


Figure VI-1-22

Loops found in obstructive and restrictive disease are shown below in Figure VI-1-23.

Obstructive Disease

In obstructive disease, the flow-volume loop begins and ends at abnormally high lung volumes, and the expiratory flow rates are lower than normal (often exhibiting a scooped out appearance). Inspiratory flow rates remain relatively normal so that the inspiratory portion of the loop is of nearly normal size.

Restrictive Disease

In restrictive disease, the flow-volume loop begins and ends at unusually low lung volumes. When expiratory flow rates are compared at specific lung volumes, the rates in restrictive disease are somewhat greater than normal.

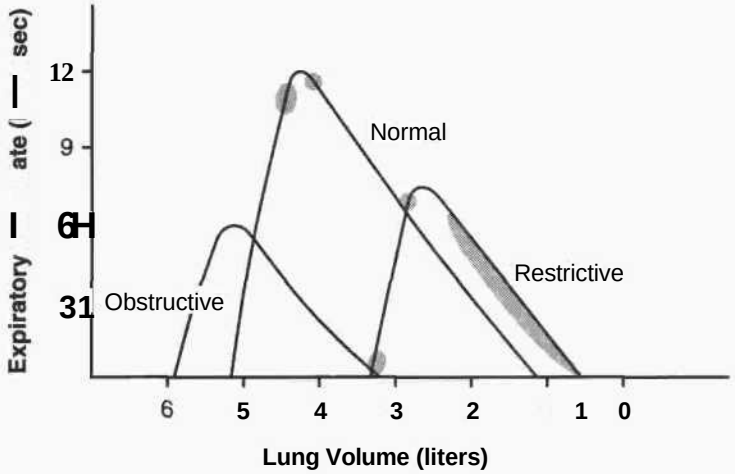


Figure VI-1-23

SUPPLEMENTARY TOPIC: THE VALSALVA MANEUVER

In many cases, before performing the Valsalva maneuver, the individual performs a maximal inspiration, creating the situation illustrated in Figure VI-1-24.

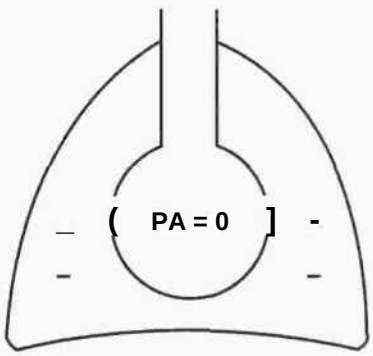


Figure VI-1-24

Characteristics at the end of maximal inspiration:

- Very negative intrapleural pressure
- Large lung volume, large lung recoil

To initiate the Valsalva maneuver, the glottis is closed and the expiratory muscles are contracted vigorously to create a very positive intrathoracic pressure. This is illustrated in Figure VI-1-25.

IWUC. expiration reflex contraction of airways called dynamic compresion of airways.

The flow rate is independent of effort

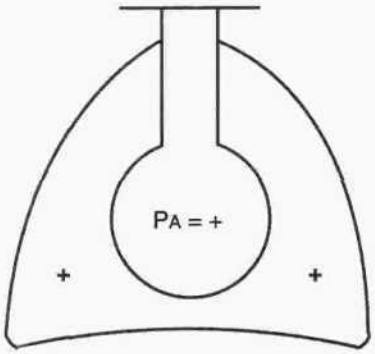


Figure VI-1-25

Characteristics during Valsalva maneuver:

- Large lung volume with a large, constant lung recoil
- Large positive intrapleural pressure

Alveolar pressure is the sum of the positive intrapleural force and the recoil force of the lungs. Thus, alveolar pressure is always greater than intrapleural by an amount equal to recoil.

During the Valsalva maneuver, any change in intrapleural pressure will cause an equivalent change in alveolar pressure.

bp/t = keeps falling and you become hypotensive. This is why you fall down.

Alveolar press. becomes ⊕

Chapter Summary

Functional residual capacity is the neutral or equilibrium point of the respiratory system. Residual volume is the air remaining in the respiratory system after a maximal expiration. Vital capacity is the difference between total lung capacity and residual volume.

Dead space is air in the respiratory system that is not exchanging gas with capillary blood.

The first 150 ml of an inspiration fills the anatomical dead space with room air. This volume contributes to total but not alveolar ventilation. Alveolar ventilation represents the inspired volume beyond 150 ml. It is the inspired air that actually reaches the respiratory zone.

During restful breathing, intrapleural pressure is always negative. It becomes more negative during inspiration and more positive during expiration. Alveolar pressure is slightly negative during inspiration and slightly positive during expiration.

Compliant lungs are easy to inflate and possess low recoil. Noncompllant or stiff lungs are difficult to inflate and have a large recoil force.

The main component of lung recoil represents the surface tension forces of the fluid lining the alveoli. Surfactant reduces surface tension forces.

A deficiency of surfactant reduces lung compliance and promotes atelectasis and the development of pulmonary edema.

A maximal expiration is associated with a partial collapse of the large airways, which increases resistance and limits the maximum flow rate.

An obstructive pattern is often associated with large lung volumes (TLC), but a small volume is expired slowly.

A restrictive pattern is associated with reduced lung volumes (TLC), but the small volume is often expired rapidly.

Alveolar-Blood Gas Exchange

2

THE NORMAL LUNG

Introduction

Partial Pressure of a Gas in Ambient Air

Patm = atmospheric pressure; Pgas = partial pressure of a gas; Fgas = concentration of a gas

Pgas = Fgas X Patm

By convention, the partial pressure of the gas is expressed in terms of its dry gas concentration.

Example: The PO_2 in ambient air: $PO_2 = 0.21 \times 760 = 160$ mm Hg

Partial Pressure of a Gas in Inspired Air

Inspired air is defined as air that has been inhaled, warmed to 37°C, and completely humidified. The partial pressure of H_2O is dependent only on temperature and at 37° is 47 mm Hg. Humidifying the air reduces the partial pressure of the other gases present.

Plgas = partial pressure of inspired gas; PH_2O = partial pressure of H_2O vapor

Plgas = Fgas (Patm - PH_2O)

Example: The PO_2 of inspired air: $PlO_2 = 0.21(760 - 47) = 150$ mm Hg

What the USMLE Requires You to Know

- The normal PO_2 and PCO_2 in the alveolar, pulmonary end capillary, and systemic arterial blood.
- Factors that affect alveolar PCO_2
- Factors that affect alveolar PO_2
- The effect of alveolar $PC0_2$ on alveolar PO_2
- Factors that affect the rate of gas diffusion across lung membranes

Figure VI-2-1 shows the pressures of oxygen and carbon dioxide in the alveolar, pulmonary end capillary, and systemic arterial blood.

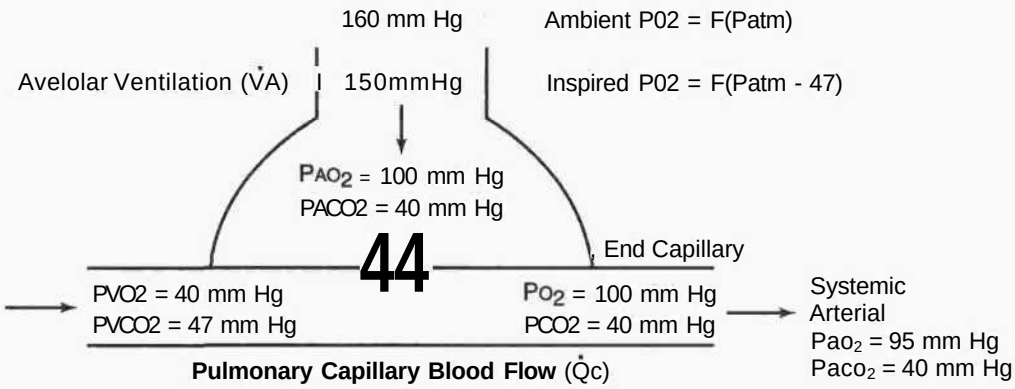


Figure VI-2-1

A = alveolar

a = systemic arterial

Under normal conditions, the PO_2 and PCO_2 in the alveolar compartment and pulmonary end capillary blood are the same. There will be a slight change (PO_2 ↓, PCO_2 ↑ if) between the end capillary compartment and the systemic arterial blood because of a small but normal shunt through the lungs.

Alveolar-systemic arterial differences (usually PO_2) = A - a. This difference often provides information about the cause of a hypoxemia. There is a small difference normally because of a small amount of shunting through the lungs (5-10 mm Hg). The difference will increase in certain specific pulmonary system problems.

Whatever factors that affect Alveolar affects arterial.

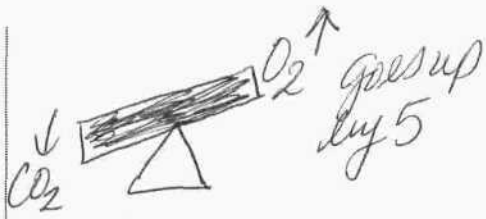
FACTORS AFFECTING ALVEOLAR PCO2

Only two factors affect alveolar PCO2. They are metabolic rate and alveolar ventilation, as shown in the following equation.

$$P_{A}CO_{2} \propto \frac{\text{metabolic CO2 production}}{\text{alveolar ventilation}}$$

Alveolar Ventilation

There is an inverse relationship between $PACO_2$ and alveolar ventilation. This is the main factor affecting alveolar PCO_2. Therefore, if ventilation increases, $PACO_2$ decreases; if ventilation decreases, $PACO_2$ increases.



Hyperventilation keeps alveolar CO_2 normal

During hyperventilation, there is an inappropriately elevated level of alveolar ventilation, and $PACO_2$ is depressed.

If $\dot{V}A$ is doubled, then $PACO_2$ is decreased by half.

e.g., $PACO_2$ = 40 mm Hg

2 X $\dot{V}A$ $PACO_2$ = 20 mm Hg

$\dot{V}$

$$PACO_2 = \frac{mr}{V_A}$$

$$PACO_2 \uparrow = \frac{mr \uparrow}{Va \uparrow}$$

Hypoventilation

During hypoventilation, there is an inappropriately depressed level of alveolar ventilation, and $PACO_2$ is elevated.

If $\dot{V}A$ is halved then $PACO_2$ is doubled

e.g., $PACO_2$ = 40 mm Hg

1/2 $\dot{V}A$; $PACO_2$ = 80 mm Hg

Half an hour ago pt. had $PaCO_2$ = 80 then pt. goes into state of hyperventilation his $PaCO_2$ = 40 now $PaCO_2$ = 44 what do you expect to happen to his $PaCO_2$? ↓ by 4

Metabolic Rate

There is a direct relationship between alveolar PCO_2 and body metabolism. For $PACO_2$ to remain constant, changes in body metabolism must be matched with equivalent changes in alveolar ventilation.

If $\dot{V}A$ matches metabolism, then $PACO_2$ remains constant.

For example, during exercise, if body metabolism doubles, then $\dot{V}A$ must double if $PACO_2$ is to remain constant.

If body temperature decreases and there is no change in ventilation, $PACO_2$ will decrease, and the individual can be considered to be hyperventilating.

FACTORS AFFECTING ALVEOLAR PO_2

The Alveolar Gas Equation

The alveolar gas equation includes all the factors that can affect alveolar PO_2.

$$PAO_2 = (Patm - 47)FO_2 - \frac{PA}{\wedge}\frac{O_2}{}$$

Three important factors can affect PAO_2:

Patm = atmospheric pressure, at sea level 760 mm Hg

An increase in atmospheric pressure will increase alveolar PO_2> and a decrease (high altitude) will decrease alveolar PO_2.

FO_2 = fractional concentration of oxygen, room air 0.21

An increase in inspired oxygen concentration will increase alveolar PO_2.

$PACO_2$ = alveolar pressure of carbon dioxide, normally 40 mm Hg

An increase in alveolar PCO_2 will decrease alveolar PO_2, and a decrease will increase alveolar PO_2.

if pt. is on ventilation and ↓ PaO_2 (pf\ 1004 move to 90 then

The fourth variable is R. It is fairly constant and close to 1.0.

R = respiratory exchange ratio = $\frac{CO_2 \text{ produced ml/min}}{O_2 \text{ consumed ml/min}}$ normally 0.8

Example: person breathing room air at sea level

$$PAO_2 = (760 - 47)\ 0.21 - 40/0.8 = 100 \text{ mm Hg}$$

4 make this one to be easier

Person breathing air at 747 mmHg and pt. has fraction of O_2 = 17% Partial press of CO_2 = 40 inspired O_2 = 110 mmHg What is the PaO_2?

$$PIO_2 - \frac{PACO_2}{1}$$

$$110 - 40/1 = 70$$

The Effect of $PACO_2$ on PAO_2

Figure VI-2-2 shows equations listing factors that determine PO_2 in the conducting airways during inspiration and in the alveolar compartment.

PIO_2 = P inspired O_2, i.e., the PO_2 in the conducting airways during inspiration

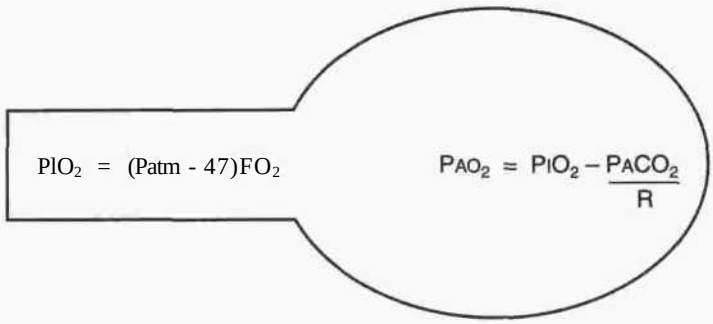


Figure VI-2-2

$= (760\text{-}47)0.21$ $= 150 - 40$

$= 150$ mm Hg $= 110$ mm Hg

The calculation of PAO_2 here is performed by using R = 1. If the normal value of 0.8 is used, PAO_2 would be 100 mm Hg.

The main point is that when the room air, passing through the conducting zone during inspiration, reaches the respiratory zone, the CO_2 in this compartment causes a decrease in the PO_2 by an amount approximately equal to the PCO_2 in this compartment, i.e., 40 mm Hg.

Because $PACO_2$ affects alveolar PO_2, hyperventilation and hypoventilation also affect PAO_2.

Hyperventilation (e.g., $PACO_2$ = 20 mm Hg)

$PAO_2 = PIO_2 - PACO_2$ (assume R = 1)

normal = 150 - 40 = 110 mm Hg

hyperventilation = 150 - 20 = 130 mm Hg

Hypoventilation (e.g., $PACO_2$ = 80 mm Hg)

normal = 150 - 40 = 110 mm Hg

hypoventilation = 150 - 80 = 70 mm Hg

With hyperventilation and hypoventilation, alveolar PCO_2 and PO_2 change in opposite directions approximately an equal amount in mm Hg.

If CO_2 decreases by 20 mm Hg, PO_2 increases by 20 mm Hg.

If CO_2 increases by 40 mm Hg, PO_2 decreases by 40 mm Hg.

ALVEOLAR-BLOOD GAS TRANSFER: FICK LAW OF DIFFUSION

Simple diffusion is the process of gas exchange between the alveolar compartment and pulmonary capillary blood. Thus, those factors that affect the rate of diffusion also affect the rate of exchange of O_2 and CO_2 across alveolar membranes. (An additional point to remember is that each gas diffuses independently.)

$$\dot{V}gas = Y \times D \times \frac{A}{T} \times (Pi - P2)$$

$\dot{V}gas$ **is the rate of gas diffusion**

Two structural factors and two gas factors affect the rate of diffusion.

Structural Features That Affect the Rate of Diffusion

A = surface area for exchange, ↓ in emphysema, ↑ in exercise

T = thickness of the membranes between alveolar gas and capillary blood, ↑ in fibrosis and many other restrictive diseases

A structural problem in the lungs is any situation in which there is a loss of surface area and/or an increase in the thickness of the membrane system between the alveolar air and the pulmonary capillary blood. In all cases, the rate of oxygen and carbon dioxide diffusion decreases. The greater the structural problem, the greater the effect on diffusion rate.

Factors That Are Specific to Each Gas Present

D (diffusion constant) = Main Factor Is Solubility

The only clinically significant feature of D is solubility. The more soluble the gas, the faster it will diffuse across the membranes. CO_2 is the most soluble gas with which we will be dealing. The great solubility of CO_2 is the main reason why it diffuses faster across the alveolar membranes than O_2.

Gradient Across the Membrane

(P_2 - P_2): This is the gas partial pressure difference across the alveolar membrane. The greater the partial pressure difference, the greater the rate of diffusion.

Under resting conditions, when blood first enters the pulmonary capillary, the gradient for O_2 is:

100 - 40 = 60 mm Hg

An increase in the PO_2 gradient across the lung membranes will compensate for a structural problem. If supplemental O_2 is administered, alveolar PO2 will increase, along with the gradient. This increased gradient will return the rate of O2 diffusion toward normal. The greater the structural problem, the greater the gradient necessary for a normal rate of O_2 diffusion.

The gradient for CO_2 is 47 - 40 = 7 mm Hg.

Even though the gradient for CO_2 is less than for O_2, CO_2 still diffuses faster because of its greater solubility.

Which diffuses faster O_2 from alveoli to blood or CO_2 from blood to alveoli?

m

Which of following gases would be the best to measure diffusing capacity of lung
a. O_2
b. CO_2
c. CO
d. N_2

Chapter Summary

In a normal resting individual at sea level, the partial pressures of oxygen and carbon dioxide are not significantly different among the alveolar, pulmonary end capillary, and systemic arterial compartments ($P0_2$ = 100 mm Hg and PCO_2 = 40 mm Hg).

Only two factors affect alveolar $PC0_2$: body metabolism and alveolar ventilation. If body metabolism is constant, there is an inverse relationship between alveolar ventilation and alveolar PCO_2.

Three important factors affect alveolar $P0_2$: atmospheric pressure, oxygen concentration in the inspired air, and alveolar PCO_2.

A change in alveolar PCO_2 will cause a change in alveolar PO_2. They will change in opposite directions approximately the same amount in mm Hg.

Two structural factors and two gas factors affect the rate of gas diffusion across lung membranes.

Diffusion rate is directly proportional to membrane surface area and inversely proportional to membrane thickness.

CO_2 diffuses faster than other gases because it is more soluble.

The partial pressure gradient is the driving force for diffusion. Supplemental oxygen raises the oxygen gradient and can compensate for a structural problem.

Transport of O_2 and CO_2 and the Regulation of Respiration

3

TRANSPORT OF OXYGEN

Units of Oxygen Content

Oxygen content = the concentration of oxygen in the blood, e.g., arterial blood = 20 volumes % = 20 volumes of oxygen per 100 volumes of blood = 20 ml of oxygen per 100 ml of blood = 0.2 ml of oxygen per ml of blood.

Dissolved Oxygen

Oxygen is not a very soluble gas in plasma; very little is present in this form. Thus, only a very small amount of oxygen is delivered to the capillaries as dissolved oxygen.

However, there is a direct linear relationship between PO_2 and dissolved oxygen (Figure VI-3-1). When the PO_2 is 100 mm Hg, 0.3 ml O_2 is dissolved in each 100 ml of blood (0.3 vol%).

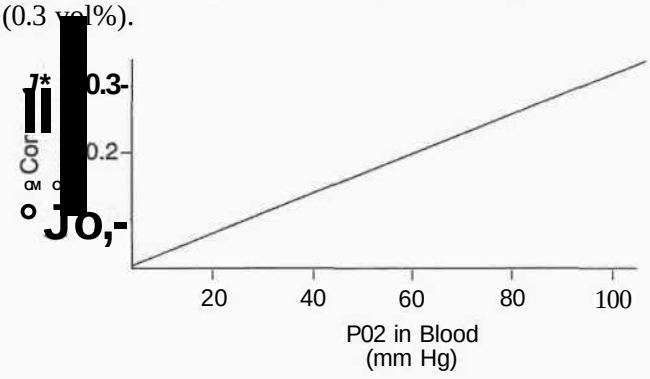


Figure VI-3-1

What the USMLE Requires You to Know

- The different forms of oxygen in the blood
- Characteristics of the oxygen-hemoglobin dissociation curve
- Consequences of shifting the curve to the left and right
- Changes in anemia, polycythemia, and acute carbon monoxide poisoning
- Carbon dioxide transport as plasma bicarbonate
- Central versus peripheral control of alveolar ventilation
- Acute and chronic changes at high altitudes

Also PO_2 is a force created by dissolved oxygen, which acts to keep oxygen on hemoglobin (Hb).

Whether oxygen is attached to a site on Hb depends on the affinity of that site for oxygen and the PO_2. The greater the affinity of a site for oxygen, the lower the required PO_2 to keep the oxygen attached.

Oxyhemoglobin

Each Hb molecule can attach and carry up to four oxygen molecules. Binding sites on Hb have different affinities for oxygen. Also, the affinity of a site can and does change as oxygen is loaded or unloaded from the Hb molecule and as the chemical composition of the plasma changes.

Site 4 - O_2 attached when the minimal PO_2 *3* 100 mm Hg	systemic arterial blood = 97% saturated
Site 3 - O_2 attached when the minimal PO_2 **S** 40 mm Hg	systemic venous blood = 75% saturated (resting state)
Site 2 - O_2 attached when the minimal $PO_2 \equiv$ 26 mm Hg	P50 for arterial blood. P50 is the PO_2 required for 50% saturation

Site 1 - O_2 usually remains attached under physiological conditions. Under physiological conditions, only sites 2, 3, and 4 need to be considered

Site 2 has the greatest affinity of the three sites and thus requires the lowest PO_2 for an oxygen to remain attached. The minimum PO_2 to keep an oxygen attached at this site is about 26 mm Hg. As long as the PO_2 of the plasma is 26 mm Hg or above, oxygen remains on this site.

Site 3: When oxygen attaches to the second site, all sites gain affinity but the ranking does not change. The third site has less affinity than the second. It thus requires a greater PO_2 to maintain the attachment of oxygen, about 40 mm Hg.

Site 4: The last site has the least affinity for oxygen and thus requires the greatest PO_2 to maintain attachment. This is just above 100 mm Hg. At a PO_2 of 100 mm Hg, the hemoglobin is approximately 97% saturated.

Most of the oxygen in systemic arterial blood is oxygen attached to Hb. The only significant form in which oxygen is delivered to systemic capillaries is oxygen bound to Hb.

The number of ml of oxygen carried in each 100 ml of blood in combination with Hb depends on the Hb concentration [Hb]. Each gram of Hb can combine with 1.34 ml of O_2. If the [Hb] is 15 g/100 ml (15 g%), then the maximal amount of O_2 per 100 ml (100% saturation) in combination with Hb is:

$1.34([Hb]) = 1.34(15) = 20$ ml O_2/100 ml blood = 20 vol%

The Hb in systemic arterial blood is about 97% saturated with oxygen, which means slightly less than 20 vol% is carried by Hb.

The total oxygen content of arterial blood is approximately:

1.	attached to hemoglobin	≡19.4vol%
2.	dissolved in the plasma	0.3 vol%
	total	S19.7vol%

When blood passes through a systemic capillary, it is the dissolved oxygen that diffuses to the tissues. However, if dissolved oxygen decreases, PO_2 also decreases, and there is less force to keep oxygen attached to Hb. Oxygen comes off Hb and dissolves in the plasma to maintain the flow of oxygen to the tissues.

Hyperventilation or supplementing the inspired air with additional oxygen in a normal individual can significantly increase the PaO_2 but with little effect on total oxygen content. For example:

	Dissolved O_2	HbO_2	Total O_2 content
If PaO_2 = lOOmmHg	0.3	= 19.4	= 19.7 vol%
If PaO_2= 130mmHg (hyperventilation)	0.4	= 19.4	= 19.8 vol%

Basically shows relationship

6

Oxygen-Hb Dissociation Curves

Figure VI-3-2 represents four major points on the oxygen-hemoglobin dissociation curve. The numbered sites refer to the hemoglobin site numbers discussed just previously.

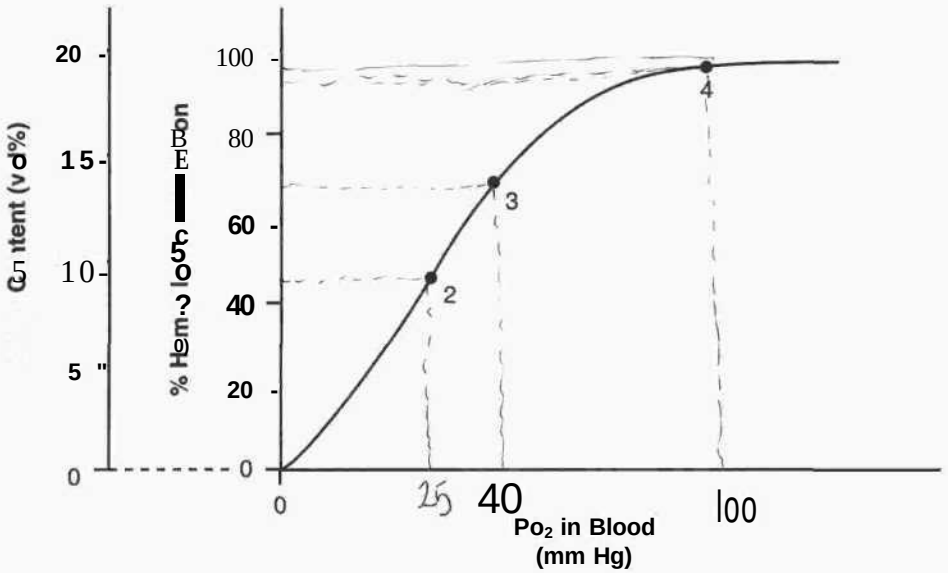


Figure VI-3-2

Shifting the Curve

The following will shift the curve to the right: increased CO_2 (Bohr effect), increased hydrogen ion (decrease pH), increased temperature, increased 2,3-diphosphoglycerate.

In each case, the result can be explained as a loss of affinity of the Hb molecule for oxygen. However, carrying capacity is not changed, and systemic arterial blood at a PO_2 of 100 mm Hg will still be close to 100% saturation.

The opposite chemical changes will shift the curve to the left.

Figure VI-3-3 shows the result of a shift in the O_2-Hb dissociation curve. Note that only points on the steep part of the curve are affected.

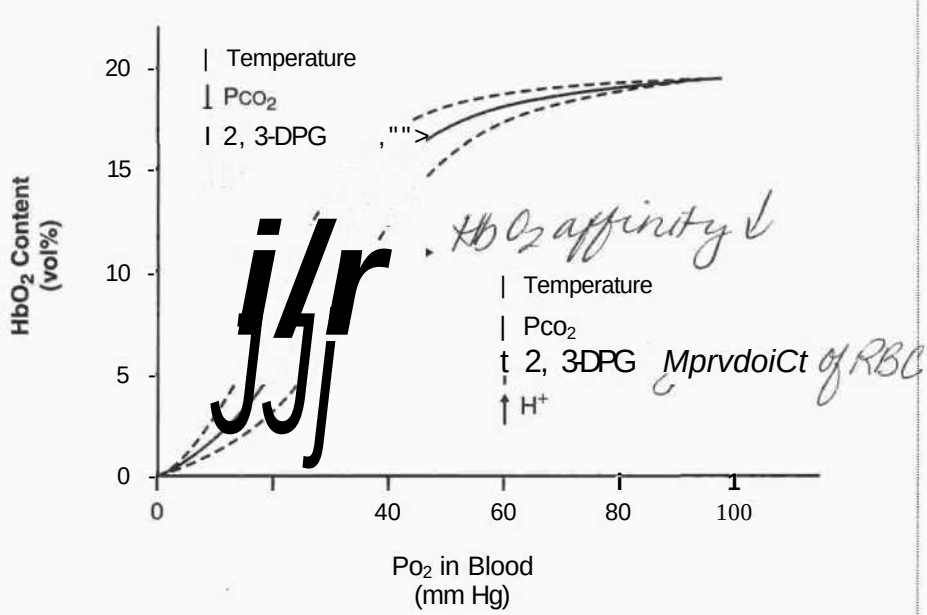


Figure VI-3-3

Shift to the right:	Shift to the left:
Easier for tissues to extract oxygen	More difficult for tissues to extract oxygen
Steep part of curve, O_2 content decreased	Steep part of curve, O_2 content increased
P_{50} increased	P_{50} decreased

Stored blood loses 2,3-diphosphoglycerate, causing a shift to the left. Fetal hemoglobin is also shifted to the left.

Hb Concentration Effects

Anemia

Characterized by a reduced concentration of Hb in the blood.

Polycythemia

Characterized by a higher than normal concentration of Hb in the blood.

P_{50}

In simple anemia and polycythemia, the P_{50} does not change without tissue hypoxia; e.g., a PO_2 of 26 mm Hg will produce 50% saturation of arterial hemoglobin.

Figure VI-3-4 illustrates the effects of an increase and a decrease in hemoglobin concentration. The main change is the plateau or carrying capacity of the blood. Note that the point halfway up each curve, the P_{50}, is still close to 26 mm Hg.

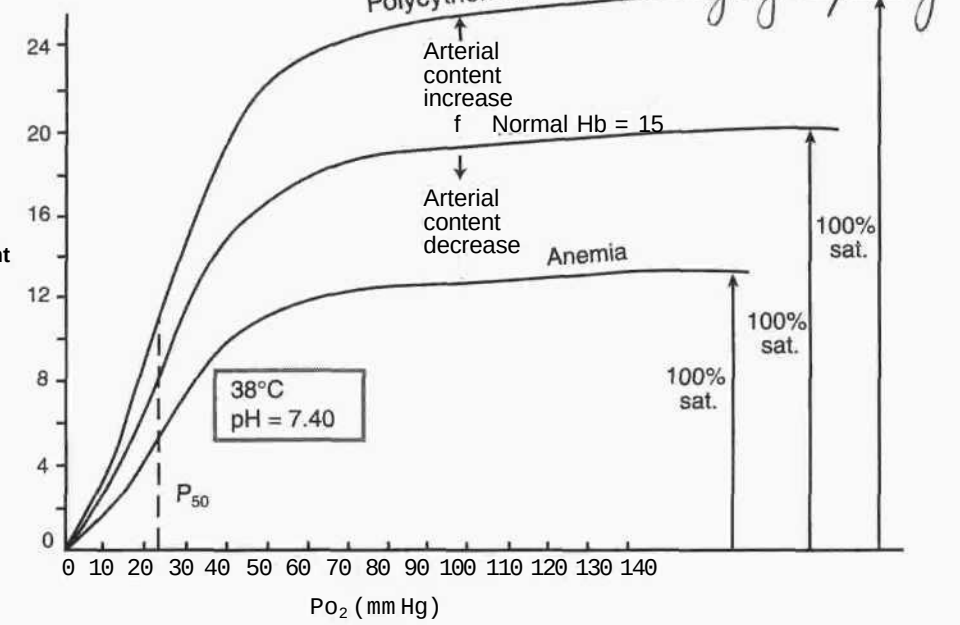


Figure VI-3-4

Effects of Carbon Monoxide

Carbon monoxide has a greater affinity for Hb than does oxygen (240 X greater). For all practical purposes, the partial pressure of carbon monoxide in the blood can be considered close to zero and all the carbon monoxide molecules attached to Hb. Figure VI-3-5 shows that with CO the O_2-Hb dissociation curve is shifted to the left and carrying capacity is reduced.

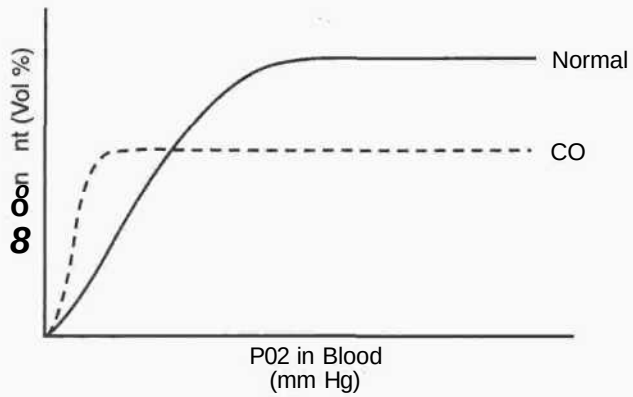


Figure VI-3-5

Table VI-3-1 is a summary of the effects of anemia, polycythemia, and carbon monoxide poisoning.

Table VI-3-1. Systemic Arterial Blood

	PO_2	Hb concentration	O_2 per g Hb	O2 content
Anemia	N	↓	N	↓
Polycythemia	N	↑	N	↑
CO poisoning (acute)	N	N	⇓	⇓

N = normal O_2 per g Hb = % saturation

In anemia, hemoglobin is saturated, but arterial oxygen content is depressed because of the reduced concentration of hemoglobin.

In polycythemia, arterial oxygen content is above normal because of an increased hemoglobin concentration.

In CO poisoning, arterial PO_2 is normal, but oxygen saturation of hemoglobin is depressed.

Transport of Carbon Dioxide

Dissolved Carbon Dioxide

Carbon dioxide is 24 times more soluble in blood than oxygen is. Even though the blood has a PCO_2 of only between 40 and 47 mm Hg, about 5% of the total CO_2 is carried in the dissolved form.

Carbamino Compounds

Carbon dioxide reacts with terminal amine groups of proteins to form carbamino compounds. The protein involved appears to be almost exclusively hemoglobin. About 5% of the total CO_2 is carried as carbamino compounds. The attachment sites that bind CO_2 are different from the sites that bind O_2.

Bicarbonate

About 90% of the CO_2 is carried as plasma bicarbonate.

In order to convert CO_2 into bicarbonate or the reverse, carbonic anhydrase (CA) must be present.

$$CO_2 + H_2O \overset{O}{\leftrightarrow} H_2CO_3 \leftrightarrow H^+ + HCO_3^-$$

Figure VI-3-6 illustrates the steps in the conversion of CO2 into bicarbonate in a systemic capillary.

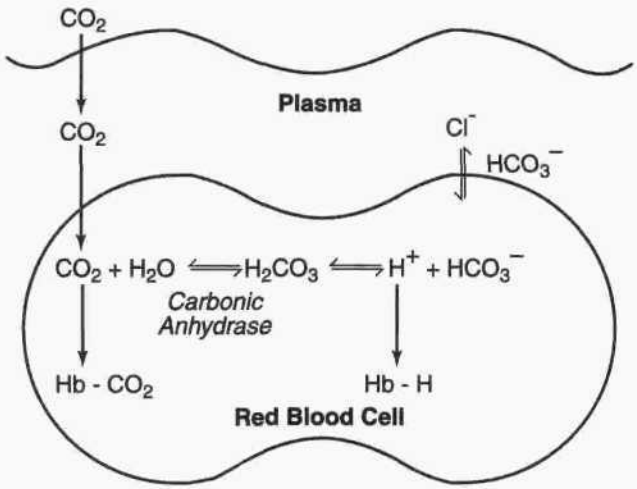


Figure VI-3-6

Plasma contains no carbonic anhydrase; therefore, there can be no significant conversion of CO_2 to HCO_3~ in this compartment.

Because deoxygenated Hb is a better buffer, removing oxygen from hemoglobin facilitates the formation of bicarbonate in the red blood cells (Haldane effect).

To maintain electrical neutrality as HCO_3~ moves into the plasma, Cl~ moves into the red blood cell (chloride shift).

In summary, the bicarbonate is formed in the red blood cell, but it is carried in the plasma compartment.

The PCO_2 determines the volume of CO_2 carried in each of the forms listed above. The relationship between the PCO_2 and the total CO_2 content is direct and nearly linear, as shown in Figure VI-3-7.

make sure you remember where chloride shift is happening (in tissue or blood)

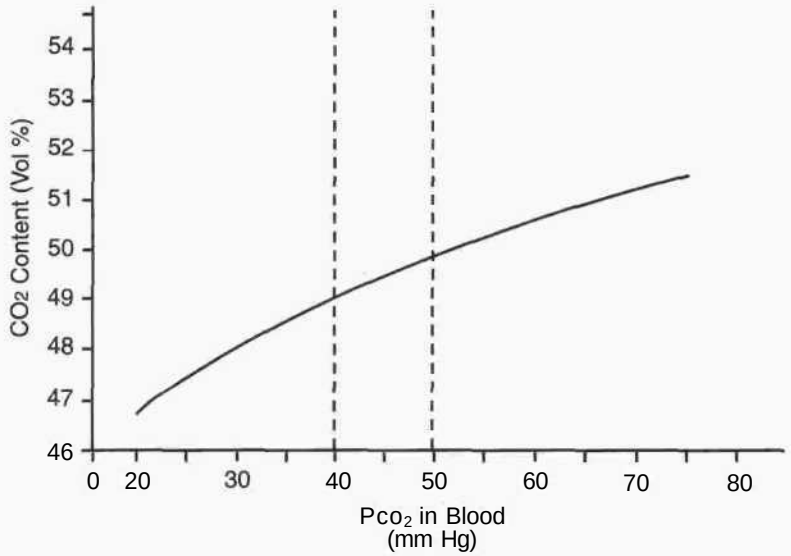


Figure VI-3-7

THE REGULATION OF ALVEOLAR VENTILATION

The level of alveolar ventilation is driven mainly from the input of specific chemoreceptors to the centrajjiei'vous system. The stronger the stimulation of these receptors, the greater the level of alveolar ventilation. Chemoreceptors monitor the chemical composition of body fluids. In this system, there are receptors that respond to pH, PCO_2, and PO_2. There are two groups of receptors, and they are classified based upon their location.

chemoreceptors

Central — $PaCO_2$/H^+

Peripheral — PaO_2/CO_2

PCO_2 ↑ HUIA substance driving

Central Chemoreceptors

These receptors are located in the central nervous system—more specifically, close to the surface of the medulla.

The receptors directly monitor and are stimulated by cerebrospinal fluid [H^+] and CO2. The hydration of CO_2 and subsequent dissociation of H2CO3 in the CSF generates H^+. CSF H^+ is the stimulus to the central chemoreceptor.

Because the blood-brain barrier is freely permeable to CO_2, the activity of these receptors changes with increased or decreased systemic arterial PCO_2.

These receptors are very sensitive and represent the main drive for ventilation under normal resting conditions at sea level.

Therefore, the main drive for ventilation is CO_2 (H^+) on the central chemoreceptors.

Figure VI-3-8 illustrates the relationship between the central chemoreceptors and the systemic arterial blood.

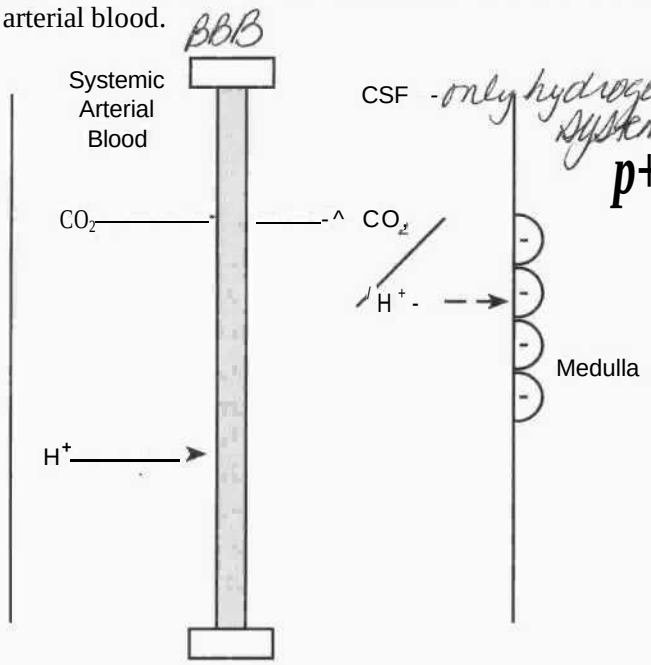


Figure VI-3-8

The system does adapt, usually within 12 to 24 hours. The mechanism of adaptation may be the pumping of HCO3 into or out of the CSF. There are no central PO_2 receptors.

Also, the central chemoreceptors can be considered very sensitive to any change in CSF H^+ but much less sensitive to a change in systemic arterial H^+. This is due to the fact that H^+ passes slowly across the blood-brain barrier.

Peripheral Chemoreceptors

These receptors are found within small bodies at two locations:

Carotid bodies: near carotid sinus, afferents to CNS in glossopharyngeal nerveDC

Aortic bodies: near aortic arch, afferents to CNS in vagus nerve X

The carotid body is the most important peripheral chemoreceptor in humans. Because it receives the most blood per gram of tissue in the body and is so small, it can meet all of its metabolic requirements for O2 by utilizing the O2 that is dissolved in the blood. The peripheral chemoreceptors are bathed in arterial blood, which they monitor directly. These bodies have two different receptors:

1. H^+/CO_2 receptors

   These receptors are less sensitive than the central chemoreceptors, but they still contribute to the normal drive for ventilation.

   Therefore, under normal resting conditions at sea level, for all practical purposes, the total drive for ventilation is CO_2, mainly via the central chemoreceptors but with a small contribution via the peripheral chemoreceptors.

2. PO_2 receptors

   The factor monitored by these receptors is PO_2, not oxygen content. Because they respond to PO_2, they are actually monitoring dissolved oxygen and not oxygen on Hb. When systemic arterial PO_2 is close to normal (= 100 mm Hg) or above normal, there is little if any stimulation of these receptors. Thus, they do not contribute to our normal drive for ventilation.

   They are strongly stimulated only by a dramatic decreas e in syslemic arter rial PC[1]?. They do not begin to fire significantly until the PaO_2 falls to 50-60 mm Hg. Under these conditions, there is an increased drive for ventilation, and alveolar ventilation usually increases. In most situations where the systemic arterial PO_2 is dramatically reduced, the main drive for ventilation is the low PO_2 stimulation of the peripheral chemoreceptors. Sensitivity to hypoxia increases with CO_2 retention.

These receptors do not adapt.

Abnormal Situations

Chronic Hypoventilation

Though the PaCO2 is increased, only the peripheral chemoreceptors are driving respiration. Giving supplemental oxygen to these individuals and raising the arterial PO_2 dramatically can eliminate their PO_2 drive for respiration.

Anemia

Total O2 content is decreased, but the PaO2 is normal. Therefore, there is no ventilatory response to this kind of hypoxia. This also applies to CO poisoning, and in addition, because of the leftward shift in the oxy-Hb dissociation curve, it is life-threatening (Figure VI-3-9).

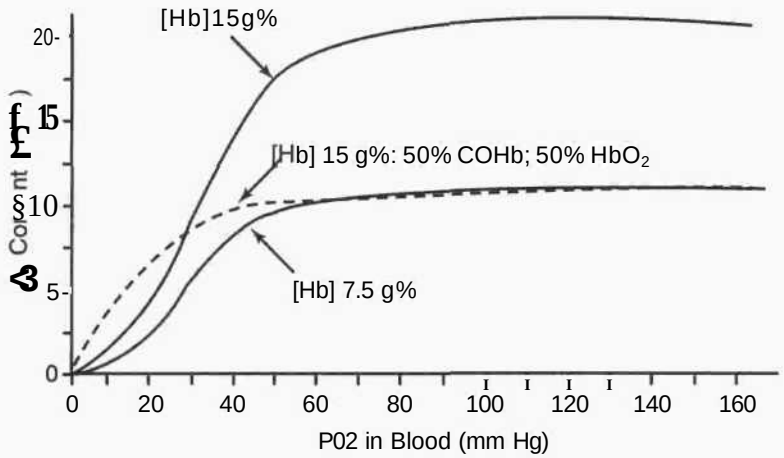


Figure VI-3-9

The Central Respiratory Centers

Medullary Centers

Site of the inherent rhythm for respiration.

- Inspiratory center
- Expiratory center

For spontaneous breathing, an intact medulla must be connected to the diaphragm (via the phrenic nerve). Thus a complete Cl or C2 lesion will prevent diaphragmatic breathing but not a complete C6 or lower lesion.

Apneustic Breathing

An abnormal breathing pattern characterized as prolonged inspirations alternating with a short period of expiration.

Apneustic Center

Located in the caudal pons. This center has an intrinsic rhythm and, when active, promotes prolonged inspirations.

PneumotaxicCenter

Located in the rostral pons. This center normally has an inhibitory influence on the apneustic center.

If the connection between the pneumotaxic center and the apneustic center is severed, apneustic breathing will develop.

Figure VI-3-10 illustrates the main features involved in the central control of ventilation.

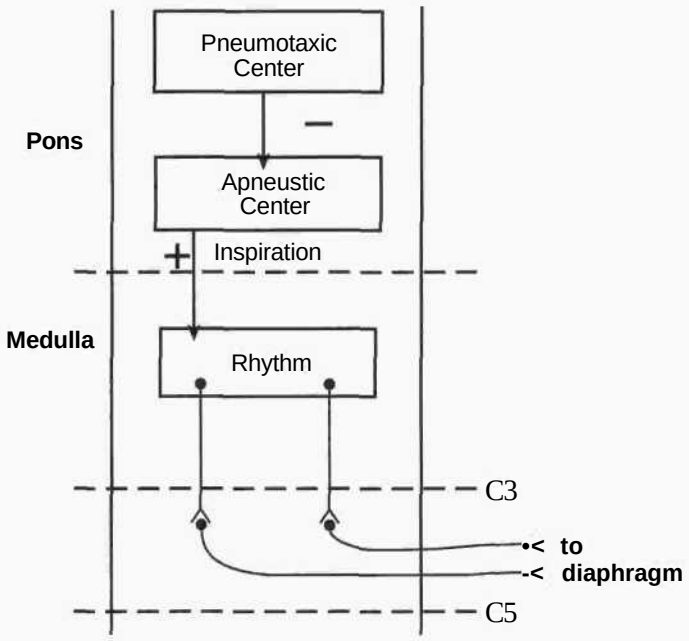


Figure VI-3-10

UNUSUAL ENVIRONMENTS

High Altitude

The major problem at high altitude is that atmospheric pressure is reduced from the 760 mm Hg of sea level. Because atmospheric pressure is a factor that determines room air and alveolar PO_2, these two values are also reduced. These two values are permanently depressed unless enriched oxygen is inspired.

Therefore, PAO_2 <100, PaO_2 <100, and the low arterial PO_2 will stimulate the peripheral chemoreceptors and increase alveolar ventilation. At high altitude, then, the main drive for ventilation changes from CO_2 on the central chemoreceptors at sea level to a low PO_2 drive of the peripheral chemoreceptors, and hyperventilation ensues.

Table VI-3-2. Acute Changes and Long-Term Adaptations (Acclimatization)

	Acute changes	Acclimatization
PAO_2 and PaO_2	decrease	remains decreased
$PACO_2$ and $PaCO_2$	decrease	remains decreased
Systemic arterial pH	increase	decreases to normal via renal compensation
Hb concentration	no change	increases (polycythemia)
Hb % sat	decreased	remains decreased
Systemic arterial O_2 content	decreased	increases to normal

At high altitude, hypoxia can develop, resulting in increased circulating levels of erythropoietin. Erythropoietin will increase red blood cell production and eventually cause an adaptive polycythemia.

When you arrive at the mountains your resp. rate ↑ due to stim. of peripheral receptors. A month later you have acclimatized. What will your resp. rate be and why? The resp. rate will still be ↑ return back to normal due to peripheral rec.

acclimatization means pH is normal again

Reason for danger of breathing 100% O_2. O_2 radicals can destroy capillary wall. This will lead to leakage and edema.

High-Pressure Environment

In a hyperbaric environment breathing room air (21% O_2 and 79% N_2), the partial pressure of O_2 and N_2 will increase in the alveoli and systemic arterial blood. The pressure of nitrogen will also increase in other body compartments. The adverse effect of a high PO_2 can be oxygen toxicity. The high PN_2 can cause nitrogen narcosis, but, more important, it can lead to the bends (caisson disease).

There are two prerequisites for the bends:

Breathing high-pressure nitrogen for a prolonged period of time

Sudden decompression

The sudden decompression causes bubbles of nitrogen (emboli) in the bloodstream and tissues. Treatment is recompression and a slow, gradual decompression.

Chapter Summary

The only significant form in which oxygen is delivered to systemic tissues is oxygen attached to hemoglobin. However, PO_2 created by dissolved oxygen is a force necessary to keep oxygen bound to hemoglobin.

Normal hemoglobin in the systemic arterial system will be almost completely saturated with oxygen when the $P0_2$ is 100 mm Hg. Mixed venous hemoglobin in a resting individual will be about 75% saturated.

Increased H+, CO_2, temperature, and 2,3-diphosphoglycerate will shift the Hb-O_2 curve to the right. This assists in the unloading of oxygen to systemic tissues but does not prevent complete loading of oxygen in lung capillaries.

The normal drive for ventilation is $C0_2$, mainly on the central chemoreceptors.

When the systemic arterial $P0_2$ dramatically decreases, the main drive for ventilation is the low PO_2 on the peripheral chemoreceptors.

Spontaneous rhythmic breathing requires an intact medulla connected, via the phrenic nerves, to the diaphragm.

At high altitude, there is a permanent depression in alveolar and systemic arterial $P0_2$. The low $P0_2$ stimulates the peripheral chemoreceptors, inducing a hyperventilation and a decrease in alveolar and systemic arterial $PC0_2$. The loss of $C0_2$ produces a respiratory alkalosis. To compensate, the kidney loses bicarbonate to return arterial pH close to normal. Acutely, arterial oxygen content is depressed because of reduced hemoglobin saturation. Acclimatization returns oxygen content toward normal because of an increase in hemoglobin concentration.

Four Causes of Hypoxemia

4

VENTILATION-PERFUSION DIFFERENCES IN THE LUNG

Regional Differences in Ventilation

At the end of a normal expiration, the mean value for intrapleural pressure is -5 cm H_2O. However, there are regional differences, and the reason for these differences is gravity. In an upright individual, there is a column of fluid and tissue in the chest cavity. Toward the lung apex (against gravity), intrapleural pressure decreases (becomes more negative); more toward the lung base, pressure increases (becomes more positive). These differences are illustrated in Figure VI-4-1.

What the USMLE Requires You to Know

- The basis for regional differences in alveolar ventilation and pulmonary blood flow
- A mismatch between alveolar ventilation and blood flow as a cause of hypoxemia
- Hypoventilation as a cause of hypoxemia
- Diffusion impairment as a cause of hypoxemia
- Carbon monoxide as a diffusion limited gas
- A pulmonary (right-to-left) shunt as a cause of hypoxemia
- The consequences of a left-to-right shunt

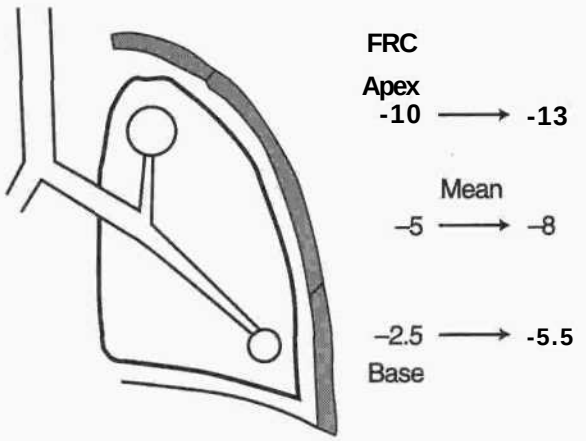


Figure VI-4-1

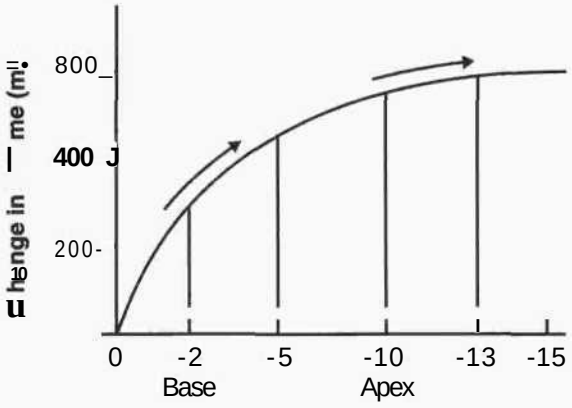


Figure VI-4-2

At the apex, intrapleural pressure is -10 cm H_2O, which represents a low pressure but a large force expanding the alveoli. Therefore, at the beginning of inspiration, alveoli at the apex are large and stiff and contain a large volume of air.

At the base, intrapleural pressure is -2.5 cm H_2O, which represents a higher pressure but a smaller force expanding the alveoli. Therefore, at the beginning of inspiration, alveoli at the base are small and very compliant and contain a small volume of air.

Inspiration at the Apex

Intrapleural pressure decreases from -10 to -13 cm H_2O. But because the alveoli were almost completely inflated (low compliance) before inspiration begins, they change little during inspiration. Thus, very little room air flows into these alveoli. The amount of room air entering an alveolus during inspiration represents alveolar ventilation ($\dot{V}A$). Consequently, under resting conditions, alveoli at the apex are large but receive a low level of alveolar ventilation.

Inspiration at the Base

Intrapleural pressure decreases from -2.5 to -5.5 cm H_2O. The base alveoli at the beginning of inspiration are small, but they are on the steep part of the pressure-volume curve (very compliant). Because of this, during inflation there is a large change in size and volume. Consequently, under resting conditions, alveoli at the base are always smaller than those at the apex but receive a high level of alveolar ventilation.

Regional Differences in Blood Flow

Even in a normal individual, there are regional differences in blood flow through the pulmonary circuit. These differences, for the most part, can be attributed to the effect of gravity. Everything stems from the fact that in the upright individual, as blood moves against gravity (toward the lung apex), pressure decreases, and as blood moves toward the base of the lung, pressure increases.

Toward the Apex

Pulmonary arterial pressure decreases.

Vessels are less distended and thus represent a higher resistance system.

Therefore, lower perfusing pressures and higher resistance mean less blood flow to the apex.

Toward the Base

Pulmonary arterial pressure increases.

Vessels are more distended, thus a lower resistance system.

Therefore, no loss in perfusing pressure and a lower resistance pathway mean more blood flow to the base.

Ventilation-Perfusion Relationships

Apex: Least ventilation (ml/min) and blood flow (ml/min).

Base: Greatest ventilation (ml/min) and blood flow (ml/min).

Blood flow and ventilation are greatest at the base and decrease toward the apex. Although the relationship between the two is similar, quantitative differences exist.

In the normal individual, there is an ideal relationship between blood flow and ventilation. The ideal relationship depends on a number of variables. In a normal individual under resting conditions, it is close to 0.8.

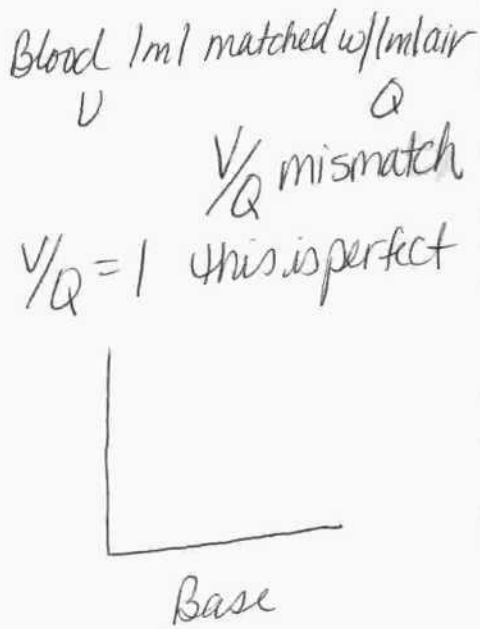


Figure VI-4-3 shows the relative differences in blood flow ($\dot{Q}$) and alveolar ventilation ($\dot{V}A$) between the lung base and apex in an upright individual.

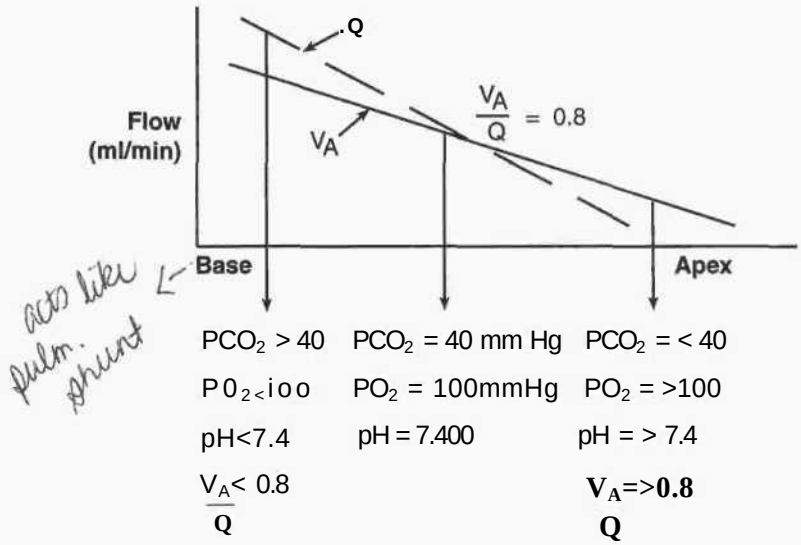


Figure VI-4-3

Even though the base receives the greatest ventilation, it is not high enough for the very high blood flow. Therefore, the base can be considered an underventilated region.

Even though the apex receives the least ventilation, it is still too high for the very low blood flow. Therefore, the apex can be considered an overventilated region.

InSummary

When the ratio is less than 0.8 under resting conditions, the lung unit is underventilated.

When the ratio is greater than 0.8, it is overventilated.

Problem

The following ratios represent two different lung units under resting conditions:

$$\dot{V}A/Q$$
$$A = 0.62$$
$$B \; s \; 0.73$$

Lung units A and B are both underventilated, but of the two, B is better ventilated.

Which lung unit had the greatest:

$PACO_2$, end capillary PCO_2? (Answer: A)

PAO_2, end capillary PO_2? (Answer: B)

end capillary pH? (Answer: B)

Hypoxic Vasoconstriction

This is a clinically important phenomenon that is unique to the pulmonary circulation. Whenever there is a decrease in alveolar PO_2, a local vasoconstriction of pulmonary blood vessels is produced. The result is a lowering of blood flow through that lung unit.

Problem

If a person inhales a peanut that lodges in a peripheral airway, what changes would you expect for the following variables in the peanut-occluded unit?

$PACO_2$ (increase)

PAO_2 (decrease)

pulmonary end capillary pH (decrease)

blood flow in that lung unit (decrease)

All answers here are based on the fact that blocking the airway would decrease the $\dot{V}A/Q$ ratio. The blood flow decreases because of hypoxic vasoconstriction. Low $\dot{V}A/Q$ ratios are associated with hypoxic vasoconstriction.

Problem

If a small thrombus lodges in a pulmonary artery, what changes would you expect for the following variables in the thrombus-occluded unit?

$PACO_2$ (decrease)

PAO_2 (increase)

pulmonary end capillary pH (increase)

All answers here are based on the fact that the thrombus would increase the $\dot{V}A/Q$ ratio.

R→L shunts
↓ PO_2 → cyanosis

If some peanut what happens to a
↓ P_aO_2
↑ P_aCO_2
↓ pH
↓ blood flow only in unit that occluded
↓V/Q↑ (resembles base)

If someone develops thrombus (give heparin)
↑V/↓Q (resembles apex)
P_aO_2
P_aCO_2
↑ pH
↑ blood flow

55yr. old man w/ P_aO_2=60
-The man has hypoxemia
Diff. Diagnosis
Hypoventilation
diffusion impairment (fibrosis)
perfusion limited (pulm shunt necrosis)
V/Q

Consequences of $\dot{V}A/Q$ Mismatches

$\dot{Q}$ $\dot{V}A/Q$ < 0.8: If we take the situation to the extreme, where there is blood flow but minimal ventilation, this lung unit would resemble a pulmonary shunt. Thus, as the ratio goes below 0.8, the lung unit begins to act like a shunt. The lower the ratio, the more that lung unit acts like a pure shunt.

$\dot{V}A/Q$ > 0.8: If we take this situation to the extreme, where there is ventilation but minimal blood flow, the lung unit would act as dead space. The greater the ratio, the more that lung unit acts like dead space.

Exercise

In exercise, there is increased ventilation and pulmonary blood flow. The ideal $\dot{V}A/Q$ is no longer 0.8; it is greater than 0.8. Thus, during exercise, ventilation increases more than cardiac output. Also, the base-apex flows are more uniform.

Cyanosis congenital Begins w/ T

(A-a) = 0

atmosphere pressure = CO_2

Alveolar O_2

Pt. Tract
Pt. heart.
lungs

Mr. Jones comes in & PaO2=60 PO_2=100

100-60=40

to differentiate you give him 100% O_2 for 15 min.

If ↑ more than 5 then diffusion problem. If remained constant then shunt

NORMAL STATE

In the normal individual, alveolar ventilation maintains a PACO2 close to 40 mm Hg and a PAO2 of about 100 mm Hg. Equilibration will occur between the alveolar and pulmonary capillary compartments, and thus pulmonary end capillary blood PCO2 and PO2 will equal alveolar. Although a mismatch between alveolar ventilation and blood flow is normally present, there is little change in PCO2 and PO2 between end capillary and systemic arterial blood (A-a gradient minimal, about 5-10 mm Hg).

In the normal lung, the alveolar PO_2 (PAO_2), pulmonary end capillary PO_2, and systemic arterial PO_2 (PaO_2) will all be approximately the same. This is illustrated in Figure VI-4-4.

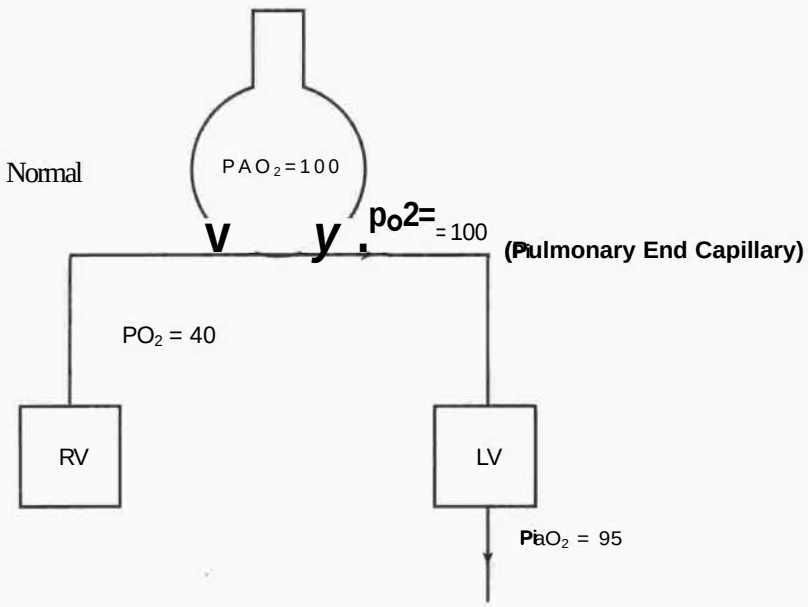


Figure VI-4-4

HYPOVENTILATION

Hypoventilation elevates alveolar PCO2, and the increase in PCO2 decreases PO2. For example, if alveolar ventilation decreases by 50%, alveolar PCO2 becomes 80 mm Hg (an increase of 40 mm Hg). Assuming a respiratory ratio close to 1.0, alveolar PO2 will decrease by about 40 mm Hg to 60 mm Hg. If no other problem exists, pulmonary end capillary and systemic arterial PO2 will also decrease to 60 mm Hg. This is illustrated in Figure VI-4-5.

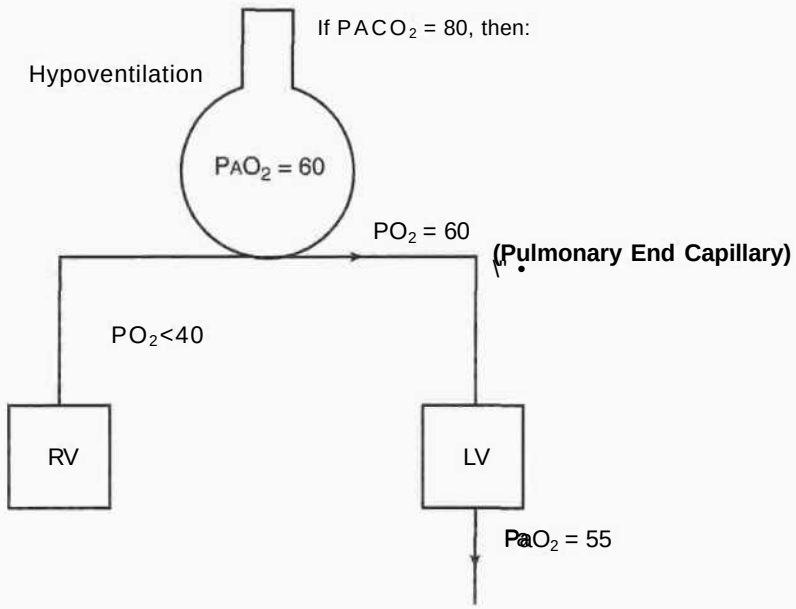


Figure VI-4-5

Hypoventilation is characterized as an equal decrease in PO_2 in all three compartments.

As a result, there will not be an increase in the alveolar, systemic arterial PO_2 difference (A-a normal), and end-tidal PO_2 will still be a good index of systemic arterial PO_2.

In patients who are hypoxemic and retaining CO_2, if the PO_2 A-a is normal, one can assume that gas exchange is not defective and that the observed hypoxemia can be corrected entirely by increasing ventilation. This could also be achieved by increasing the inspired oxygen. If PO_2 A-a is elevated, there is a defect in gas transfer.

Also, because arterial PO_2 decreases in hypoxemia, systemic venous and pulmonary arterial PO_2 will also decrease.

Definition

If equilibrium occurs between the alveolar gas and the capillary blood, it is referred to as a perfusion-limited situation for that particular gas.

DIFFUSION IMPAIRMENT

Diffusion impairment means a structural problem in the lung. This can be produced by a decreased surface area and/or increased thickness of lung membranes. The consequences of diffusion impairment are illustrated in Figure VI-4-6 and summarized following the figure.

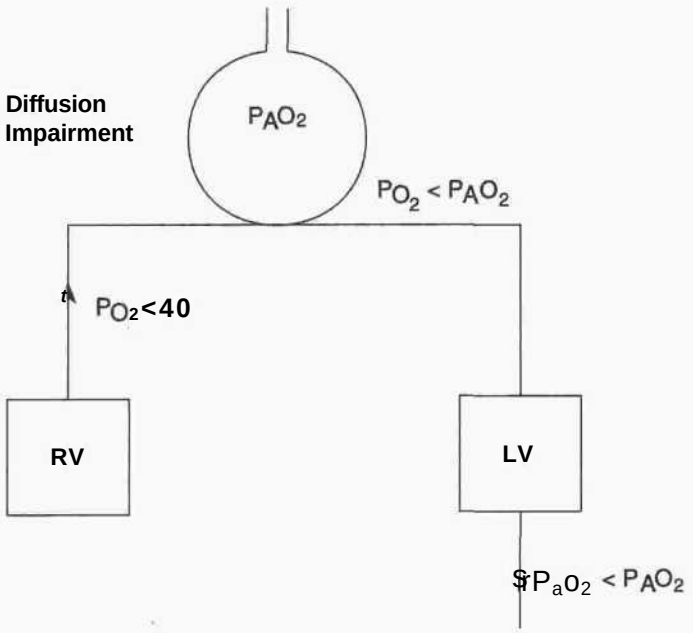


Figure VI-4-6

In marked diffusion impairment, pulmonary end capillary PO_2 will be less than alveolar PO_2, and a difference will exist between the alveolar and systemic arterial blood (A-a). Thus, end-tidal PO_2 will not be a good index of systemic arterial PO_2.

In diffusion impairment, supplemental oxygen will increase the gradient across the alveolar membranes and return arterial PO_2 toward normal.

Definition

If the alveolar gas and the capillary blood do not equilibrate, it is a diffusion-limited situation for that particular gas.

CARBON MONOXIDE—
A GAS THAT IS ALWAYS DIFFUSION LIMITED

Carbon monoxide has an extremely high affinity for hemoglobin. When it is present in the blood, essentially all is combined with hemoglobin, and the amount dissolved in the plasma is zero (therefore, partial pressure in the plasma is zero). Thus, the alveolar partial pressure is the gradient ($P_j - P_2$). At a constant and known alveolar partial pressure, the uptake of carbon monoxide depends only on the structural features of the lung, as illustrated in Figure VT-4-7.

$$\dot{V}gas = \pounds \times D \times (P \wedge P \wedge$$

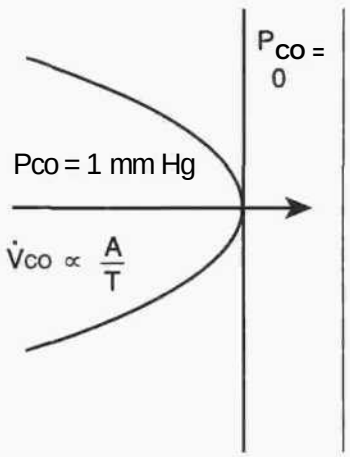


Figure VI-4-7

$$\dot{V}co = \frac{A}{Y} \times D \times P_{A^{CO}}$$

In a young individual with normal lung surface area (A) and thickness (T), a 1-mm Hg gradient of carbon monoxide will produce an uptake of 25 ml/min.

This measured uptake of carbon monoxide is called the diffusion capacity of the lung (DL; ml/min/mm Hg). It is an index of overall surface area and membrane thickness. With a structural problem, it correlates with the extent of lung damage and is particularly useful when measured serially over time.

DL (rate of CO diffusion) decreases in emphysema and fibrosis but increases during exercise.

PULMONARY SHUNT

A pulmonary shunt is also known as a right-to-left shunt. By definition, systemic venous blood is delivered to the left side of the heart without exchanging oxygen and carbon dioxide with the alveoli. A good example is blood passing through a region of atelectasis. A right-to-left shunt always leads to hypoxemia.

Figure VI-4-8 illustrates the consequences of a pulmonary shunt. The solid line regions represent the normal areas of the lung. The dashed line represents the shunted blood, which is passing from the right heart to the left heart without a change in chemical composition.

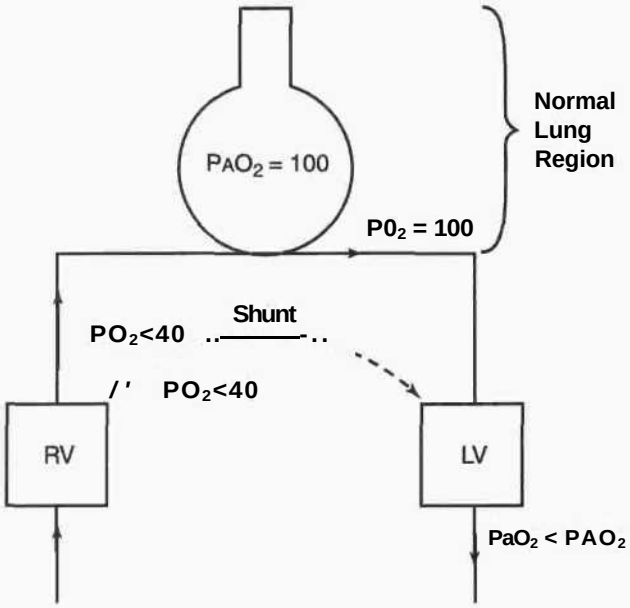


Figure VI-4-8. Pulmonary Shunt

With a pulmonary shunt, systemic arterial PO_2 will be less than alveolar and end-capillary PO_2. A widening of the PO_2 A-a difference will occur, and end-tidal PO_2 will not reflect systemic arterial PO_2.

When a significant pulmonary shunt exists, breathing pure O_2 will elevate systemic arterial PO_2 a small amount, but it will never produce full saturation of the hemoglobin.

The failure to obtain a significant increase in arterial PO_2 following the administration of supplemental oxygen in hypoxemia is strong evidence of the presence of a pulmonary shunt.

SHUNTING OF BLOOD IN THE HEART

The consequences are quite different from a pulmonary shunt because pressures are usually higher on the left side of the heart (atria and ventricles), and thus flow is normally left to right. A major characteristic is that hypoxemia never develops in a left-to-right shunt. The principal example is an atrial or ventricular septal defect.

Figure VI-4-9 illustrates the normal PO2 values in the left and right compartments. Note from the descriptions that follow where the first increase in PO2 develops on the right side.

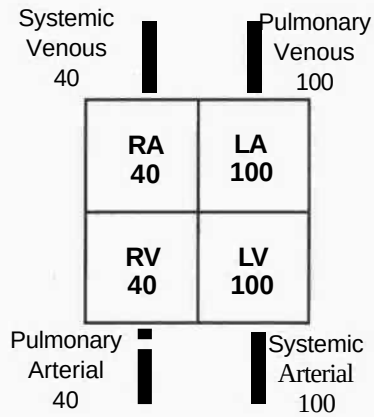


Figure VI-4-9

Table VI-4-1. The Consequences of Three Different Left-to-Right Shunts

	Atrial Septal Defect	Ventricular Septal Defect	Patent Ductus (newborn)
Systemic arterial PO_2	no change	no change	no change
Right atrial PO_2	↑	no change	no change
Right ventricular PO_2	↑	↑	no change
Pulmonary arterial PO_2	↑	↑	↑
Pulmonary blood flow	↑	↑	↑
Pulmonary arterial pressure	↑	↑	↑

Atrial septal defect: PO_2 increase first appears in the right atrium.
Ventricular septal defect: PO_2 increase first appears in the right ventricle.
Patent ductus: PO_2 increase appears in pulmonary artery.

If pressures on the right side exceed those on the left, the situation is equivalent to a pulmonary shunt. If, for example, pressure in the right atrium exceeds left atrial pressure, a septal defect will produce a right-to-left shunt, and the oxygen content of the blood in the left heart will decrease.

Chapter Summary

The ideal $\dot{V}A/Q$ ratio at rest is close to 0.8. A ratio greater than 0.8 is an overventilated lung unit (dead space component), and a ratio less than 0.8 is an underventilated lung unit (pulmonary shunt component).

A low $\dot{V}/Q$ ratio or any other decrease in alveolar PO_2 will initiate a vasoconstriction of the pulmonary vasculature.

Hypoventilation is associated with equal decreases in the PO_2 of the alveolar, pulmonary end capillary, and systemic arterial compartments. There is no widening of the A-a gradient, and an increase in alveolar ventilation will return arterial PO_2 to normal. This can also be achieved with supplemental oxygen.

Diffusion impairment is a structural problem of the lung. When it is severe, blood leaving a pulmonary capillary will not have equilibrated with the alveolar air. There is a widening of the A-a gradient, and supplemental oxygen will return arterial PO_2 toward normal.

A pulmonary (right-to-left) shunt will produce a widening of the A-a gradient and is the only cause of hypoxemia that will not respond significantly to supplemental oxygen.

A left-to-right shunt can lead to pulmonary hypertension but will not produce hypoxemia.

RESPIRATION

Review Questions

Lung Compartments

Directions: Select the ONE best answer.

1. Which of the following formulas is correct?
   A. Vital capacity = inspiratory volume + expiratory reserve volume.
   B. Dead air space = resting tidal volume + residual volume.
   C. Alveolar ventilation = (respiratory rate) X (tidal volume - dead air space).
   D. Vital capacity = inspiratory reserve volume + resting tidal volume + expiratory reserve volume + residual volume.
   E. Inspiratory reserve volume = vital capacity - resting tidal volume.

2. Which of the following could produce a decrease in alveolar ventilation with no change in total ventilation?
   A. A decreased functional residual capacity
   B. A decreased respiratory rate and tidal volume
   C. An increased respiratory rate and decreased tidal volume
   D. A decreased respiratory rate and increased tidal volume
   E. An increased respiratory rate and tidal volume

Lung Mechanics

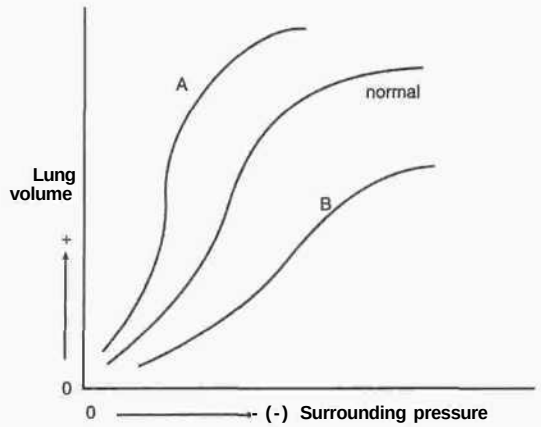
Directions for Questions 1-6: Select the ONE best answer.

1. If surfactant is absent from the alveoli, the lungs':
   A. airway resistance will decrease.
   B. compliance will increase.
   C. compliance will decrease.
   D. O_2 diffusing capacity will increase.
   E. recoil will decrease.

2. During inspiration (as compared to expiration):
   A. intrapleural pressure is increasing.
   B. lung recoil is increasing.
   C. abdominal muscles are normally contracting.
   D. both A and B are correct.
   E. all of the above are correct.

3. If a person inspires maximally, closes his glottis, and contracts his expiratory muscles as hard as he can (Valsalva maneuver):

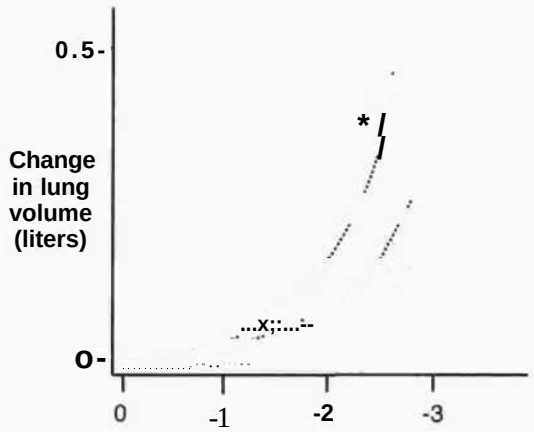
A. intrapleural pressure is higher than alveolar pressure.
B. intrapleural pressure and lung recoil both act to increase pressure within the alveoli.
C. intrapleural pressure at the apex is below atmospheric but above atmospheric at the base.
D. none of the above are correct.
E. all of the above are correct.



4. The above represents the inflation pressure-volume curve of three different lungs. If the middle curve represents a normal lung, which of the following statements is correct?

A. The compliance of lungs A and B are both greater than normal.
B. Lung A is more compliant than normal, and at any lung volume recoil will be greater than in normal lungs.
C. Lung B is more compliant than normal, and at any given lung volume recoil will be greater than in normal lungs.
D. Lung A is more compliant than normal, and for a given change in surrounding pressure, a greater change in lung volume will occur than in normal lungs.
E. Lung B is more compliant than normal, and for a given change in surrounding pressure, a greater change in lung volume will occur than in normal lungs.

5. The following pressure-volume curves were obtained from subjects X and Y during quiet breathing at a rate of 14/min.



(esophageal pressure is an index of intrapleural pressure)

What conclusion can you draw from these curves? Subject X has the:

A. higher pulmonary compliance
B. higher tidal volume
C. higher pulmonary compliance and tidal volume
D. lower pulmonary compliance
E. lower pulmonary compliance and tidal volume

6. Resistance in the airways of the lungs decreases:

A. in response to sympathetic nerve stimulation
B. in response to parasympathetic nerve stimulation
C. in response to a decrease in alveolar PCO_2
D. as the diameter of the air tubes decreases
E. as the velocity of air flow increase

Lung Compartments: Answers

1. **Ans** C. Alveolar ventilation represents the amount of new fresh air that reaches the alveoli. For each inspiration it will be tidal volume minus dead space (anatomical). For alveolar ventilation per minute we must multiply by the respiratory rate.

   Vital capacity is the maximum tidal volume possible. It will be the tidal volume plus inspiratory reserve volume plus expiratory reserve volume.

   Dead space will be the volume of the conducting airways.

   Inspiratory reserve volume will be vital capacity minus resting tidal volume minus expiratory reserve volume.

2. **Ans** C. Ans A. FRC is irrelevant, it is not a determinant of ventilation.

   Ans B. A decrease in the respiratory rate and tidal volume will decrease alveolar ventilation, but total ventilation will also decrease.

   Ans C. An increase in the respiratory rate and a decrease in tidal volume indicate a pattern of rapid shallow breathing. If the total ventilation does not change, alveolar ventilation will decrease because of the fact that the first 150 ml of each inspiration is dead space breathing. An increase in the rate means an increase in dead space breathing.

   Ans D. This situation is the reverse of Ans C. Again total ventilation must remain constant. Under these conditions a decreased rate means less dead space breathing. Thus, alveolar ventilation must increase.

   Ans E. An increase in the rate and depth of breathing will increase total and alveolar ventilation.

Lung Mechanics: Answers

1. **Ans** C. A loss of surfactant will mean that recoil increases and compliance decreases (stiffer lung). Thus, more negative intrapleural pressures are necessary to keep the lung open and to inflate the lung.

   Ans A. This is a complex situation. The more negative intrapleural pressures will actually decrease resistance in the large airways, but peripheral congestion and collapse will produce the opposite.

   Ans D. The diffusing capacity for all gases will decrease because of the peripheral congestion and collapse. This will effectively decrease surface area for exchange. Interstitial edema will also increase membrane thickness.

2. **Ans** B. During inspiration intrapleural pressure is becoming more negative, which means the pressure is decreasing. Since the lung enlarges, recoil is increasing. The abdominal muscles are expiratory since they raise abdominal pressure and force the diaphragm into the thorax.

3. **Ans** B. During the Valsalva maneuver the contraction of expiratory muscles creates a very positive pressure in the thoracic cavity. This represents a force acting to collapse the lung. Since the glottis is closed and no air can flow, the positive intrapleural pressure and the force of recoil will combine to create a positive alveolar pressure. Alveolar pressure will be greater than intrapleural pressure by an amount equal to the force of recoil.

4. **Ans** D. Curve A represents an increase in compliance. Recoil will be less at any given volume, and there will be a greater change in volume for a given change in intrapleural pressure. Curve B is a less compliant lung (stiffer lung). At any given lung volume, recoil will be greater and a large change in intrapleural pressure will be required for a given change in lung volume.

5. **Ans** C. In subjects X and Y, the decrease in intrapleural pressure was the same (close to 3 cm H_2O). However, the inspired volume of X was greater than Y. The greater inspired volume of X with the same change in intrapleural pressure as Y means the lungs of subject X are more compliant.

6. **Ans** A. Sympathetic stimulation of airway smooth muscle causes a relaxation and parasympathetic stimulation causes constriction. Thus sympathetics cause a decrease in airway resistance.

Ans C. There is a local phenomenon in the lung system whereby if $PACO_2$ decreases, there is a decrease in alveolar ventilation due to constriction of the alveolar ducts. This is not nearly as important as hypoxic constriction, but it does tend to keep $\dot{V}/\dot{Q}$ closer to the ideal value.

Ans D. As the diameter of a tube decreases, resistance would increase.

Ans E. An increase in velocity promotes turbulence. A more turbulent system means a higher resistance.

Alveolar-Blood Gas Exchange: Review Questions

Directions for Questions 1-3: Select the ONE best answer.

1. The alveolar PO_2 of an individual breathing 30% O_2 at an atmospheric pressure of 747 mm Hg will be (in mm Hg). Assume R = 1.0 and P_ACO_2 = 40 mm Hg

   A. 224
   B. 210
   C. 170
   D. 164
   E. 100

2. If alveolar PCO_2 was originally 40 mm Hg but body temperature increased and CO_2 production doubled while no change occurred in alveolar ventilation, what decrease should occur in alveolar PO_2 (assume R = 1.0)?

   A. 10 mm Hg
   B. 20 mm Hg
   C. 30 mm Hg
   D. 40 mm Hg
   E. no change

3. An individual's inspired PO_2 was 150 mm Hg and his alveolar PCO_2 was 40 mm Hg. If this person's alveolar ventilation then doubled, his alveolar PO_2 would be expected to change by (assume a new steady state and an R value of 1.0):

   A. 20 mm Hg
   B. 25 mm Hg
   C. 40 mm Hg
   D. 50 mm Hg
   E. no change

Alveolar-Blood Gas Transfer: Review Questions

Directions: Select the ONE best answer unless otherwise stated.

1. A series of gas mixtures is inhaled by a healthy subject. Which one of the following gases would diffuse most slowly from the lungs into the blood?

   A. CO_2 at PCO_2 of 60 mm Hg
   B. CO at a PCO of 0.5 mm Hg
   C. O_2 at a PO_2 of 130 mm Hg
   D. O_2 at a PO_2 of 150 mm Hg

2. Which of the following would be expected to decrease the rate of O_2 diffusion across the alveolar-capillary membrane of the lung? (More than one answer is correct.)

   A. A decrease in PO_2 difference between the alveolus and pulmonary capillary blood
   B. An increase in the surface area of the alveolar-capillary membrane
   C. An increase in the thickness of the alveolar-capillary membrane
   D. A decrease in O_2 solubility in the alveolar membrane

3. A subject inspires a mixture of gases containing CO and holds his breath for 10 seconds. It is calculated that during the 10 seconds when the subject held his breath, the alveolar PCO is 0.5 mm Hg, and the CO uptake is 25 ml/min. What is the diffusing capacity for CO(DL)?

   (DL is uptake of CO in ml/min/mm Hg.)

Alveolar-Blood Gas Exchange: Answers

1. **Ans** C. The calculation involves the alveolar PO_2 equation and the appropriate values will be:

$$P_AO_2 = (P_{atm} - 47) F_{O_2} - \frac{P_ACO_2}{R}$$

$$P_AO_2 = (747 - 47) 0.30 - \frac{40}{1.0} = 170 \text{ mm Hg}$$

2. **Ans** D. If CO_2 production doubled, the amount of CO_2 entering the alveoli from pulmonary capillary blood would also double. If alveolar ventilation doubled, alveolar PCO_2 would stay at 40 mm Hg. If alveolar ventilation did not change, alveolar PCO_2 would go from 40 to 80 mm Hg. Since P_ACO_2 affects P_AO_2, the P_AO_2 will also change. An increase in P_ACO_2 will cause approximately the same decrease in P_AO_2. Therefore, if P_ACO_2 increases by 40 mm Hg, P_AO_2 will decrease by 40 mm Hg.

3. Ans A. An inspired PO_2 of 150 mm Hg and an alveolar PCO_2 of 40 mm Hg is normal. If this individual's alveolar ventilation doubles (hyperventilation), alveolar PCO_2 would be cut in half to 20 mm Hg. If the alveolar PCO_2 decreases by 20 mm Hg, alveolar PO_2 would increase by 20 mm Hg.

Alveolar-Blood Gas Transfer: Answers

1. **Ans** B. The factors that affect the rate of gas diffusion are all included in the following equation:

$$\dot{V}gas = \frac{A}{T} \times D \times (P_1 - P_2)$$

Since we are dealing with the same lung, A (surface area) and T (thickness) will be constant for each gas. Therefore the rate at which each gas diffuses will depend upon its solubility and the partial pressure difference across the alveolar membrane (Pj - P2). CO2 is a very soluble gas and diffuses quickly. The remainder are less soluble, and relative diffusion rates will be determined by the partial pressure gradients. The PCO of capillary blood is about zero and if the P^CO is 0.5 mm Hg, the gradient will be only 0.5 mm Hg, **a very small gradient.** Therefore, CO will be diffusing very slowly across the membrane. On the other hand, the gradients for oxygen will be much greater, thus oxygen will be diffusing much faster than CO.

2. **Ans** A, C, D The factors that affect the rate of oxygen diffusion are in the following equation:

$$\dot{V}gas = \frac{A}{T} \times D \times (P_1 - P_2)$$

A decrease in the PO_2 difference across the membranes (Pj - P_2) will slow oxygen diffusion. An increase in the surface area will increase the rate of diffusion for all gases. Diffusion is inversely related to membrane thickness; thus an increase in membrane thickness will slow diffusion. A decrease in solubility, the main factor determining D, will also slow diffusion.

3. **Ans 50 ml/min/mm Hg.** The diffusing capacity is the uptake of CO in specific units: ml/min/mm Hg. Given that the uptake is 25 ml/min, we need simply divide by the partial pressure of CO in the alveoli (0.5 mm Hg) to obtain the appropriate units. Therefore,

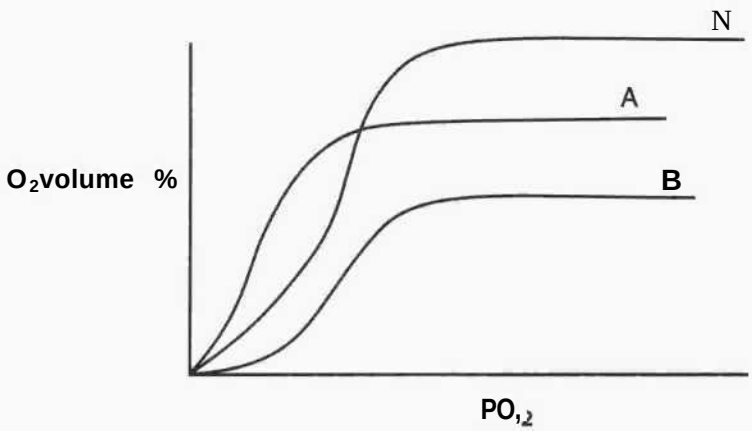
$$\frac{25 \text{ ml/min}}{0.5 \text{ mm Hg}} = 50 \text{ ml/min/mm Hg}$$

The numbers given at the front end of the question are not relevant to the calculation.

Oxygen, Carbon Dioxide Transport: Review Questions

Directions for Questions 1-9: Select the ONE best answer.

Curves N and B have the same P_{50}
Curve A has a lower P_{50}



1. In the above figure if curve N represents the oxygen-Hb dissociation curve of a normal individual, then curve A represents:
   A. polycythemia and B represents anemia.
   B. anemia and B represents polycythemia.
   C. anemia and B represents carbon monoxide poisoning.
   D. carbon monoxide poisoning and B represents anemia.
   E. carbon monoxide poisoning and B represents polycythemia.

2. Which of the following best represents the systemic arterial blood of an individual with anemia?
   A. low PO_2, low hemoglobin, normal O_2 content.
   B. low PO_2, low hemoglobin, low O_2 content.
   C. normal PO_2, low hemoglobin, low O_2 content.
   D. normal PO_2, normal hemoglobin, low O_2 content.
   E. low PO_2, normal hemoglobin, low O_2 content.

3. Which of the following best characterizes the systemic arterial blood of an individual suffering from carbon monoxide poisoning?
   A. low hemoglobin, low O_2 content, low PO_2
   B. low hemoglobin, normal O_2 content, low PO_2
   C. low hemoglobin, low O_2 content, normal PO_2
   D. normal hemoglobin, low O_2 content, low PO_2
   E. normal hemoglobin, low O_2 content, normal PO_2

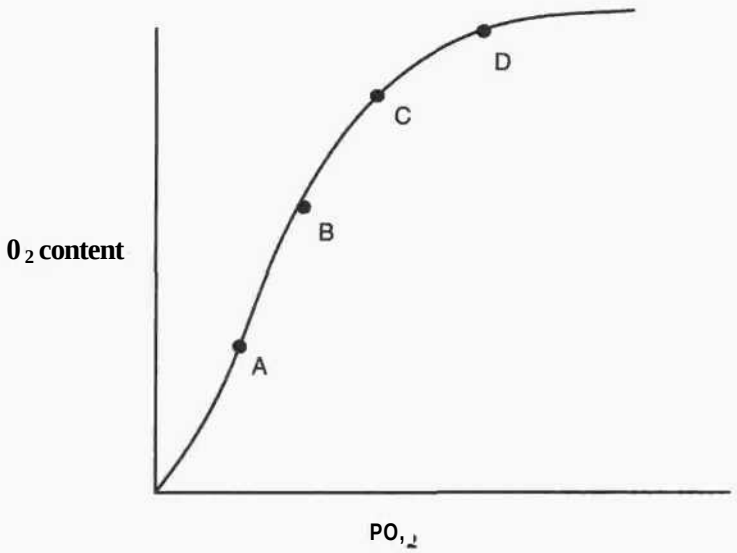
4. A decrease in blood pH will displace the hemoglobin dissociation curve to the:
   A. right and reduce O_2 carrying capacity.
   B. right with no change in O_2 carrying capacity.
   C. left and reduce O_2 carrying capacity.
   D. left with no change in O_2 carrying capacity.

5. Which of the following will decrease the O_2 carrying capacity of blood?
   A. increased PCO_2.
   B. increased temperature.
   C. decrease in pH.
   D. decreased hemoglobin.

6. Normally, as the alveolar PO_2 is increased from 110 to 950 mm Hg, the amount of oxygen:
   A. dissolved in plasma increases, amount associated with hemoglobin remains almost constant.
   B. dissolved in plasma increases, amount associated with hemoglobin decreases.
   C. dissolved in plasma remains constant, amount associated with hemoglobin increases.
   D. dissolved in plasma remains constant, amount associated with hemoglobin remains constant.

7. Most of the carbon dioxide carried by the blood is:
   A. dissolved as CO_2.
   B. plasma bicarbonate.
   C. red blood cell bicarbonate.
   D. carbamino compounds.
   E. combined with plasma proteins.

Questions 8-9. Use the following O_2 dissociation curve.



8. Which letter on the above graph most closely represents systemic arterial blood?

9. Which letter on the above graph most closely represents mixed venous blood?

Control of Breathing: Review Questions

Directions: Select the ONE best answer.

1. The peripheral chemoreceptors for oxygen (in carotid and aortic bodies) increase their rate of discharge primarily in response to:
   A. a decrease in blood oxygen content.
   B. a decrease in the partial pressure of blood oxygen.
   C. a decrease in blood H^+ concentration.
   D. a decrease in dissolved oxygen in cerebral spinal fluid.
   E. an increase in percent saturation of hemoglobin with oxygen.

2. In a normal individual respiration (alveolar ventilation) is regulated mainly via:
   A. peripheral chemoreceptors responding to changes in PO_2
   B. peripheral chemoreceptors responding to changes in PCO_2
   C. central chemoreceptors responding to changes in PO_2
   D. central chemoreceptors responding to changes in PCO_2
   E. central chemoreceptors responding to changes in both PCO_2 and PO_2

3. An increase in the activity of the afferent nerves associated with the Hering-Breuer reflex would indicate:
   A. expiration is occurring.
   B. inspiration is occurring.
   C. a decreasing blood volume with the pulmonary vasculature.
   D. pulmonary congestion.

4. The inherent rhythm for respiration appears to be located within the:
   A. apneustic center.
   B. upper pons.
   C. lower pons.
   D. medulla.

Questions 5-6. Given the composition of the following gas mixtures (balance nitrogen):

	$\%O_2$	$\%CO_2$	%CO
A	**21**	**-**	**0.1**
B	**95**	**5**	**-**
C	**20**	**2.5**	**-**
D	**20**	**2.5**	**0.1**

5. Switching from breathing room air to which gas mixture for 2-3 minutes would produce the greatest change in alveolar ventilation in a normal resting individual?

6. Switching from breathing room air to which gas mixture for 2-3 minutes would produce the least change in alveolar ventilation in a normal resting individual?

Unusual Environments: Review Questions

Directions: Select the ONE best answer.

1. After living at an altitude of 3,500 meters for two months, a subject will have:
   A. Higher than normal arterial PCO_2.
   B. Elevated hematocrit.
   C. Abnormally low pressure in the pulmonary artery.
   D. Elevated erythropoietin.

2. A diver working at five times normal atmospheric pressure breathes a mixture of 50% helium and 50% oxygen for four hours. Even before he begins to surface, he may encounter which of the following problem(s)?
   A. Bends.
   B. N_2 narcosis.
   C. Pneumothorax.
   D. Oxygen toxicity.

Oxygen, Carbon Dioxide Transport: Answers

1. Ans D. Curve N and curve B have the same P_{50}, therefore the Hb has the same affinity for oxygen. However, carrying capacity is reduced in B. This curve fits anemia where there is normal Hb but the concentration is below normal. In curve A the carrying capacity is reduced and the P_{50} is also reduced. A reduced P_{50} means the Hb has a greater affinity for oxygen and a lower PO_2 produces 50% saturation. The combination of a reduced carrying capacity but increased affinity is consistent with carbon monoxide poisoning. Carbon monoxide molecules attached to Hb make these sites unavailable to oxygen and because of cooperative binding, the remaining sites with oxygen have greater affinity. Polycythemia would be characterized as having a normal P_{50} but a greater than normal carrying capacity.

2. Ans C. The characteristic feature of anemia is a low Hb concentration but the affinity for oxygen is normal. Because alveolar PO_2 is still 100 mm Hg and equilibration still occurs with pulmonary capillary blood, systemic arterial Hb is fully saturated and the plasma has a PO_2 of 100 mm Hg. Remember that blood PO_2 is determined by dissolved oxygen. The systemic arterial oxygen content is decreased because of the low concentration of Hb, dissolved oxygen is normal.

3. Ans E. In carbon monoxide poisoning, Hb cannot be fully saturated with oxygen because some sites are occupied by carbon monoxide. Therefore, even though Hb concentration is normal (acute poisoning), the oxygen content is depressed because of the reduced oxygen saturation. As long as room air is inspired (21% O_2) alveolar PO_2 and systemic arterial PO_2 are normal (depends on dissolved oxygen). An important point is that in an individual with carbon monoxide poisoning and breathing room air, systemic arterial PO_2 should be normal.

4. Ans B. A decrease in pH, which is increased acidity, will shift the O_2-Hb dissociation curve to the right due to the loss of Hb affinity for oxygen. However, this will only affect points on the steep part of the curve, making it easier to release oxygen to the tissues. Points on the plateau where Hb is fully saturated, like arterial blood, will be unaffected. This plateau is referred to as carrying capacity. Thus, systemic arterial oxygen content will be normal.

5. Ans D. Increased PCO_2, temperature, and a decreased pH will shift the O_2-Hb dissociation curve to the right due to a loss of Hb affinity for oxygen. However, only points on the steep part of the curve will be affected. The plateau (carrying capacity) will not change, and systemic arterial oxygen content will not change. A reduced Hb

concentration (e.g., anemia) will cause, even though the Hb may be saturated, the maximum oxygen content (carrying capacity) to be reduced.

6. **Ans** A. As the PO_2 rises above 100 mm Hg, there is no significant increase in the oxygen content of the blood. This is because Hb is almost fully saturated when the PO_2 reaches 100 mm Hg. If the PO_2 does rise above 100 mm Hg, there is only a slight increase in content due to an increase in dissolved oxygen.

7. **Ans** B. CO_2 is a very soluble gas, and a significant amount is carried dissolved in the plasma. But this amounts to only about 5% of the total. Also, a similar amount is carried attached to proteins as carbamino compounds. The main protein is Hb. Most of the CO_2 is carried as plasma bicarbonate. It is formed from CO_2 in the red blood cells, which contain carbonic anhydrase, but the formed bicarbonate enters the plasma in exchange for chloride.

8. **Ans** D. Systemic arterial Hb is 97% saturated with oxygen. This would represent a point just barely below the actual plateau. Point D represents such a point. A point further along the plateau would represent someone breathing an enriched oxygen mixture.

9. **Ans** C. Systemic venous mixed blood Hb under resting conditions is about 75% saturated with oxygen. This would represent a point about 3/4 up the steep part of the curve. Point B would not be correct since it is only half-way up the curve. This point would be an appropriate answer for P^Q. Point C is about 3/4 up the curve and is the best answer.

Control of Breathing: Answers

1. Ans B. The peripheral chemoreceptors for oxygen only monitor PO_2. They are not active under normal conditions and fire only when systemic arterial PO_2 decreases dramatically. They do not monitor oxygen content or the amount of oxygen attached to Hb.

2. **Ans** D. The main drive for ventilation under normal conditions is CO_2 on the central chemoreceptors. There are no central PO_2 receptors, and those that are present in the peripheral chemoreceptors are not active under normal conditions. A small component of the normal drive for ventilation is CO_2 stimulation of the peripheral chemoreceptors, but it is subservient to the central chemoreceptors.

3. **Ans** B. These receptors respond to a stretch of the airways. This occurs during inspiration when intrapleural pressures are becoming more

negative. Their function is to limit tidal volumes and prevent overdistention of the lungs. Even though they are described in most textbooks, they probably have little if any function in humans.

4. **Ans** D. As mentioned in the notes, the inherent rhythm for respiration resides in the medulla. The pons contributes by providing the regularity of the rhythm.

5. **Ans** B.

6. **Ans** A. Ventilation will be stimulated only if CO_2/H^+ increases or there is a dramatic decrease in systemic arterial PO_2. The presence of CO will not affect ventilation because no receptor can pick up the decrease in oxygen content. With CO poisoning, the arterial PO_2 is generally normal. Mixture A will be no different from breathing room air, thus switching to this gas mixture will produce no change in ventilation. There is no significant decrease of oxygen in any of the gas mixtures, therefore there is no low O_2 stimulus for breathing. There is however, some CO_2 added to three of the mixtures. This will raise arterial CO_2 and provide a greater stimulus mainly to the central chemoreceptors. The greater the CO_2 added, up to a point beyond which it acts to depress breathing, the greater the stimulus. Mixture B has the greatest CO_2 thus the greatest stimulus.

Unusual Environments: Answers

1. **Ans** B. After living at high altitude for 2 months, acclimatization changes will be evident. One such change will be the development of polycythemia expressed as an increase in Hb concentration and hematocrit. Ventilation will remain elevated because of the stimulation of the peripheral chemoreceptors by the low PO_2. The hyperventilation will maintain a low arterial PCO_2. The low alveolar PO_2 may produce hypoxic vasoconstriction and raise pulmonary arterial pressures.

2. **Ans** D. The bends will develop after breathing high-pressure nitrogen for a prolonged period, then decompressing suddenly. By replacing the nitrogen with helium, a less soluble gas than nitrogen, there is less gas dissolved in body fluids and therefore on decompression less tendency to form emboli. The lack of nitrogen also means no nitrogen narcosis. The main problem here is the high PO_2 values; 50% oxygen inspired at a high pressure will result in the development of oxygen toxicity.

Ventilation-Perfusion: Review Questions

Direction: Select the ONE best answer.

1. Which of the following best shows the apex vs. the base of the lung in a standing subject (> = greater than; < = less than)?

	Ventilation($\dot{V}$) {tnl/min **per unit volume)**	**Perfusion($\dot{Q}$)** (ml/min **per unit volume)**	$\dot{V}/\dot{Q}$
A.	apex > base	apex > base	apex > base
B.	apex > base	apex > base	apex < base
C.	apex > base	apex < base	apex < base
D.	apex < base	apex < base	apex > base
E.	apex < base	apex < base	apex < base

2. If alveolus X has a ventilation-perfusion ratio of 0.85 and alveolus Y has a ventilation-perfusion ratio of 0.65, which alveolus has:

A. The higher PO_2
B. The higher PCO_2

Capillary blood leaving which alveolus will have:

A. The greatest O_2 content.
B. The greatest CO_2 content.
C. The highest pH.

3. Which of the following statements best characterizes the pattern of ventilation in the lungs during quiet breathing?

A. Surfactant keeps each region of the lung equally distended and ventilated.
B. Gravity in the erect individual keeps the base of the lung more poorly expanded and it receives less ventilation than the apex.
C. Gravity in the erect individual keeps the base of the lung more poorly expanded but it receives more ventilation than the apex.
D. Gravity in the erect individual keeps the base of the lung more expanded and ventilated than the apex.
E. Gravity in the erect individual keeps the base of the lung more expanded and less ventilated than the apex.

4. When the ventilation-perfusion ratio of a lung unit decreases, the alveoli in that unit develop a:

A. Higher PO_2
B. Lower PN_2
C. Higher PO_2 and lower PCO_2
D. Higher PCO_2
E. Higher PN_2 and higher PO_2

Ventilation-Perfusion: Answers

1. Ans D. There is greater ventilation and blood flow at the base of the lung (ml/min per unit volume). This flow decreases to a minimum at the apex. The important variable, however, is the matching of blood flow and ventilation expressed as $\dot{V}/\dot{Q}$ This ratio is greater at the apex and decreases toward the base.

2. A. Ans X
   B. Ans Y
   The $\dot{V}/\dot{Q}$ for both X and Y is < 1.0. Thus, there is a mismatch with both, and since the ratio is below 1.0, we can interrupt both as being underventilated. However, in comparing the two, we can also conclude that because X has a higher ratio, it is better ventilated than Y. If X is better ventilated, it should have the higher PO_2 and the lower PCO_2. It follows then that Y should have the lower PO_2 and the higher PCO_2.
   Capillary blood:
   A. greatest O_2 content—X because of a higher PO_2
   B. greatest CO_2 content—Y because of a higher PCO_2
   C. the highest pH—X because of the lower CO_2

3. Ans C. Surfactant does not act to keep alveoli equally distended. The degree of distension depends upon intrapleural pressure. The more negative intrapleural pressure, the more the alveolus will be distended. In the erect individual intrapleural pressure is more negative at the apex compared to the base. Thus, alveoli are more distended at the apex than at the base. During inspiration though, there is a greater increase in alveolar size at the base, therefore there is more ventilation at the base of the lung.

4. Ans D. When the $\dot{V}/\dot{Q}$ ratio decreases, the lung unit is moving toward underventilation. Thus PO_2 would decrease and PCO_2 would increase. There will be no significant change in PN_2. The slight changes that do occur are the result of R being not exactly 1.0.

SECTION VII

Renal Physiology

Renal Processes

1

INTRODUCTION TO THE RENAL SYSTEM

Functional Organization of the Kidney

Figure VII-1-1 illustrates the cortical versus the medullary organization of the kidney. Nephrons with glomeruli in the outer cortex have short loops of Henle (cortical nephrons). Those with glomeruli in the inner cortex have long loops of Henle, which penetrate the medullary region (juxtamedullary nephrons).

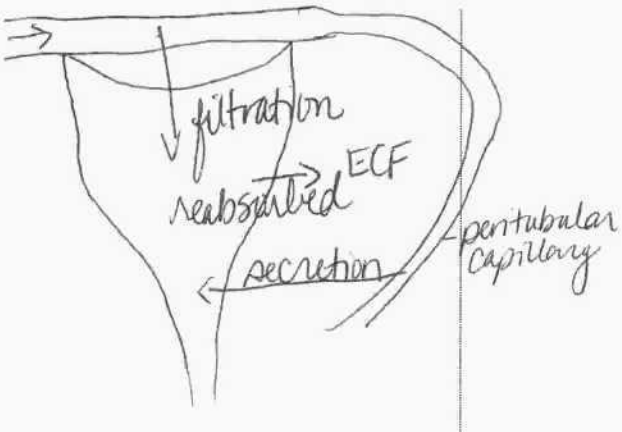
7/8 of all nephrons are cortical nephrons

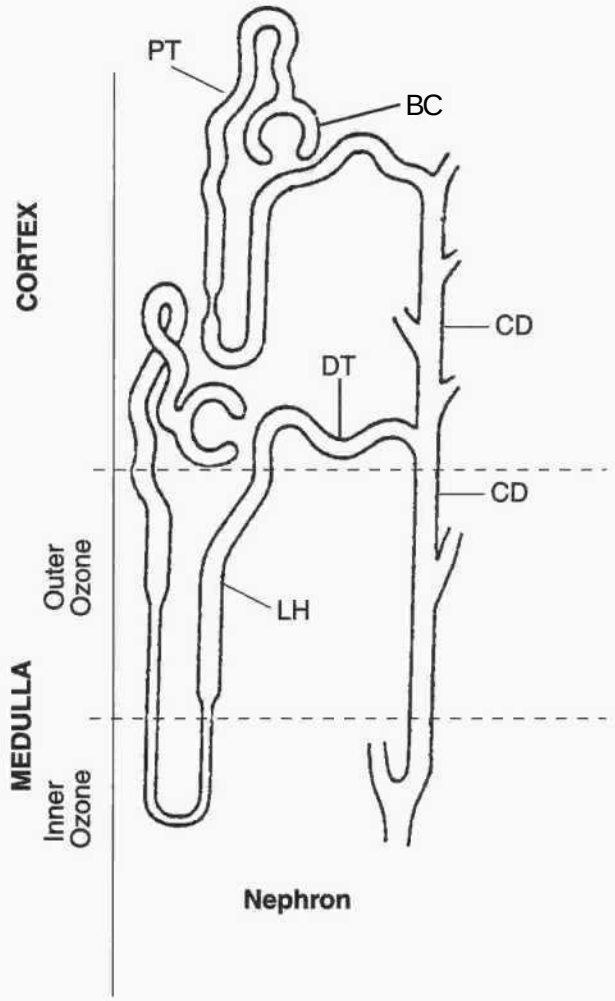
1/8 of all nephrons are juxtamedullary nephrons

Nephron structures in the medulla consist of the long loops of Henle and the terminal regions of the collecting ducts. All other structures, including the first section of the collecting ducts, are in the cortex.

What the USMLE Requires You to Know

- The series system vasculature of a single nephron
- Factors affecting the glomerular filtration rate (GFR)
- Factors affecting filtration fraction (FF)
- Directional changes in GFR and FF in altered states
- Dynamics of an active reabsorbing system exhibiting T_M dynamics, e.g., glucose
- Sodium reabsorption in the proximal tubule as a gradient-time system
- Dynamics of a secretory T_M system, e.g., PAH
- Nephron net transport





BC = Bowman's capsule
PT = proximal tubule
LH = loop of Henle
DT = distal tubule
CD = collecting duct

Figure VIM-1

NEPHRON HEMODYNAMICS

Series Hemodynamics

The individual nephrons that make up both kidneys are connected in parallel. However, the flow through a single nephron represents two arterioles and two capillary beds connected in series.

The following represents some of the basic consequences of a series hemodynamic system. This information and additional details were presented in the peripheral circulation discussion (Section III, Chapter 1).

Flow must be equal at all points in a series system. If flow changes, it changes equally at all points in a series system.

Figure VII-1-2 represents a model with three resistors connected in series.

The total resistance is the sum of the individual resistances.

Therefore, the total is always greater than any of the individual resistances.

Adding a resistor in series increases the resistance of the system.

Connecting resistors in series results in a high-resistance system.

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

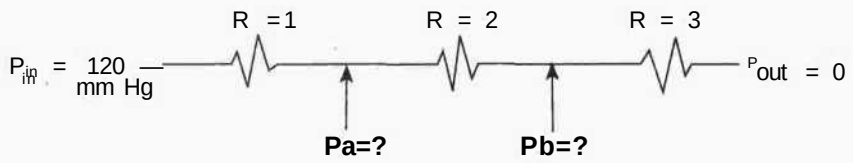


Figure VIM-2

If P^ and P_{out} are kept constant, this is what happens to the following variables if the central resistance increases:

Flow through R,, R_2, and R_3 will decrease equally.

P_b pressure downstream decreases.

P_a pressure upstream increases.

HemodynamicsofaSingleNephron

Figure VII-1-3 represents the hemodynamics of a single nephron. Connected in series are the high-pressure filtering capillaries of the glomerulus and the low-pressure reabsorbing peritubular capillaries.

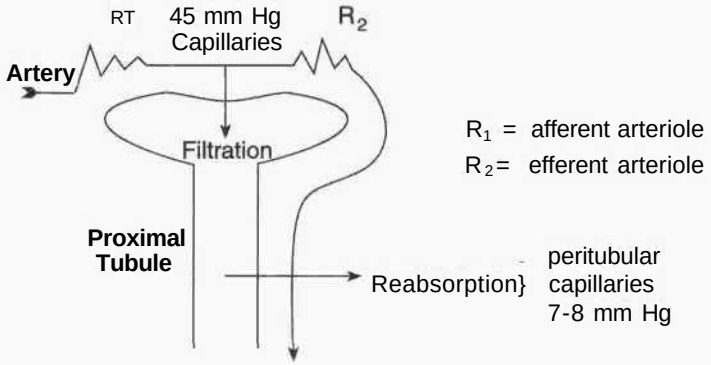


Figure VIM-3

Independent Response of the Afferent and Efferent Arterioles

Table VII-1-1 illustrates the expected consequences of independent isolated constrictions or dilations of the afferent and efferent arterioles.

Table **VII-1-1. Consequences of Independent Isolated Constrictions or Dilations of the Afferent and Efferent Arterioles**

	Glomerular cap pressure	Peritubular cap pressure	Nephron plasma flow
1. constrict efferent	if	⇓	**ft**
2. dilate efferent	⇓	tr	ir
3. constrict afferent	⇓	⇓	**ft**
4. dilate afferent	⇑	**11**	it

GLOMERULAR FILTRATION

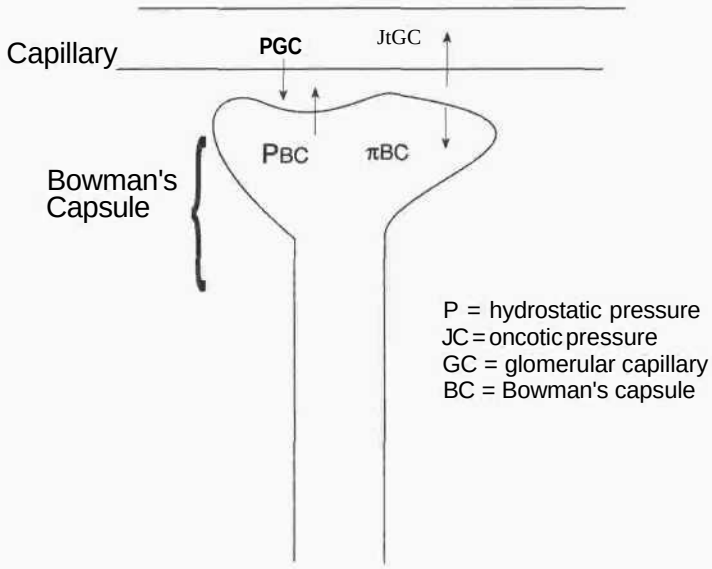
Determinants of Filtration

Glomerular filtration rate (GFR) is the rate at which plasma is filtered into Bowman's capsule. The units of filtration are a volume filtered per unit time, e.g., ml/min or liters/day.

The same factors that affected filtration previously discussed for peripheral circulation (Section III, Chapter 1) apply here. The only difference is that fluid is filtering into Bowman's capsule instead of the interstitium.

The Four Factors That Affect Filtration

Figure VII-1-4 illustrates the role of the four factors that affect filtration.



Give drug that is a venous constrictor what will happen to GFR? f

Figure VII-1-4. Determinants of Filtration

The Hydrostatic Pressure of the Glomerular Capillaries

PGC: The hydrostatic pressure of the glomerular capillaries promotes filtration. Under normal conditions, this is the main factor that determines GFR.

The Oncotic Pressure of the Plasma

TTGC: The oncotic pressure of the plasma varies with the concentration of plasma proteins. Because fluid is filtered but not protein, oncotic pressure, which opposes filtration, will increase from the beginning to the end of the glomerular capillaries (see Fig VII-1-5). The increased concentration of protein will be carried into the peritubular capillaries and promote reabsorption.

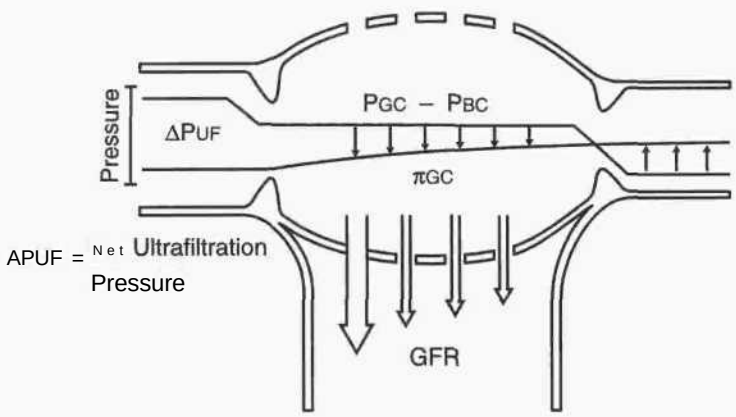


Figure VIM-5

The Hydrostatic Pressure in Bowman's Capsule

PBC: The hydrostatic pressure in Bowman's capsule opposes filtration. Normally, it is low and fairly constant and does not affect the rate of filtration. However, it will increase and reduce filtration whenever there is an obstruction downstream, such as a blocked ureter or urethra (postrenal failure).

Protein or Oncotic Pressure in the Capsule

irBC: This represents the protein or oncotic pressure in the capsule. Very little if any protein is present, and for all practical purposes this factor can be considered zero.

Normal Values

PBC = 10 mm Hg

PGC = 45 mm Hg

irBC = 0 mm Hg

TTGC = 27mmHg

Net filtration pressure = PGC - irGC - PBC = 45 - 27 - 10 = 8 mm Hg

Materials Filtered

Freely Filtered

The following are easily or freely filtered:

Major electrolytes
- Sodium
- Chloride
- Potassium
- Bicarbonate

Metabolic waste products
- Urea
- Creatinine

Metabolites
- Glucose
- Amino acids
- Organic acids (ketone bodies)

Nonnatural substance
- Inulin
- PAH (p-aminohippuric acid)

Lower weight proteins and peptides
- Insulin
- Myoglobin

NotFreelyFiltered

The following are not freely filtered:

Albumin and other plasma proteins

Lipid-soluble substances transported in the plasma attached to proteins
- Lipid-soluble bilirubin
- T_4 (thyroxine)
- Other lipid-soluble hormones

Negative Charge on the Filtering Membrane

There is a negative charge on the filtering membrane that inhibits the filtering of protein anions. If this negative charge is not present, significant protein filtration takes place. This simply points out that the glomerular capillaries are very permeable.

Fluid Entering Bowman's Capsule

The fluid entering Bowman's capsule is an ultrafiltrate of plasma; that is, the filtrate has the same concentration of dissolved substances as plasma, except proteins.

The osmolarity of the filtrate is 300 mOsm/L. The criteria for effective osmolarity are the same as those previously stated for extracellular fluid (Section I, Chapter 2).

If a substance is freely filtered by the kidney, the ratio of the filtrate concentration/plasma concentration $\frac{TF}{P} = 1.0$. This rqgans the concentrations in Bowman's capsule and the plasma willjje the same.

If you inject 300mOsm of drug X in and 300mOsm in tubular filtrate then 300/300 = 1 so the drug is freely filtered.

Factors Affecting GFR and Filtration Fraction (FF)

The following formula for the filtration fraction and the normal values given should be memorized.

FF = fraction of the material that enters the kidney that is filtered normally 0.20 or 20% for a freely filtered substance

$$FF = \frac{GFR}{RPF}$$

GFR = 120 ml/min
RPF (renal plasma flow) = 600 ml/min

$$= \frac{120 \text{ ml/min}}{600 \text{ ml/min}} = 0.20 \text{ or } 20\%$$

Determinants of GFR

Except for an unusual situation when plasma protein concentration changes dramatically or renal obstruction develops, the main factor determining GFR is glomerular capillary pressure.

An increase in capillary pressure increases GFR, and a decrease in capillary pressure decreases GFR.

Flow does have a small effect on GFR; an increase in flow will independently increase GFR.

Factors Affecting FF

In many circumstances, the main factor affecting FF is renal plasma flow. The longer the fluid remains in the glomerular capillaries, the greater the percentage of the fluid that tends to be filtered.

Therefore, as flow decreases, FF will always have a tendency to increase.

Based on the preceding discussion, the following should be expected for afferent versus efferent constriction:

	Afferent constriction	Efferent constriction
Glomerular filtration pressure	⇓	⇑
GFR		
Renal plasma flow	⇓	⇓
FF		⇑

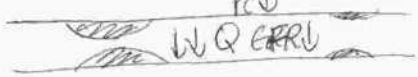
what happens to filtration when afferent constriction occurs and also GFR?
GFR ↓
filtration ⓪ (uncharged) bc proportional decrease in GFR/Q both

Effects of Sympathetic Nervous System

Stimulation of the sympathetic neurons to the kidney generally causes vasoconstriction:

constricts afferent more than efferent

⇓ GFR



tt Factors promoting reabsorption in the peritubular capillaries, i.e., lower capillary hydrostatic pressure and an increase in plasma oncotic pressure (proteins are more concentrated)

Effects of Angiotensin II (AII)

Because angiotensin constricts the efferent more thar *the* afferent arterioles, it tends to preserve glomerular capillary pressure as renal plasma flow decreases. Thus, GFR may show only a minimal decrease under these conditions.

Filtered Load

Filtered load is the rate at which a substance filters into Bowman's capsule. Units are an amount per unit time, e.g., mg/min.

Filtered load = GFR X P_x

GFR = glomerular filtration rate

units = volume/time, e.g., ml/min, L/day

P_s = concentration of the substance in the plasma

units = amount/volume, e.g., mg/ml

Question

Given the following information:

GFR= 120 ml/min

plasma glucose = 100 mg/100 ml

inulin = 2 mg/ml

plasma bicarbonate = 24 mEq/L

Calculate the filtration rate (load) of the preceding substances.

Answer

Glucose: 120 mg/min

Inulin: 240 mg/min

Bicarbonate: 2.88 mEq/min

TUBULAR REABSORPTION

Active Mechanisms

There are two types of active reabsorption based on system dynamics: T_M and gradient-time.

Transport Maximum (T_M) Systems

For example, proximal tubular reabsorption of glucose.

General Characteristics of T_M Systems

Carriers are easily saturated.

Carriers have a high affinity for the substrate.

Low back leak.

Back leak refers to the back diffusion of the substance into the tubule after it is reabsorbed into the interstitium. Minimal back leak of glucose occurs because the proximal tubule is not permeable to glucose.

Summary Statement

The entire filtered load is reabsorbed until the carriers are saturated; then the excess is excreted.

Dynamics of Glucose Filtration

Figure VII-1-6 graphically represents the dynamics of glucose filtration, reabsorption, and excretion.

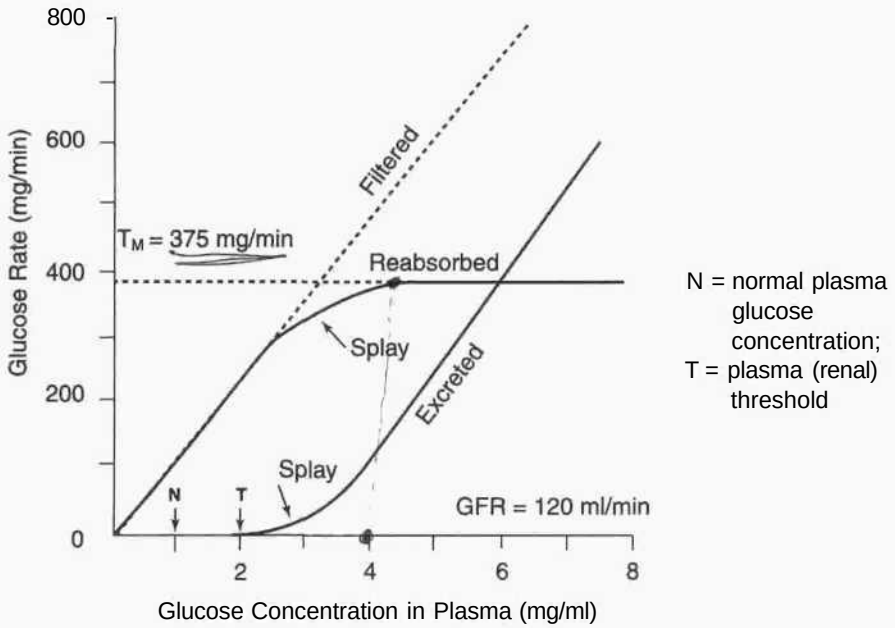


Figure VII-1-6

At low plasma levels, the filtration rate and the reabsorption rate of glucose are equal, and glucose does not appear in the urine.

T_M is the maximal reabsorption rate of glucose. It is the rate at which all the carriers are saturated. T_M is an index of the number of functioning carriers. This also means that T_M can be utilized as an estimate of the number of functioning nephrons.

The rounding of the reabsorption curve into the plateau is called *splay* because some nephrons reach T_M before others. Thus, T_M for the entire kidney is not reached until after the region of splay.

Plasma (or renal) threshold is the plasma glucose concentration at which glucose first appears in the urine. This occurs at the beginning of splay.

Substances Reabsorbed

Almost all natural organic and some inorganic substances that are reabsorbed by the nephron are reabsorbed by a T_M system. These substances include glucose, amino acids, small peptides and proteins, ketone bodies, calcium, and phosphate. An exception with respect to natural organic substances is urea. Urea is freely filtered and partially reabsorbed, mainly by passive mechanisms.

Gradient-Time System

For example, the proximal tubular reabsorption of sodium

General Characteristics

Carriers appear to be never saturated.

Carriers have a low affinity for the substrate.

High back leak.

High back leak means that some of the sodium that is actively reabsorbed back diffuses into the proximal tubule. The proximal tubule has leaky tight junctions to sodium and also to a few other substances, such as potassium, chloride, and water.

Summary Statement

Approximately a constant percentage of the filtered sodium is reabsorbed in the proximal tubule. Under normal conditions, it is close to 66%, which means about two-thirds of the filtered sodium is reabsorbed in the proximal tubule.

Also, the active reabsorption of sodium by the proximal tubule is the main metabolic process going on in the kidney. Thus, oxygen consumption of the kidney is directly proportional to sodium reabsorption and GFR.

TUBULAR SECRETION

Transport Maximum System

p-Aminohippuric Acid (PAH) Secretion

PAH secretion from the peritubular capillaries into the proximal tubule is an example of a transport maximum system. As a T_M system, it has the general characteristics discussed for the reabsorption of glucose except for the direction of transport.

At Low Plasma Concentrations

Figure VII-1-7 illustrates the renal handling of PAH at low plasma concentrations.

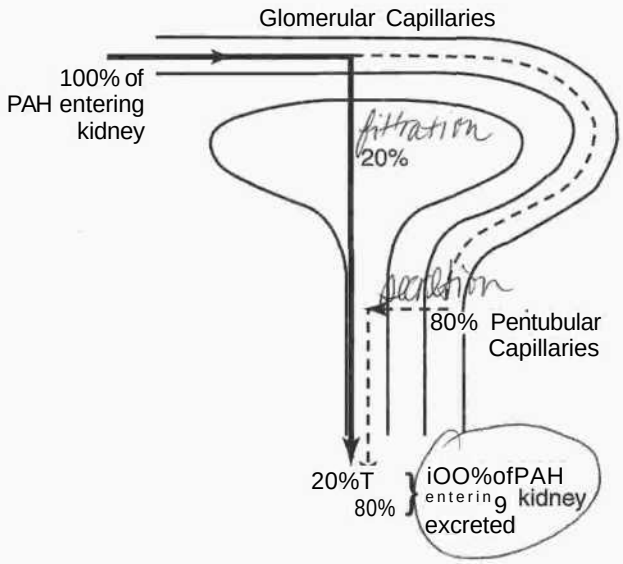


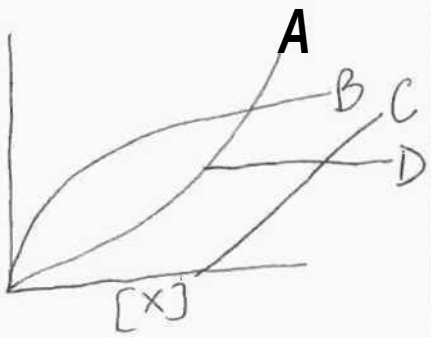
Figure VIM-7

At low plasma levels, 20% of the PAH entering the kidney is filtered, and 80% is actively secreted. Because PAH does not exhibit reabsorption, under these conditions all the PAH entering the kidney is excreted, and no PAH appears in the renal venous plasma. It also means that secretion is four times the rate of filtration.

As the plasma PAH rises, 20% continues to be filtered, but because the plasma concentration is increasing, the filtered load is increasing (amount filtered per unit time). The remaining 80% continues to be secreted until the carriers in some nephrons become saturated (beginning of splay). At this point, not all the 80% is secreted, and PAH will appear in the renal venous plasma.

secreting PAH = 4x filtered amt. to be secreted

Inject 100mg. complete 100mg excreted then inject another 100mg. what will happen? only 20mg will be excreted from filtration the secretion carriers are saturated so the 80mg to be secreted are left



A= filtration
B= excretion of PAH
C= excretion of glucose
D* secretion & reabsorption

Figure VII-1-8 graphically depicts the renal handling of PAH at increasing plasma concentrations.

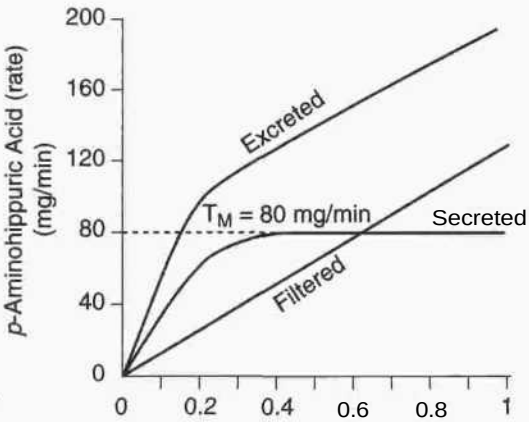


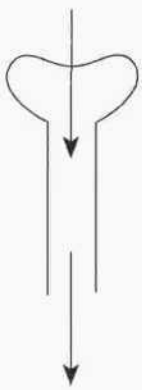
Figure VII-1-8

Filtration: linear relationship with plasma concentration and represents 20% of the PAH delivered to the kidney.
Secretion: initially 4 times filtration rate and represents 80% of the PAH delivered to the kidney.
Therefore, initially all of the PAH delivered to the kidney is removed—20% by filtration and 80% by secretion—and the concentration of PAH in the renal venous plasma should be zero. As the plasma level rises, secretion increases, reaching a maximum rate (T_M) when the carriers are saturated. PAH appears in the renal venous plasma at the beginning of the splay region in the secretion curve.

Excretion: the sum of the filtration rate and the secretion rate. Once TM is reached, increases in excretion parallel increases in filtration.

NET EFFECTS OF REABSORPTION AND SECRETION

Figure VII-1-9 illustrates that net transport is determined simply by comparing the filtration rate (filtered load) versus the excretion rate of a substance. Both variables are expressed as an amount of substance per unit time, and the units must be the same for meaningful comparisons, e.g., mg/min.



Filtered Load	=	GFR	x	P_x
amount/time		volume/time		amount/volume
mg/min		ml/min		mg/ml

Excretion	=	U_x	x	V
amount/time		amount/volume		volume/time
mg/min		mg/ml		ml/min

U_x = urine concentration of substance
V = urine flow rate

Figure VII-1-9

No Net Tubular Modification

Filtration rate = Excretion rate

The amount filtered and amount excreted per unit time are always the same, e.g., inulin, mannitol.

Net Reabsorption

Filtration > Excretion

Excretion is always less than filtered load, e.g., glucose, sodium, urea.

If the substance is completely reabsorbed, the rate of filtration and the rate of reabsorption are equal.

If the substance is partially reabsorbed, excretion is less than filtration.

Reabsorption = filtration - excretion

Net Secretion

Filtration < Excretion

5% secreted

Excretion is always greater than filtered load, e.g., PAH, creatinine.

Creatinine is freely filtered, and a very small amount is secreted.

Secretion = excretion - filtered load

The following formula is sometimes used to calculate net transport. The sign of the calculated number will indicate the three basic categories:

0 = no net transport

+ = net reabsorption

- = net secretion

$$\text{net transport rate} = \text{filtered load} - \text{excretion rate}$$

$$= (GFR \times P_x) - (U_x \times V)$$

Filtered load - Excreted load
(GFR × P_x) − $U_x V$ (U_{flow} × $U_{glucose}$)
(120 × 3) − (2 × 10)
360 − 20
= 340 mg/min

Question

Given the following information, calculate the reabsorption rate for glucose.

GFR = 120 ml/min

plasma glucose = 300 mg/100 ml

urine flow = 2 ml/min

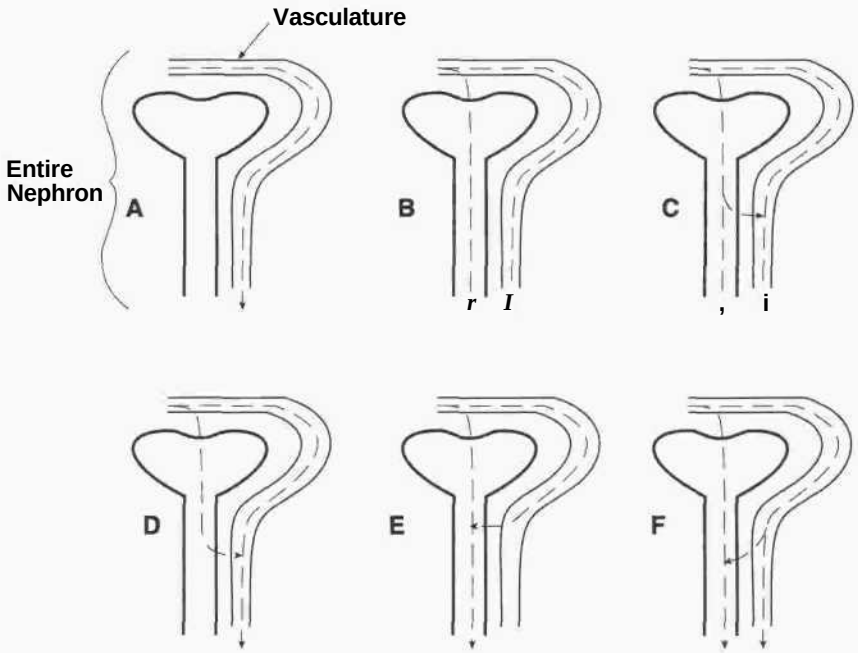
urine glucose = 10 mg/ml

Answer

340 mg/min

The illustrations in Figure VII-1-10 represent the net transport of specific types of substances for a normal individual on a typical Western diet (contains red meat). The dashed lines represent the route followed by the particular substance. Quantitative aspects are not shown. For example, in B, 20% of the substance entering the kidney is filtered and excreted, and the remaining 80% passes through the kidneys without processing.

Does the prox. tubule play a role in pH buffering?
no Bicarbonates all HCO_3^-



glucose = D	sodium = C	creatinine = F
inulin = B	potassium = C	urea = C
protein = A	PAH = E	bicarbonate = D

Figure VII-1-10

Chapter Summary

Individual nephrons are organized in parallel. But the vascular system within each nephron (the afferent arteriole, glomerular capillaries, efferent arteriole, and the peritubular capillaries) are connected in series.

The major factor determining GFR is glomerular capillary hydrostatic pressure. The only other important factor in a normal kidney system is the colloid osmotic pressure of the plasma proteins.

FF is mainly determined by renal plasma flow. A decrease in flow tends to increase FF.

The rate at which a substance is filtered (filtered load) is determined by its plasma concentration and GFR.

The active reabsorption of glucose in the proximal exhibits T^ dynamics. Everything filtered is reabsorbed until the carriers in some nephrons are saturated. The plasma level at this point is called plasma (or renal) threshold, and glucose will begin to appear in the urine. This is also at the beginning of the region of splay. All transporters in all nephrons become saturated only once the plateau is reached, which is after the region of splay. At this point, the glucose reabsorption rate is maximal (T_M). T^ is an index of the number of functioning nephrons.

The active secretion of PAH in the proximal tubule exhibits T_M dynamics. At plasma levels below carrier saturation, 20% of the PAH entering the kidney is filtered, and 80% is secreted. All the PAH is excreted, and no PAH appears in the renal venous plasma (excluding plasma flow through the capsule). PAH appears in the renal venous plasma once the carriers in a few nephrons become saturated (beginning of splay).

If a substance is freely filtered and exhibits:

no net transport, filtration rate = excretion rate

net reabsorption, filtration rate is > excretion rate

net secretion, filtration rate is < excretion rate

Clearance

2

THE CONCEPT OF CLEARANCE

Clearance refers to a theoretical volume of plasma from which a substance is removed over a period of time.

For example:

If the concentration of substance x is 4 molecules per liter and the excretion of x is 4 molecules per minute, the volume of plasma cleared of x is 1 L per minute.

If the excretion of x decreases to 2 molecules per minute, the volume cleared of x is now only 0.5 L per minute.

If the concentration of x decreases to 2 molecules per liter of plasma and the excretion is maintained at 2 molecules per minute, the cleared volume is back to 1 L per minute.

What the USMLE Requires You to Know

- Concept of clearance
- Relative clearances of specific types of substances
- Clearance of inulin and the plasma concentration of creatinine as indices of GFR
- Clearance of PAH as an index of renal plasma flow
- Free water clearance

Glucose, inulin, PAH, Cr, Urea
creatinine, Na

Clearance
a. G > I > PAH
b. G > PAH > I
c. PAH > Cr > Na > glucose

most cleared
↑ PAH (100%)
creatinine (25%)
inulin (20%)
urea
Na
glucose (0%)
least cleared

These numbers are summarized in Table VII-2-1 below.

Table VII-2-1. Example Calculations of Clearance Values

Plasma concentration molecules/L	Excretion rate molecules/minute	Volume cleared L/minute
4	4	1.0
4	2	0.5
2	2	1.0

Thus, the two factors that determine clearance are the plasma concentration of the substance and its excretion rate.

$$\text{Clearance of x} = \frac{\text{excretion rate of x}}{Px} = \frac{Ux \times V}{Px}$$

Ux = urine concentration of x

V = urine flow rate

Px = plasma concentration of **x**

The plasma concentration of the substance and its urine concentration must be in the same units, which will then cancel.

Urine flow (V) is a volume per unit time, and the units of V will become the units of clearance. Clearance is a volume of plasma cleared of a substance per unit time, such as ml/min or L/day.

Question

Using the following information, calculate the clearance of x, y, and z.

V = 2 ml/min

Ux = 2 mg/ml Px = 2 mg/ml

Uy = 0 mg/ml Py = 13.6 mg/ml

Uz = 0.5 mg/ml Pz = 1 mg/ml

$\frac{Ux \times V}{Px} = \frac{2 \times 2}{2} = 2$ ml/min.

$\frac{Uy \times V}{Py} = \frac{0 \times 2ml}{13.6} = 0$ ml/min.

$\frac{Uz \times V}{Pz} = \frac{.5 \times 2}{1} = 1$ ml/min

Answer

x = 2 ml/min

y = 0

z = 1 ml/min

CLEARANCE OF CHARACTERISTIC SUBSTANCES

Characteristic substances are glucose, sodium, urea, inulin, creatinine, and PAH.

Clearance Curves for Characteristic Substances

Figure VII-2-1 plots clearance versus increasing plasma concentration for four substances. A description of each curve follows.

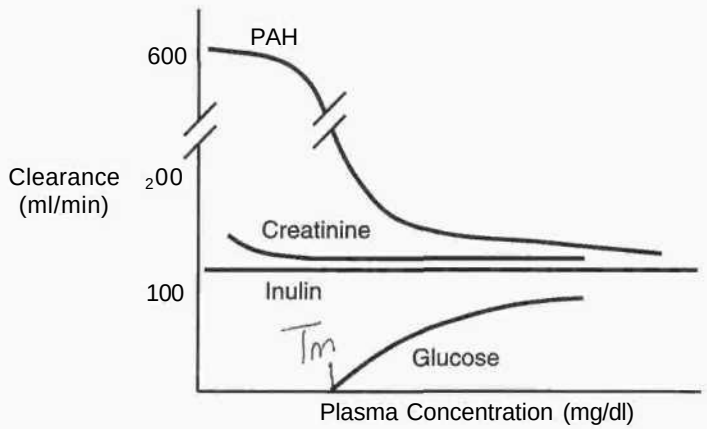


Figure VII-2-1

Glucose

At low plasma levels, the clearance of glucose is zero. As the plasma level rises, glucose will appear in the urine once some nephron's carriers are saturated. The plasma level at which glucose first appears in the urine is called the plasma (or renal) *threshold*, and at this point glucose will have a positive clearance. As the plasma level rises further, the clearance will increase and approach that of inulin. The clearance will never equal inulin because some glucose will always be reabsorbed. If the reabsorption of glucose was completely inhibited, the clearance of glucose would equal GFR.

Inulin

Inulin produces a line parallel to the x axis, and the intersection point on the y axis represents GFR. If GFR increases, the line shifts upward; likewise, if GFR decreases, the line shifts down. It is always parallel to the x axis, and the point of intersection with the y axis is always GFR.

Glucose	glucose Urine
d-100	0
b- 100	(0
c. 250	30

Which one best represent Tm? a

What substance is best \-k measure GFR? inulin (many use Cr)

Creatinine

The clearance of creatinine will always be slightly greater than the clearance of inulin and GFR because creatinine is filtered and a small amount exhibits net secretion

PAH

At low plasma concentrations, the clearance equals renal plasma flow. As the plasma concentration rises, the carriers in some nephrons will reach saturation. At this point, some PAH will appear in the renal venous plasma, and the clearance will be less than renal plasma flow. As the plasma level rises further, the clearance approaches but never equals GFR because some PAH is always secreted. If the secretion of PAH was completely suppressed, the clearance would equal GFR.

CLEARANCE OF INULIN AS AN INDEX OF GFR AND RENAL FUNCTION

Clearance of Inulin

GFR is *the* index of renal function, and inulin clearance is the gold standard of GFR.

$$C_{in} = GFR = \frac{U_{in} \times V}{P_{in}}$$

The clearance of inulin provides the GFR because inulin is freely filtered—not metabolized, not secreted, not reabsorbed.

Substances Used Instead of Inulin

Mannitol

Sucrose

The Plasma Level of Creatinine

Under many conditions, the plasma level of creatinine is a relatively good index of GFR.

Most circulating creatinine comes from skeletal muscle, and its production is fairly constant. Creatinine is freely filtered and not reabsorbed by the kidney, although a very small amount is secreted.

Creatine production = creatine excretion = filtered load of creatinine

$= [Cr]_p \times GFR$

Thus, based on the preceding, if creatinine production remains constant, a decrease in GFR would be reflected by an increase in plasma creatinine concentration, and an increase in GFR would be reflected by a decrease.

Although not quite as accurate as inulin clearance, the plasma concentration of creatinine is the clinical standard because no substance need be administered to the patient in order to obtain a value.

Concentration of Inulin in the Nephron Tubule

The concentration of inulin in the nephron tubule is an index of water reabsorption. Inulin is freely filtered; thus, its concentration in Bowman's capsule is the same as it is in the plasma. Because water is reabsorbed but inulin is not, the concentration of inulin increases throughout the nephron. The greater the water reabsorption, the greater the increase in inulin concentration.

The segment of the nephron with the highest concentration of inulin is the terminal collecting duct.

The segment of the nephron with the lowest concentration of inulin is Bowman's capsule.

Clearance of PAH

best substance to measure renal plasma flow

Renal Plasma Flow (RPF)

The clearance of PAH is generally regarded as the standard estimate of the RPF.

$$C_{PAH} = RPF = \frac{U_{PAH} \times V}{P_{PAH}}$$

The clearance of PAH provides an estimate of the RPF because PAH is freely filtered, and at low plasma concentrations all of the remainder is completely secreted. However, PAH clearance is referred to as effective renal plasma flow (ERPF) because some plasma perfuses the renal capsule. This flow (about 10%) is not cleared of PAH. Thus, PAH clearance is only 90% of the true renal plasma flow.

PAH clearance is effective renal plasma flow only when the carriers are not saturated, that is, at low plasma concentrations.

Renal Blood Flow

$$\text{Renal blood flow} = \frac{\wedge\wedge}{1\text{-Hct}}$$

If renal plasma flow is 600 ml/min and the Hct is 50%, renal blood flow is 1200 ml/min.

FREE WATER CLEARANCE

If urine osmolarity was 300 mOsm/L (isotonic urine), free water clearance would be zero.

C_{H_20} (+) = hypotonic urine is formed (osmolarity <300 rnOsm/L)

C_{H_20} (-) = hypertonic urine is formed (osmolarity >300 mOsm/L)

$$C_{H_2O} = V - \frac{U_{osm} V}{P_{osm}}$$

$$3 - \frac{800 \cdot 3}{400}$$

$$3 - 6 = -3$$

$$V = C_{H_2O} + C_{osm}$$

V= urine flow rate

U_{osm} = urine osmolarity

P_{osm} = plasma osmolarity

Sample Calculation

V= 3.0ml/min

U_{osm} = 800mOsm/L

P_{osm} = 400 mOsm/L

C_{H2O} = -3 ml/min

Chapter Summary

Substances that do not appear in the urine have a clearance of zero.

Substances filtered and partially reabsorbed have a clearance less than the GFR.

The clearance of inulin is always equivalent to the GFR because it is filtered and has no net transport.

Substances filtered and with net secretion have a clearance greater than the GFR. Because creatinine is filtered and a small amount is secreted, it always has a clearance slightly greater than the GFR and inulin. PAH is filtered and, when the remainder is secreted, its clearance equals renal plasma flow.

Regional Transport

3

THE PROXIMAL TUBULE

The fluid entering the proximal tubule is the isotonic ultrafiltrate (300 mOsm/L). The concentration of a freely filtered substance will equal its plasma concentration. Figure VII-3-1 illustrates the main cellular processes of the proximal tubular cells. A summary follows.

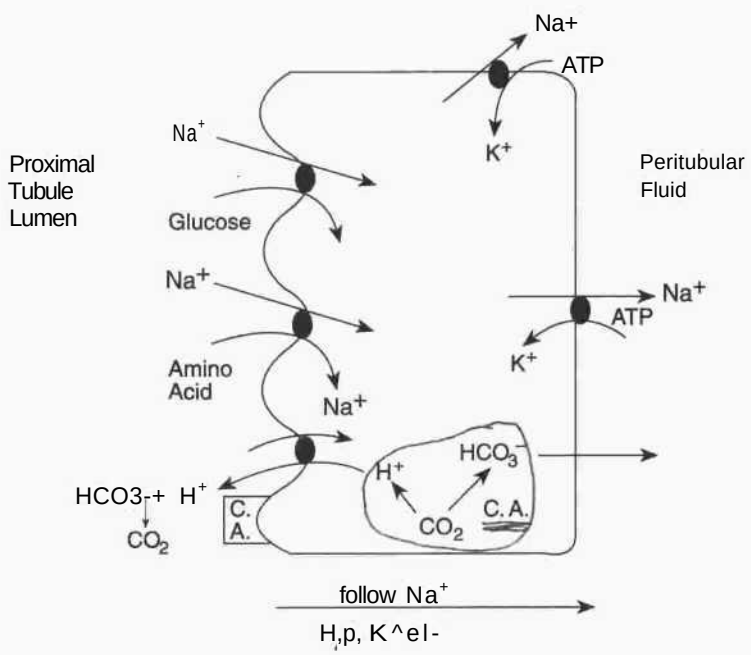


Figure VII-3-1

What the USMLE Requires You to Know

- Net transport processes in the proximal tubule
- The loop of Henle as a countercurrent multiplier
- Regulation of urine osmolarity
- Mechanisms of net acid loss by the kidney

the proximal tubule
there is no buffering
0
which of following is not likely to be involved in pH buffering?
a. distal
b. proximal
c. salivary
d. codons

Summary of Proximal Tubule Changes

Water and Electrolytes

Approximately two-thirds of the filtered sodium is reabsorbed in the proximal tubule by primary and secondary active transport.

About two-thirds of the filtered H_2O, K^+, and Cl~ follow the sodium (leaky system to these substances), and the osmolarity at the end of the proximal tubule remains unchanged at 300 mOsm/L (isosmotic reabsorption).

Therefore, at the end of the proximal tubule, osmolarity and the concentrations of Na^+, K^+, and Ch have not changed significantly from plasma, but only a third of the amount originally filtered remains.

Metabolites

Normally, all carbohydrates, proteins, peptides, amino acids, and ketone bodies are reabsorbed here via secondary active transport (requires luminal sodium, linked to sodium reabsorption).

Therefore, the concentration of the above should be zero in the tubular fluid leaving the proximal tubule (clearance is zero).

Bicarbonate

About 80-90% of the filtered bicarbonate is reabsorbed indirectly here. Because the process simply recovers the amount filtered, there is no net gain or loss of bicarbonate by the body.

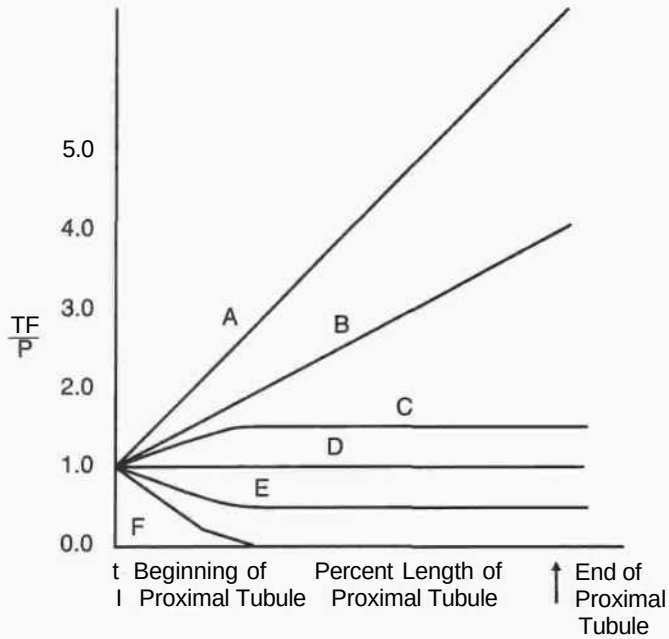
The small amount of bicarbonate that leaves the proximal tubule is normally reabsorbed in subsequent segments.

Energy Requirements

Notice that all of the active processes illustrated in Figure VII-3-1 are powered by the Na/K-ATPase primary active pump. This pump is located in the proximal tubule basal and basolateral borders and is directly or indirectly responsible for most of the water and electrolyte reabsorption in the nephron. It thus represents the most energy-demanding process of the nephron.

Effect ***of the Plasma Concentration***

Figure VII-3-2 depicts the ratio of the concentration of the substance in the proximal tubular fluid (TF) to the concentration in the plasma (P).



A = PAH
B = Inulin
C = Substance concentrated because its reabsorption is somewhat less rapid than water
D = Major electrolytes such as sodium, potassium, and chloride
E = Substance reabsorbed somewhat more rapidly than water
F = Substance completely reabsorbed in the proximal tubule, e.g., glucose

Figure VII-3-2

THE LOOP OF HENLE

Fluid entering the loop of Henle is isotonic (300 mOsm/L), but the volume is only a third of the volume originally filtered into Bowman's capsule. The loop of Henle acts as a countercurrent multiplier and as such creates a medullary interstitial osmolar gradient. The osmolarity can reach a maximum of about 1200 mOsm/L at the tip of the medullary interstitium in antidiuresis. The major cellular processes are illustrated in Figure VII-3-3. Numbers indicate fluid osmolarity.

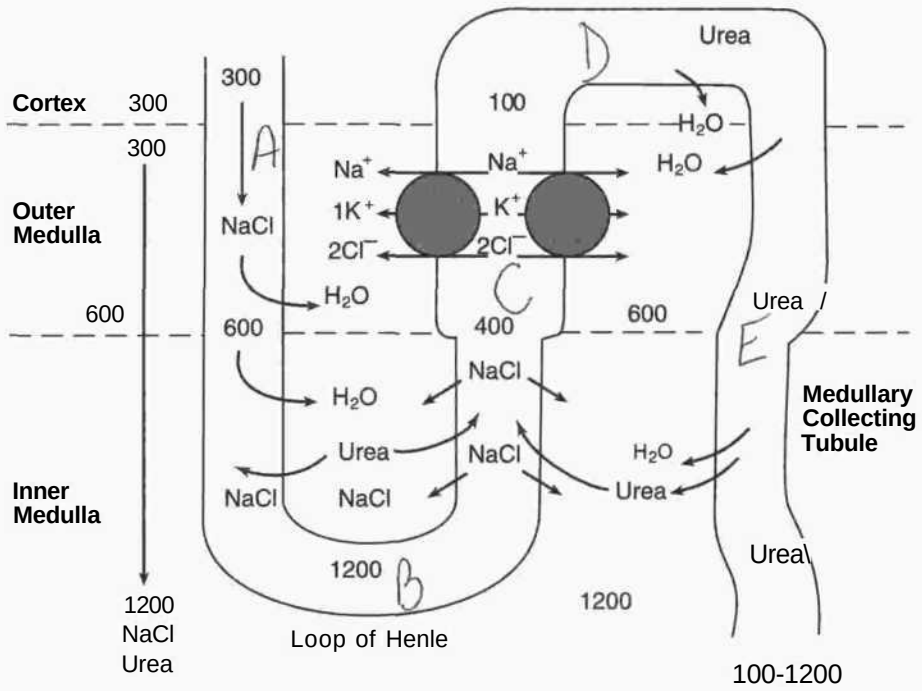


Figure VII-3-3

The following characteristics of the loop of Henle permit it to act as a countercurrent multiplier. Any disruption of these characteristics will diminish the osmolarity of the medullary interstitium and decrease the ability of the kidney to form a concentrated urine.

Countercurrent flow—opposite directional flow/

Descending limb **permeable to water**—water diffuses into the hyperosmolar medullary interstitium, and the osmolarity of the tubular fluid in the descending loop of Henle increases, reaching a maximum at the tip of the loop of Henle. This point represents the highest osmolarity of any nephron segment. The osmolarity at end of the coDecting duct can equal this value, but only with maximum ADH effect.

Ascending limb impermeable to water

NaCl pumped from ascending limb—NaCl is pumped from the tubule into the interstitium in the ascending limb of the loop of Henle. Because this segment is impermeable to water, the tubular fluid osmolarity decreases along the ascending loop and leaves the loop of Henle as hypotonic fluid. This is the diluting segment of the nephron.

Slow Flow—flow through the loop is relatively slow. This is also a characteristic of flow through the vasa recta. Anything that increases flow through the loop of Henle or vasa recta will decrease the ability of the system to maintain a high medullary osmolarity and reduce the ability of the kidney to form a concentrated urine. For example, if the proximal tubule fails to reabsorb two-thirds of the fluid and electrolytes filtered, the excessive load will overwhelm the loop of Henle, decrease interstitial osmolarity, and reduce the maximum urine osmolarity.

Collecting Duct

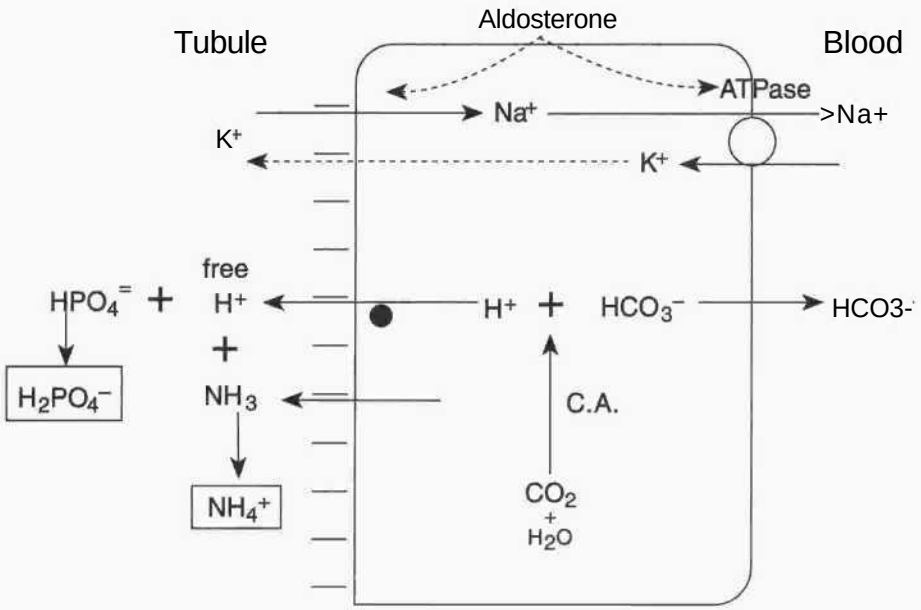
Without ADH, the collecting duct is completely impermeable to water, and the dilute fluid leaving the loop of Henle becomes hypotonic urine.

ADH increases the permeability of the collecting duct to water and allows the passive reabsorption of water and some urea. The osmolarity of collecting duct fluid can increase to, but never exceed, the osmolarity in the interstitium at the tip of the medulla.

DISTAL TUBULE AND COLLECTING DUCT ELECTROLYTES

Processes carried out in this section determine the final urine characteristics. ADH controls the final water and urea reabsorption, and aldosterone the final NaCl reabsorption and K^+ secretion. A more detailed description of the actions of ADH and aldosterone can be found in Endocrinology, Section IX.

This section of the nephron is also responsible for the final acidification of the urine. Body metabolism produces fixed acids, and the hydrogen ions must be excreted in the urine. Figure VII-3-4, which illustrates the main processes involved, is followed by a descriptive summary.



FigureVII-3-4

Descriptive Summary of Active Processes Occurring in the Distal Tubule and Collecting Duct

Sodium and Potassium

Active sodium reabsorption is stimulated by aldosterone. The passive transport of sodium across the luminal membrane is also promoted by aldosterone (inserts channels in the luminal membrane). This is a much tighter system (tight junctions) than the proximal tubule, and little back leak occurs here. Also, the active reabsorption of sodium creates a negative charge in the tubule lumen, which attracts positive ions like potassium. One result of this negative charge is a net secretion of potassium.

*Net **Secretion of H+ and Acidification of the Urine***

Hydrogen ions are actively secreted into the tubular lumen. However, very few are excreted as free ions. Almost all are buffered by two systems.

Phosphate Buffer System

Monohydrogen phosphate is freely filtered and not completely reabsorbed. The remaining fraction will buffer a fraction (approximately 33%) of the secreted hydrogen ions. Availability of phosphate largely depends on the excess provided in the diet. This can be considered the first line of buffering.

Formation of Ammonium

To buffer the remaining hydrogen ions, the kidney manufactures ammonia. It simply produces what is necessary to complete the buffering process (normally about 66%). This can be considered the second line of buffering.

Forms ofH in the Urine*

The H^+ in the urine will be in two main forms:

H_2PO_4~, dihydrogen phosphate, also called titratable acid

NH_4^+, ammonium, also called nontitratable acid

The net loss of H^+ in the urine is simply the sum of the titratable acid and the nontitratable acid.

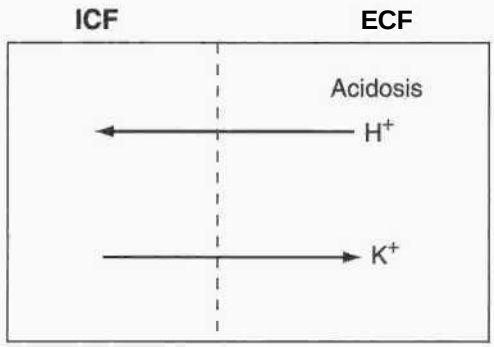
Relationship between H^+ Excretion and Bicarbonate Reabsorption

The net excretion of one H^+ results in the reabsorption of one HC03~. This represents new HCO3~added to body stores. It is a net gain in HCC>3~ only because the secreted H^+ is excreted in the urine.

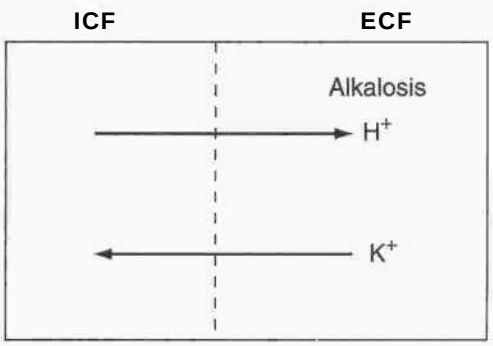
Total net loss of acid = net gain of new HCC>3~

POTASSIUM DYNAMICS IN ACIDOSIS

In a chronic acid-base disturbance, there is exchange of H^+ and K^+ between the intracellular and extracellular spaces. In an acidosis, the H^+ slowly enters cells to be buffered in large part by intracellular proteins. To maintain electrical neutrality, K^+ will leave the cell, creating an intracellular K^+ deficit. If the K^+ accumulates in the extracellular fluid, a state of hyperkalemia will exist. The reverse will occur in an alkalosis. This is illustrated in Figure VTI-3-5.



Hyperkalemia in Acidosis



Hypokalemia in Alkalosis

Figure VII-3-5

In acidosis (eg DKA, lactic acidosis) ↓
{filtration of K+ ↑
{secretion of K+ ↓
{excretion of K+ ↑

Chapter Summary

In the proximal tubule, two-thirds of the water and electrolytes are reabsorbed, along with almost all the organic molecules filtered. An exception is urea. Because equal amounts of solutes and fluid are reabsorbed, the fluid remains isotonic.

The loop of Henle, acting as a countercurrent multiplier, creates an osmotic gradient in the medullary interstitium, with the tip reaching a maximum of 1200 mOsm/L. This value determines the maximum osmolarity of the urine. Because the descending limb is permeable to water, tubular osmolarity increases in this limb. Because the ascending limb is impermeable to water and sodium chloride is reabsorbed, osmolarity decreases in this limb, and the tubular fluid leaves hypotonic.

Net acid secretion into the filtrate occurs in the distal tubule/collecting duct. This excreted acid is buffered with either phosphate or ammonia. The bicarbonate secreted to the interstitium represents a net gain to body stores.

RENAL PHYSIOLOGY

Review Questions

RenalFiltration

Questions 1-2. Select the ONE best answer.

1. Which of the following would tend to increase glomerular filtration rate?
   A. An increase in glomerular capillary oncotic pressure.
   B. Vasoconstriction of the afferent arteriole.
   C. An increase in hydraulic pressure in Bowman's capsule.
   D. An increase in renal blood flow.

2. Which of the following would be expected to cause a large reduction in glomerular filtration rate?
   A. A reduction in mean arterial pressure from 100 to 95 mm Hg.
   B. A reduction in plasma oncotic pressure by one-half.
   C. A decrease in sympathetic activity.
   D. Complete urethral obstruction.

Question 3. Select all the correct answers.

3. Sympathetic stimulation of the renal arterioles causing a marked reduction in renal blood flow results in:
   A. Increased percent reabsorption of fluid filtered by the nephron.
   B. Decreased glomerular filtration rate.
   C. Decreased peritubular hydrostatic pressure.
   D. A decreased filtration fraction.

Questions 4-6. Select the ONE best answer.

4. The glomerulus:
   A. Is permeable to all molecules with a molecular weight (M) over 5000.
   B. Contains no active transport systems (pumps) that produce an important effect on the composition of the glomerular filtrate.
   C. Produces a filtrate with a lower concentration of amino acids than found in plasma.
   D. Produces a filtrate with a higher concentration of urea than found in plasma.
   E. All of the above statements are correct.

5. The glomerular filtration rate:
   A. is greater than 50% of the plasma flow to the glomeruli
   B. falls to approximately 25% of normal when mean arterial pressure changes from 100 to 25 mm Hg
   C. is decreased by a decrease in plasma colloid osmotic pressure
   D. increases ipsilateral to a ureteral obstruction
   E. none of the above statements are true

6. Sympathetic stimulation of the renal arterioles results in:
   A. a greater percentage of filtrate being reabsorbed by the renal tubule
   B. a decreased renal filtration fraction
   C. increased peritubular hydrostatic pressure in the kidney
   D. an increased glomerular filtration rate

Question 7. True or False.

7. The filtration fraction of the kidney is normally about 20%, and is increased due to the vasoconstrictor effects of angiotensin II.

Questions 8. Select the ONE best answer.

8. In a healthy individual, what percentage of the effective renal plasma flow would you expect to pass into the glomerular capsule?

   A. less than 5%
   B. between 15% and 20%
   C. between 40% and 50%
   D. between 70% and 80%
   E. greater than 90%

9. If vascular resistance in the renal afferent arterioles decreases more than does resistance in the efferent artiole, which one of the resulting changes is **incorrect?**

   A. The filtration fraction is decreased.
   B. Pressure favoring reabsorption in the peritubular capillary is reduced.
   C. Both renal plasma flow and GFR are increased.
   D. Hydrostatic pressure favoring glomerular filtration is reduced.
   E. Extracellular fluid volume will contract.

TubularReabsorptionandSecretion

Questions 1-4: Select the ONE best answer.

1. The following data are obtained from a patient

   24-hour urine sample
   total volume = 1440 ml (1 ml/min)
   sodium concentration = 120 mEq/liter
   potassium concentration =100 mEq/liter
   creatinine concentration = 200 mg/100 ml
   urea concentration = 2050 mg/100 ml

   plasma sample taken at the midpoint during the urine collection
   sodium concentration = 140 mEq/liter
   potassium concentration = 5 mEq/liter
   creatinine concentration = 1 mg/100 ml
   urea concentration = 25 mg/100 ml

   What is the potassium excretion rate?

   A. less than 0.2 mEq/min
   B. 0.2 mEq/min
   C. 0.3 mEq/min
   D. 0.4 mEq/min
   E. more than 0.4 mEq/min

2. Toward the end of World War II, Karl Beyer and his associates noted that the injection of PAH decreased the excretion of penicillin in the urine. What would you suggest was its mechanism of action? The PAH:
   A. competes with penicillin for a site on a carrier molecule in one of the reabsorptive mechanisms
   B. prevents active reabsorption
   C. either of the above could be correct
   D. increases filtration
   E. competes with penicillin for a site on a carrier molecule in one of the secretory mechanisms

3. If a substance has a transport maximum (T_M) for absorption, this means:
   A. reabsorption is only passive
   B. only a constant fraction of the substance will be reabsorbed
   C. statements A and B are both correct
   D. below a threshold level, all of the substance will be reabsorbed
   E. phlorizin blocks reabsorption

4. Which one of the following substances does not have a T_M value: albumin, arginine, (3 hydroxybutyrate, glucose, hemoglobin, phosphate, sulfate, urea, uric acid?

Renal Answers and Annotations

Renal Filtration

1. **Ans D.** As plasma is filtered in the glomerulus the concentration of plasma proteins increases within the capillaries, reaching a maximum at the end of the capillary network. An increase in capillary protein concentration decreases the net filtration pressure. If capillary flow increases, plasma spends less time in the capillaries and filtration fraction tends to decrease. Thus the proteins become less concentrated as the plasma quickly passes, and the resulting smaller increase in plasma protein concentration in the terminal capillary region means greater net filtration pressure here. Because the terminal capillary regions will have a greater filtration rate, total filtration will increase. This effect will occur in addition to any hydrostatic pressure changes induced with the flow changes. Vasoconstriction of the afferent arteriole (upstream from the capillaries) will reduce capillary hydrostatic pressure and filtration. An increase in Bowman's capsule hydrostatic pressure will oppose filtration in the same manner that an increase in interstitial pressure will oppose filtration in other vascular beds.

2. **Ans** D. Any blockade downstream in the nephron system will cause pressure to build up in Bowman's capsule. An increase in hydrostatic pressure in Bowman's capsule is the equivalent of an increase in interstitial pressure in other vascular beds. This is a force which opposes filtration. Because the renal system exhibits strong autoregulation when there are slight changes in blood pressure, a decrease in pressure from 100 to 95 mm Hg will have minimal effects on glomerular capillary pressure and filtration. On the other hand, if it was a large drop in blood pressure, glomerular capillary pressure and filtration will decrease for 2 reasons: (1) Perfusing pressure is less. (2) The reflex increase in sympathetic activity will constrict the afferent arteriole, accentuating the drop in glomerular capillary pressure. A reduction in plasma oncotic pressure, which is directly related to plasma protein concentration, reduces a force opposing filtration. A decrease in sympathetic activity dilates the afferent arteriole, increasing glomerular capillary pressure and filtration.

3. **Ans** A, B, C. Most of the fluid reabsorption occurs in the peritubular capillary region. Sympathetic stimulation will increase the fraction of filtered material reabsorbed here for 2 reasons. The vasoconstriction upstream in the afferent and efferent arterioles will lower peritubular hydrostatic pressure, a force opposing reabsorption. Second, the tendency to increase filtration fraction when renal plasma flow decreases will increase the concentration of protein in

peritubular capillaries (oncotic pressure), a force which promotes reabsorption. Sympathetic stimulation will decrease filtration mainly because of a decrease in glomerular capillary hydrostatic pressure. Sympathetic stimulation, if anything, will decrease renal plasma flow and increase filtration fraction. Lower flow means the plasma spends more time in the glomerular capillaries, thus a greater fraction of the plasma potentially can be filtered.

4. **Ans** B. Filtration is a process driven by pressure differences between the glomerular capillaries and Bowman's capsule. No active transport is involved. The glomerular membranes are not permeable to high molecular weight substances like proteins. Amino acids and urea are freely filtered substances and, as such, their concentration in Bowman's capsule will be the same as in plasma.

5. **Ans** E. Urethral obstruction will raise hydrostatic pressure in Bowman's capsule and reduce GFR. Filtration in the contralateral nephrons will tend to increase as a compensatory mechanism. Normally, GFR represents about 20% of the renal plasma flow. If blood pressure decreases to 25 mm Hg, there will be little, if any, filtration. The drop in blood pressure will drop filtration pressure, and the reflex increase in sympathetic vasoconstriction in the renal system will drop filtration pressure even further. A decrease in plasma oncotic pressure will increase filtration. Plasma proteins create plasma oncotic pressure, a force which opposes filtration.

6. **Ans** A. Sympathetic stimulation to the kidney promotes the forces of reabsorption. The lower renal plasma flow tends to increase filtration fraction and thus the plasma oncotic pressure in the peritubular capillaries, a force promoting reabsorption. The constriction of the afferent and efferent arterioles will decrease peritubular capillary pressure, a force promoting filtration. Even though the filtration fraction tends to increase, GFR will decrease because of the drop in glomerular capillary hydrostatic pressure.

7. **Ans True.** Anything that constricts the kidney decreases renal plasma flow. This lowered plasma flow will tend to increase filtration fraction even when GFR is decreasing. All constricts the efferent arteriole more than the afferent arteriole. This minimizes the drop in glomerular capillary pressure and GFR, but there is still lower plasma flow and an increase in filtration fraction.

8. **Ans** B. This is simply asking what is the normal filtration fraction. A big point in class was that this is normally about 20%.

9. Ans D

A. The filtration fraction is decreased. This is true since the dominant change was dilation of afferent arteriole, which increases both plasma flow and GFR, but the relative, smaller change in the efferent arteriole will decrease the GFR but further increase the RPF. Therefore, the overall response is an increase in both RPF and GFR but less of an increase in GFR. Therefore, there is a decrease in the filtration fraction.

B. Pressure favoring reabsorption in the peritubular capillary is reduced as a result of the decrease in filtration fraction. The decrease in filtration fraction results in a lower oncotic pressure at the end of the glomerular capillary, which continues as a decrease in oncotic pressure in the peritubular capillary. The magnitude of the peritubular oncotic pressure is the main driving force favoring fluid reabsorption in the peritubular capillary.

C. Both renal plasma flow and GFR are increased. This is true since the dominant vasodilation is in the afferent arteriole. Vasodilation of the efferent vessel does decrease the net filtration pressure but to a minor extent. If the dominant change had been in the efferent vessel, then GFR would have increased and renal plasma flow decreased.

D. Hydrostatic pressure favoring glomerular filtration is reduced—this is not true. Decreased resistance in the afferent arteriole increases the pressure in the glomerular capillary; a greater portion of the systemic arterial pressure (100 mm Hg) is now seen by the glomerular capillary.

E. Extracellular fluid volume will contract. This is true and is based on the increased filtrate being generated (increased GFR) at the same time that there is reduced reabsorption in the peritubular capillary (decreased filtration fraction). The first body compartment that will be affected by more urine output is the extracellular space.

Tubular Reabsorption **and Secretion**

1. AnsA. Most of these data are not relevant to the question. Excretion of potassium is:

$U_K X \dot{V}$ U_K = urine concentration of potassium

$\dot{V}$= urine flow rate

Thus: UK s= 100 mEq/liter = 0.1 mEq/ml

V = 1 ml/min

Potassium excretion is 0.1 mEq/ml X 1 ml/min = 0.1 mEq/min

2. Ans E. In class we mentioned that PAH is actively secreted by a carrier that is fairly nonspecific. This carrier tends to secrete many non-natural organic compounds. Thus, if PAH is being secreted and another substance is presented that can compete for the carrier, the secretion of PAH will decrease.

3. Ans D. A T_M system is an active transporting mechanism in which the carrier has a high affinity for the substrate but the number of carriers available are limited. Thus, below saturation with substrate (renal threshold), all of the substance will be transported.

4. Ans urea. A T_M will only apply to a substance that is actively transported. A big point in class was that urea is partially reabsorbed, but the mechanism was passive. Thus, even though you may not know all the renal handing aspects of the substances listed, you should recognize that urea is a very good answer to the question.

Clearance and Calculations: Review Questions

Questions 1-8: Select the ONE best answer.

1. Which of the following substances has the greatest renal clearance?
   A. inulin
   B. sodium
   C. urea
   D. creatinine
   E. glucose

2. Determine the excretion rate of glucose given the following data:

urine glucose concentration	=	125 mg/100 ml
urine inulin concentration	=	56 mg/100 ml
plasma glucose concentration	=	90mg/100 ml
plasma inulin concentration	=	1 mg/100 ml
urine flow rate	=	2 ml/min

   A. 112mg/min
   B. 98.5mg/min
   C. 200mg/min
   D. 2.5 mg/min

3. The following data are obtained for a patient:

inulin clearance	=	170 L/day
plasma bicarbonate concentration	=	25 mmol/L
urine bicarbonate concentration	=	0 mmol/L
urine pH	=	5.8
titratable acid in urine	=	26 mmol/day
ammonium ion in urine	=	48 mmol/day

Calculate the total amount of hydrogen ions secreted by the kidney:

   A. 4250 mmol/day
   B. 26 mmol/day
   C. 74 mmol/day
   D. 4324 mmol/day

4. Calculate the renal filtered load of sodium:

glomerular filtration rate:	=	100 ml/min
urine flow rate	=	2.4 ml/min
urine concentration of inulin	=	1 mg/ml
plasma concentration of sodium	=	0.12mEq/ml

A. 20 ml/min
B. lOOmg/min
C. 12 mEq/min
D. 50 ml/min

5. Renal clearance of inulin provides a measure of:

A. renal blood flow
B. cardiac output
C. glomerular filtration rate
D. renal plasma flow

6. Calculate the bicarbonate reabsorption (proximal and distal) in a patient with the following data:

clearance of inulin:	=	175 L/day
plasma bicarbonate	=	25 mmol/L
urine bicarbonate	=	0
urine pH	=	5.8
titratable acid in urine	=	26 mmol/day
urine ammonium ion	=	48 mmol/day

A. 4449 mmol/day
B. 74 mmol/day
C. 26 mmol/day
D. 4375 mmol/day

7. How much new bicarbonate has been added to the blood of the above patient?

A. 48 mmol/day
B. 26 mmol/day
C. 4449 mmol/day
D. 74 mmol/day

8. Calculate the renal plasma flow of a patient given the data below:

   effective renal plasma flow = 585 ml/min
   unconnected measured hematocrit = 45%
   renal extraction of PAH = 0.90
   (i.e., 90% of PAH is removed from the plasma by the kidney in a single passage)

   A. 1064 ml/min
   B. 961 ml/min
   C. 1066 ml/min
   D. 650 ml/min

Questions 9 **and** 10: Answer true or false to the following statements by marking A for true and B for false.

9. The renal clearance of glucose is less than that of inulin.

10. Inulin is present at the same concentration in the glomerular filtrate and the final urine.

11. Which one of the following statements is most consistent with a filterable substance being actively reabsorbed from the renal tubular lumen?

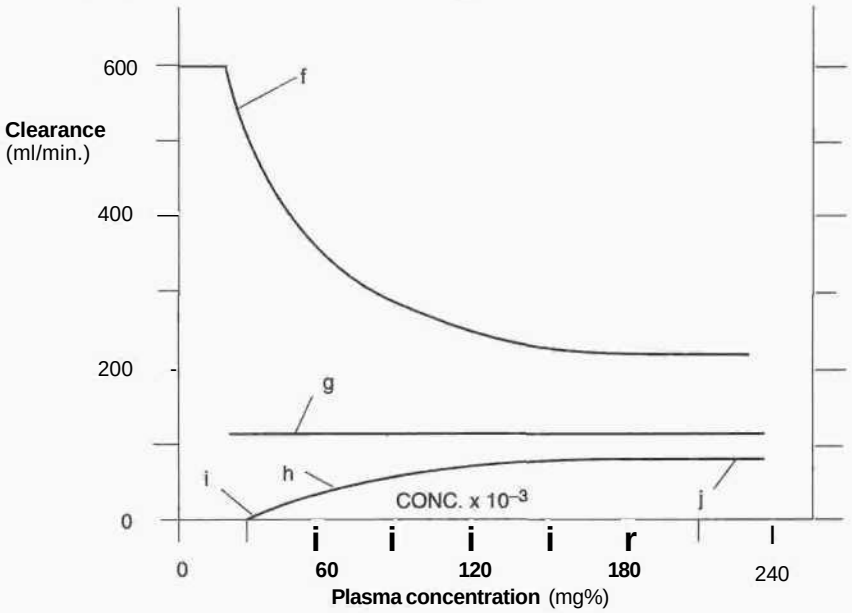
   A. Its renal clearance value is lower than that of inulin.
   B. Its renal clearance value is higher than that of inulin.
   C. The ratio of its rate of urinary excretion/plasma concentration is the same as that for glucose.
   D. The ratio of its rate of urinary excretion/plasma concentration is greater than that for glucose.
   E. Its concentration in the distal tubule is higher than that in plasma.

12. During the infusion of PAH into a patient, the concentration of PAH in the cephalic vein stabilized at 0.02 mg/ml of plasma. At this time, the two kidneys were producing 1 ml of urine per minute, and the concentration of PAH in the urine was 16 mg/ml. What was the PAH clearance? What was the effective renal plasma flow?

13. The renal clearance of (select the one best answer)

   A. a substance is measured in mg/ml
   B. a substance is measured in mg/min
   C. sodium is decreased by the injection of aldosterone
   D. inulin at a plasma concentration of 60 mg% is lower than at a plasma concentration of 120 mg%
   E. PAH at a plasma concentration of 60 mg% is higher than at a plasma concentration of 12 mg%

14. The clearance of substances f, g, and h are studied at different concentrations in the blood. The following data are obtained:



Which of the following statements best characterizes substance f? Substance f in the nephron is:

A. secreted
B. reabsorbed
C. filtered
D. filtered and reabsorbed
E. filtered and secreted

15. Which one of the following statements best characterizes substance h in question 14? Substance h in the nephron is:

A. filtered and actively secreted
B. filtered and passively reabsorbed
C. filtered, passively reabsorbed, and actively reabsorbed
D. filtered and synthesized
E. filtered, synthesized, and secreted

16. Which one of the following statements concerning curve h in question 14 is true? The plasma concentration at point:

A. i represents the transport maximum
B. i represents the splay
C. i represents the threshold
D. j represents the splay
E. j represents the threshold

17. All of the following substances are filtered into the glomerular capsule. Indicate which ones will produce a clearance curve in man similar to f, g, or h in question 14. One of these substances has a T_M value of 375 mg/min and another of 1 mg/min. Therefore, in making your comparisons, concentrate on the shape of the clearance-concentration curve, not absolute values of concentration.

___	inulin	___	penicillin	___	lysine
___	glucose	___	albumin	___	hemoglobin
___	PAH	___	arginine	___	Diodrast
___	sulfate	___	ketone bodies	___	phosphate
___	ascorbic acid				

18. Given the following data, calculate the GFR of this patient:

Plasma creatinine	0 .8 mg/100 ml
Plasma urea	15.0 mg/100 ml
24 hr urine volume	1,600 ml (= 1.1 ml/min)
Urine concentration of urea	130 mg/100 ml
Urine concentration of creatinine	72 mg/100 ml

A. 181 mL/min
B. 125 mL/min
C. 100 mL/min
D. 130 mL/min
E. 154 mL/min

19. Which one of the following statements is FALSE?

A. Normally, clearance of glucose is less than GFR.
B. Secretion = Filtration — Excretion.
C. Clearance of PAH decreases as plasma concentration increases to very high levels.
D. Inulin processing is such that what is filtered equals what is excreted.
E. The units of transport maximum (T_M) are mg/min (a rate), whereas renal threshold values are mg/ml (a concentration).

Questions 20-21: Consider the clinical situation of a markedly expanded extracellular fluid volume in an otherwise normal individual. You should assume that arterial pressure is normal and that normal renal and cardiovascular compensatory mechanisms are intact.

20. In response to this expansion all the following will increase **except:**
    A. U X $\dot{V}$ for sodium.
    B. GFR.
    C. Angiotensin II formation.
    D. ANP release.
    E. Plasma volume.

21. In response to this expansion all of the following will decrease except:
    A. Renin release.
    B. ADH release.
    C. Fraction of filtered sodium that is excreted.
    D. Aldosterone release.
    E. Renal sympathetic nerve activity.

22 It is true that:
    A. Clearance with secretion is < GFR.
    B. Reabsorption = Excretion — Filtration.
    C. T_M = Plasma level for appearance in the urine with reabsorption.
    D. Secretion = Filtration — Excretion.
    E. Clearance of Inulin > Clearance with reabsorption.

23. If a patient has a GFR value of 100 ml/min and is known to be clearing a therapeutic drug at a rate of 150 ml/min, which of the following statements accurately describes the renal processing of this drug? You have no knowledge of the specific renal processing.
    A. No overall evaluation can be made without more detailed information.
    B. Since clearance is greater than GFR, the drug is likely to be reabsorbed.
    C. Since clearance is greater than GFR, the drug is likely to be secreted.
    D. The T_M of the drug has been exceeded, causing clearance to increase above GFR.
    E. The overall processing of this drug is similar to that of amino acids.

24. As the plasma levels of PAH increase to high levels, such that the T_M is exceeded:
    A. PAH clearance continues to increase.
    B. PAH excretion becomes constant.
    C. PAH clearance becomes a good measurement of renal plasma flow.
    D The filtered load of PAH increases.
    E. PAH clearance approaches excretion.

Clearance and Calculations

1. Ans D. Substances that exhibit net secretion will have the greatest clearance. The greater the net secretion, the greater the clearance. The only substance from the choices provided that exhibits net secretion is creatinine, thus, it is the best answer. The second best answer is inulin, a substance that exhibits no net transport. Those having net reabsorption will have the lowest clearance values. Sodium, urea, and glucose all exhibit net reabsorption. The greater the net reabsorption, the lower the clearance. Since glucose is completely reabsorbed, it has a clearance of zero. Sodium does appear in the urine, **so** it has a clearance greater than glucose. Urea exhibits less net reabsorption than sodium, so its clearance is greater than sodium but below that of inulin.

2. **Ans** D. The excretion of glucose will equal:

$U_G X \dot{V}$ U_G = urine concentration of glucose

= 125 mg/100 ml

= 1.25 mg/ml

$\dot{V}$ = urine flow rate

= 2 ml/min

Thus, 1.25 mg/min X 2 ml/min = 2.50 mg/min.

3. Ans D. The total hydrogen ions secreted by the kidney represents those secreted in the proximal tubule to reabsorb filtered bicarbonate and those secreted in the distal tubule/collecting duct, which represents a net loss of H^+ by the body.

Proximal tubule: hydrogen ion secretion approximately equal to the filtered load of bicarbonate, which is:

GFR (which is inulin clearance) X plasma HCO_3~ concentration

170 L/day X 25 mmol/L = 4250 mmol/day

The H^+ secretion in the proximal tubule is 4250 **mmol/day.**

Distal tubule/collecting duct: hydrogen secreted here represents the loss of hydrogen ions in the urine. These are lost in 2 buffered forms: titratable acid (H_2PO_4~), which equals 26 mmol/day, and ammonium, which equals **48 mmol/day.**

The H^+ secretion in the distal tubule/collecting duct is 26 plus 48 = **74 mmol/day.**

The total H^+ secretion by the kidney = 4250 + 74 = **4324 mmol/day.**

4. **Ans** C. The filtered load of sodium is GFR X plasma sodium concentration:

GFR = 100 ml/min

plasma sodium = 0.12 mEq/ml

Thus: 100 ml/min X 0.12 mEq/ml = 12 mEq/min

5. **Ans** C. The clearance of any substance that is freely filtered, not metabolized by the kidney, exhibits no net reabsorption or secretion and will equal the filtration rate of the kidneys. Inulin exhibits those characteristics.

6. **Ans** A. This question is very similar to question 3. The total bicarbonate reabsorption by the kidney will equal the total hydrogen ion secretion by the kidneys. This will occur in the proximal tubule where H^+ secretion reabsorbs filtered bicarbonate and in the distal tubule/collecting duct where H^+ secretion creates new bicarbonate that is absorbed into the general extracellular fluid.

Proximal tubule = GFR (inulin clearance) X plasma HCO_3~ concentration = filtered load of HCO_3~

= 175 L/day X 25 mmol/day = **4375 mmol/day**

Distal tubule/collecting duct = titratable acid + ammonium in the urine

= 26 mmol/day + 48 mmol/day = **74 mmol/day**

Total **a** 4375 + 74 = **4449 mmol/day**

7. **Ans D.** The new bicarbonate added to body stores is represented by the rate of H^+ secretion in the distal tubule/collecting duct. This occurs only because the H^+ secreted is lost in the urine. Thus the rate of H^+ lost in the urine is equal to the new bicarbonate added to body stores. Hydrogen ions are lost as titratable acid and ammonium. Thus, 26 + 48 = 74 mmol/day, which is the new bicarbonate added to body stores.

8. **Ans** D. If the renal extraction of PAH was complete, the clearance of PAH would equal renal plasma flow. In this example the renal extraction of PAH was only 90%. Therefore, the clearance of PAH will equal only 90% of renal plasma flow. Clearance = 585 ml/min = 90% of renal plasma flow. 100% of renal plasma flow = 650 ml/min.

585 ml/min = 90%

x 100%

9. **Ans** A. **true** Any substance that exhibits net reabsorption will have a clearance less than inulin; this includes glucose.

10. **Ans** B. **false** Inulin is freely filtered and exhibits no net reabsorption or secretion. The concentration of inulin in Bowman's capsule equals that in the plasma. As the filtrate proceeds along the nephron, water is reabsorbed but not inulin. As the water is reabsorbed, the concentration of inulin increases. The greatest concentration of inulin will be found at the end of the system in the urine.

11. **Ans** A. Any substance that exhibits net reabsorption will have a clearance less than inulin. Answer C will apply only to substances that are completely reabsorbed by the kidney. It will not apply to substances that are partially reabsorbed like urea and sodium. A renal clearance greater than inulin would mean net secretion. A substance that exhibits net reabsorption can have a concentration in the distal tubule higher than in plasma if water reabsorption is even greater. Substances that are not reabsorbed and those exhibiting a net secretion will also fall into the same category.

12. **Ans 800 ml/min.** The clearance of PAH and renal plasma flow are the same. The calculation is as follows:

$$C_{PAH} = \frac{U_{PAH} \times \dot{V}}{P_{PAH}} = \frac{16 \text{ mg/ml} \times 1 \text{ ml/min}}{0.02 \text{ mg/ml}} = 800 \text{ ml/min}$$

13. **Ans** C. Aldosterone increases the reabsorption of sodium. The greater the net reabsorption, the lower the clearance. If the substance is completely reabsorbed, its clearance is zero. Therefore increased circulating aldosterone will decrease the clearance of sodium. The units for clearance are volume/time. It is the volume of **plasma** cleared of a substance per unit time. The clearance of inulin is independent of its plasma concentration. If the plasma concentration changes from 60 mg% to 12 mg%, the clearance of inulin will be unchanged. The clearance of inulin is GFR. If GFR does not change, the clearance of inulin does not change. When the plasma level of PAH increases, more PAH is delivered to the peritubular capillaries. This will eventually saturate the carriers, and the plasma will not be completely cleared of PAH. Thus, raising the plasma level of PAH will decrease its clearance but only after the carriers become saturated.

14. **Ans** E. At low plasma levels, the clearance of substance f is close to renal plasma flow. As the plasma level increases, the clearance initially is unchanged but at some point begins to decrease. This is characteristic of a substance like PAH. The decrease in clearance is due to the saturation of the carriers. The decrease will approach but never

equal GFR because the substance is filtered and will always show some net secretion.

15. **Ans** C. At low plasma levels, the substance has a clearance of zero. This means that what is filtered is completely reabsorbed, or the substance is not even filtered. As the plasma level increases beyond a certain point, the substance has a positive clearance, which means the substance now appears in the urine. This substance has characteristics similar to that of glucose. As the plasma level rises, the clearance increases but never reaches a value equal to GFR because there will always be some net reabsorption.

16. **Ans** C. Point i represents the plasma level at which the substance begins to have a positive clearance. This means the substance now appears in the urine, and reabsorption was not complete because the carriers are now saturated, at least in some nephrons. By definition this plasma level is the renal threshold for that substance. Transport maximum is the maximum rate at which the substance can be actively transported (reabsorbed) by the carriers. The units would be something like mg/min and are not displayed on this graph. The amount of splay represents the point where the substance first appears in the urine to the point where all the carriers are saturated and the reabsorption rate is at T_M. This is also not displayed on the graph.

17. Curve f is similar to PAH—freely filtered and completely secreted up to the point of carrier saturation. These substances would be PAH, penicillin, and Diodrast. The carrier for PAH is fairly nonspecific, transporting a large number of nonnatural organic compounds. Curve g is similar to inulin—freely filtered with no net reabsorption or secretion. Clearance will be equal to GFR and independent of plasma concentration. Inulin is the only substance listed, but similar substances would be mannitol and sucrose. Curve h is similar to glucose-filtered and completely reabsorbed until the transport carriers are saturated. This would include glucose, sulfate, ascorbic acid, arginine, ketone bodies, lysine, and phosphate. It would also include calcium although it is not listed. Curve h also is the best answer for albumin and hemoglobin even though very little is filtered under normal conditions.

18. **Ans** C. The clearance of creatinine can be used to accurately estimate GFR in humans, using the excreted amount in 24 hours and the plasma level during the 24 hours. Since plasma creatinine levels are quite constant in any one individual, one or two plasma measurements give an accurate estimate of true plasma levels over the 24-hr period. Recalling the formula Clearance = UV/P, U is 72 mg/100 ml

and $\dot{V}$is 1,600 ml in 24 hr = 1.11 ml/min. The product $U\dot{V}$= 0.72 mg/min X 1.11 ml/min = 0.80 mg/min. Dividing 0.80 mg/min ($U\dot{V}$) by 0.8 mg/100 ml (P) = 100 ml/min.

19. **Ans** B. A. Normally clearance of glucose is less than GFR because glucose is reabsorbed completely in normal individuals.

B. Secretion = Filtration — Excretion. This is false; excretion is determined by what is filtered and substances that are secreted are added to the filtrate. Putting this into a formula, excretion = filtration + secretion, which cannot be arranged like the statement for answer B. To be correct it should be secretion = excretion - filtration.

C. Clearance of PAH decreases as plasma concentration increases to very high levels. This is true. With low levels of PAH, 20% is filtered and the rest secreted so that renal venous plasma has no PAH and the PAH clearance is the same as renal plasma flow. At high plasma levels, 20% is still filtered but the remainder is too great to be completely secreted in a single pass, and a significant amount appears in the renal venous plasma. Since not all was **cleared** in a single pass, the clearance is less than renal plasma flow.

D. Inulin processing is such that what is filtered equals what is excreted. This is true since inulin is only filtered and neither reabsorbed nor secreted.

E. The units of T_M are mg/min (a rate) whereas renal threshold values are mg/ml (a concentration). This is correct. In the case of glucose, the transport max is the maximal filtered load (GFR X plasma glucose) that can be reabsorbed before there is glucosuria. The threshold refers to the plasma level at which glucosuria is observed. The glucose level in the plasma at which glucosuria is observed times the GFR would be the transport maximum.

20. **Ans** C. A. In response to an extracellular fluid volume expansion, $U\dot{V}$for sodium is increased. That is, sodium excretion is increased as a normal compensation to the expansion.

B. In response to an extracellular fluid volume expansion, GFR is increased. This is true and is an important compensation to the expansion to cause more glomerular filtrate and ultimately more urine to be formed, thus reducing the expansion.

C. In response to an extracellular fluid volume expansion, angiotensin II formation is not increased but in fact will be reduced. Angiotensin II formation will increase in response to a reduced extracellular fluid volume contraction.

D. In response to an extracellular fluid volume expansion, atrial natriuretic peptide release will indeed increase. This will cause relaxation of smooth muscle with a reduction in blood pressure as well as interference with the renin-angiotensin-aldosterone system and increased sodium and water loss. ANP will compensate for the increased extracellular fluid volume expansion.

E. In response to an extracellular fluid volume expansion, plasma volume will also expand. This is true and reflects the fact that the plasma compartment is a component of the extracellular space.

21. **Ans** C. A. In response to expansion of the extracellular fluid volume, **renin release will decrease.** Signals which stimulate renin release are those associated with a decreased extracellular fluid volume, i.e., decreased blood pressure, increased sympathetic nerve activity, and decreased flow past the macula densa.

B. In response to expansion of the extracellular fluid volume, **ADH release will decrease.** Volume contraction will stimulate ADH release, which will conserve water and compensate for the decrease in fluid volume. With an expansion of extracellular fluid, the compensation will be to remove water, and increased urine volume by a decrease in ADH release would be expected.

C. In response to extracellular fluid volume expansion, **the fraction of filtered sodium that is excreted will actually increase.** This is because the compensation to the expansion will be to lose solute and water by decreasing the mechanisms conserving sodium and water. These mechanisms include aldosterone and ADH.

D. In response to extracellular fluid volume expansion, **aldosterone release will be decreased.** This is a direct reflection of decreased renin release as explained in A because renin release controls angiotensin II, which stimulates aldosterone release.

E. In response to extracellular fluid volume expansion, **renal sympathetic nerve activity will decrease.** This is largely due to baroreceptor activity, which senses pressure in the carotid sinus. With increased pressure, as would be expected to occur with expanded vascular volume, a decrease in sympathetic nerve activity results.

22. Ans E.

A. Clearance with secretion is not less than but actually greater than the GFR. Secretion adds substances that are filtered (normally 20% is filtered) to the urine space by way of the peritubular capillary.

B. Reabsorption equals filtration minus excretion not excretion minus filtration. Use the generalized formula of what is excreted equals what is filtered minus what is reabsorbed plus what is secreted.

C. That T_M equals the plasma level for appearance in the urine with reabsorption is false. The plasma level for appearance in the urine is the renal threshold, whereas this plasma level times the GFR would give the T_M, the maximal filtered load that can be reabsorbed.

D. Secretion equals filtration minus excretion is not correct. See explanation in B.

E. Clearance of inulin is greater than clearance of some substance that is also reabsorbed. This is correct and is related to answer A. Reabsorption removes substances that are filtered from the urine space and returns them to the blood, so that less appears is the urine than what was filtered. Therefore, less is cleared from the plasma than if there was just filtration.

23. Ans C.

A. No overall evaluation can be made without more information is not correct. Based on the comparison with the GFR, estimates can be made about reabsorption and secretion.

B. The drug is not likely to be reabsorbed since the clearance is greater than with just filtration—with reabsorption one would expect a clearance less than the GFR.

C. This is correct—since the clearance is greater than the GFR, the drug is likely to be secreted.

D. That T_M of the drug has been exceeded, causing clearance to increase above GFR, is not correct. If the drug is reabsorbed then very high plasma levels should result in clearance increasing above what would normally occur at low plasma levels, but clearance with reabsorption would never be as great as the GFR. That is, clearance would never be greater than that due to filtration alone (20% of which is the GFR), and there will always be some reabsorption.

E. That overall processing of this drug is similar to that of amino acids is not correct. Amino acids are totally reabsorbed like glucose, and answer B should be referred to.

24. Ans D.

A. As the plasma levels of PAH increase to high levels such that the T_M is exceeded, PAH clearance does not continue to rise but in fact decreases. As plasma levels increase, less of the total load presented to the kidney is excreted, and therefore less plasma has PAH completely removed from it.

B. As the plasma levels of PAH increase to high levels such that the T_M is exceeded, PAH excretion becomes constant is not correct. As PAH levels in plasma rise, PAH excretion also continues to rise. Remember, excretion is basically urine concentration times urine volume, and assuming volume is constant, concentration increases as plasma levels increase.

C. As the plasma levels of PAH increase to high levels such that the T_M is exceeded, PAH clearance becomes a good measurement of renal plasma flow is not correct. In fact, only when plasma PAH levels are low, when the transport maximum is not exceeded, does the PAH clearance give a good measure of renal plasma flow. With elevated plasma levels where the T_M is exceeded, PAH clearance will be much lower than renal plasma flow.

D. As the plasma levels of PAH increase to high levels such that the T_M is exceeded, the filtered load of PAH increases is correct. Consider answer B where excretion of PAH increases as plasma levels increase, which is a reflection of the increase in filtered load. With GFR constant (assumption) and increasing plasma levels, the filtered load (by definition, the GFR X plasma levels) has to increase.

E. As the plasma levels of PAH increase to high levels such that the T_M is exceeded, PAH clearance approaches excretion is not correct. PAH clearance with very high plasma levels approaches the GFR (gets smaller and smaller), but the excreted amount ($U\dot{V}$) gets larger and larger. At increasing plasma levels, the contribution of secretion to PAH clearance gets smaller and smaller in that more and more appears in the renal vein, which means that less and less of renal plasma coming to the kidney is cleared of PAH per minute.

Regional Transport: Review Questions

Questions 1-2: Select the ONE best answer.

1. Increased blood flow through the vasa recta of the kidney allows less time for equilibrium between the medullary interstitium and the blood. This would be expected to:

A. increase the solute concentration gradient between the medullary interstitial fluid and collecting duct.
B. concentrate the urine.
C. facilitate the action of antidiuretic hormone.
D. reduce the osmolarity of the urine.

2. The following description is most characteristic of which renal tubular segment:

Most of the filtered sodium and water are reabsorbed in this segment. Fluid reabsorption is isotonic. This is the primary site for glucose and amino acid reabsorption. The cells are cuboidal to columnar in appearance, and possess a regular brush border along the luminal surface.

A. proximal tubule.
B. thick ascending limb of Henle's loop.
C. distal convoluted tubule.
D. medullary collecting duct.

Questions 3-11. Select all the correct answers.

3. Which of the following describe glucose reabsorption by the kidney?

A. Secondary active cotransport at the luminal membrane.
B. Characterized by a transport maximum of approximately 200 mg per 100 ml of plasma.
C. The filtered load and reabsorption rate are the same at plasma concentrations below threshold.
D. Active extrusion of glucose across the contraluminal membrane by the Na/K-ATPase.

4. A person in previously normal potassium balance maintains neurotic hyperventilation for several days. During this period, what happens to potassium balance?

A. Hyperkalemia is observed.
B. Aldosterone stimulates potassium reabsorption.
C. Renal excretion of potassium is unchanged.
D. Renal tubular secretion of potassium is increased.

5. Potassium:
   A. reabsorption occurs primarily in the late distal and collecting tubule
   B. excretion would be expected to increase in response to a diuretic which inhibits reabsorption of sodium chloride in the proximal tubule
   C. secretion is under the control of aldosterone, by inhibiting Na/K-ATPase activity in the renal proximal tubule
   D. has a direct effect on cells of the zona glomerulosa of the adrenal cortex to secrete aldosterone

6. Which of the following are cotransported with sodium in the renal proximal tubule?
   A. phosphate
   B. amino acids
   C. glucose
   D. potassium

7. An osmotic diuretic would be expected to:
   A. increase urine flow.
   B. reduce net reabsorption of sodium in the renal proximal tubule.
   C. enhance sodium excretion.
   D. increase back diffusion of sodium in the renal proximal tubule.

8. Reabsorption of filtered bicarbonate:
   A. contributes to excretion of titratable acid.
   B. is reduced during respiratory acidosis, resulting in increased excretion of bicarbonate.
   C. is accomplished by net secretion of sodium.
   D. is enhanced by carbonic anhydrase.

9. If renal tubular carbonic anhydrase were completely inhibited, you would expect increased excretion of which of the following?
   A. sodium
   B. water
   C. bicarbonate
   D. potassium

10. The renal countercurrent multiplier is characterized by:
   A. A low water permeability in the thick ascending limb of Henle's loop.
   B. Permeability of the descending limb of Henle's loop to water.
   C. Active salt reabsorption in the thick ascending limb of Henle's loop.
   D. Tubular fluid in the thick ascending limb of Henle's loop which is more concentrated than the interstitial fluid at that level.

11. An osmotic diuretic would be expected to:

A. Enhance net reabsorption of sodium in the proximal tubule.
B. Increase urine volume.
C. Reduce potassium excretion.
D. Increase back diffusion of sodium in the proximal tubule.

Questions 12-14: Select the ONE best answer.

12. Which of the following structures in the kidney would you expect to be most involved in concentrating the urine?

A. Superficial nephrons.
B. The proximal tubule.
C. Bowman's capsule.
D. The glomerulus.
E. Juxtamedullary nephrons.

13 Which one of the following statements describing sodium processing by the nephron is FALSE?

A. Sodium reabsorption is greatest in the proximal convoluted tubule and thick ascending limb of the loop of Henle.
B. Sodium is reabsorbed with ions other than chloride in the first half of the proximal convoluted tubule.
C. Sodium is cotransported with Cl^- and K^+ in the thick ascending limb of the loop of Henle.
D. Sodium is transported against a high gradient in the distal convoluted tubule.
E. Sodium concentrations are elevated above plasma in the thick ascending limb of the loop of Henle.

14. Formation of concentrated urine is:

A. dependent on the collecting duct being impermeable to water.
B. related to a high urea concentration in the renal cortex.
C. facilitated by a very high vasa recta (medullary) blood flow.
D. associated with a water diuresis.
E. dependent on a high solute concentration in the medullary interstial space.

Regional Transport

1. **Ans D.** Any increase in flow through the medullary region of the kidney, whether it is an increase in vasa recta flow or an increase in flow through the loop of Henle, will tend to reduce medullary osmolarity. This will decrease the ability of the kidney to form a concentrated urine by reducing the ability of ADH to cause water reabsorption in the collecting duct. Remember, the maximum urine osmolarity is determined by the medullary interstitial osmolarity.

2. **Ans** A. In any question involving regional transport that asks where does **most** of the following occur, the correct answer is usually the proximal tubule. This is where most of the filtered substances are reabsorbed. The correct answer can be obtained by simply reading the first sentence.

3. **Ans** A, C. Glucose reabsorption has the characteristics of a T_M system, the cellular mechanism being secondary active transport linked to sodium at the luminal membrane. One characteristic of a T_M system is that everything is reabsorbed when the carriers are not saturated. This would mean, under these conditions, that the filtered load and the reabsorption rate are the same. T_M is the maximum transport rate, which for glucose is measured in mg/min. The plasma level of glucose that produces a filtration rate that overwhelms the carriers is called the renal threshold and is a **concentration** measured in mg per ml of plasma. The Na/K pump at the contraluminal membrane (basal membrane) does not pump glucose directly. Its role is to maintain low intracellular sodium to preserve a large force for sodium entry at the luminal surface.

4. **Ans** D. The hyperventilation produces an alkalosis. As a result, hydrogen ions begin to move slowly from the intracellular compartment to the extracellular space to buffer the alkalosis. To maintain electrical neutrality, K ions increase intracellularly and thus their extracellular concentration tends to decrease, producing, if anything, hypokalemia. The alkalosis also affects secretion in the distal tubule. Since there is an alkalosis, the secretion of hydrogen ions decreases. Since H^+ ions tend to neutralize the intralurninal negative charge in the distal tubule, decreased H^+ secretion preserves a more negative charge in this compartment. This represents a larger force attracting K^+, and thus potassium secretion tends to increase. Aldosterone stimulates sodium reabsorption and potassium secretion.

5. **Ans** B, D. A major factor affecting potassium secretion in the distal tubular region is flow. An increase in tubular fluid flow will increase potassium secretion unless by another mechanism a potassium-sparing effect is produced. The adrenal cortex increases aldosterone secretion in response to All but also directly responds to an increase in potassium concentration of the extracellular fluid. The primary target for aldosterone in the kidney is the distal tubule/collecting duct regions. Reabsorption of potassium occurs mainly in the proximal tubule.

6. **Ans** A, B, C. An important point in class was that amino acids and glucose are cotransported with sodium across the luminal membrane in the proximal tubule. This also applies to phosphate. At the basal membrane there is a sodium/potassium **counter** transport.

7. **Ans** A, B, C,D. An osmotic diuretic holds water within the tubule. This makes it more difficult to reabsorb sodium even though the pumping action of sodium is intact. Since the proximal tubule is fairly leaky to sodium, less of the pumped sodium is reabsorbed and more back diffuses to the tubule. Other substances that follow sodium (potassium and chloride) also remain in the tubule, and overall more fluid and electrolytes will be lost in the urine.

8. **Ans** D. Reabsorption of almost all the filtered bicarbonate occurs in the proximal tubule. This is a neutral system where there is no net gain or loss of bicarbonate from the body. Under normal conditions (acid urine is formed), the proximal tubular reabsorption of bicarbonate does not participate in acid-base regulation. This takes place in the distal tubule/collecting duct region. In any acidosis, reabsorption of bicarbonate would be beneficial and is fully maintained in a respiratory acidosis. Carbonic anhydrase is required for bicarbonate reabsorption, and it plays a role in the proximal and distal tubule/collecting duct regions.

9. **Ans** A, B, C, D. With decreased reabsorption of any substance in the proximal tubule, water is also retained in the tubule. The proximal tubule is fairly permeable to water, and the fluid remains isotonic in this segment. Decreasing water reabsorption makes it more difficult to reabsorb sodium and those substances that follow sodium. Consequently the excretion rates of all the substances listed tend to increase.

10. **Ans** A, B, C. These three statements are true and are important characteristics of the loop of Henle that permit it to act as a countercurrent multiplier. Loss of any one of these characteristics means the medullary interstitial osmolarity will decrease and the kidney's ability to form a concentrated urine will diminish.

11. **Ans** B, D. An osmotic diuretic will diminish the reabsorption of water and secondarily decrease the reabsorption of the major electrolytes, thus increasing their excretion.

12. Ans E. Concentrating the urine depends on the long loops of Henle of the juxtamedullary nephron producing a high osmolarity in the interstitium at the tip of the medulla. Even though the normal functioning of all nephron segments is important, E is the best answer.

13. Ans E

A. Sodium reabsorption is greatest in the proximal convoluted tubule and thick ascending limb of the loop of Henle is correct. Anatomically, this is the location of most sodium reabsorption.

B. Sodium is reabsorbed with ions other than chloride in the first half of the proximal convoluted tubule is correct. Sodium is reabsorbed with glucose and amino acids and organic anions in the first half but then with chloride in the second half.

C. Sodium is cotransported with Cl and K in the thick ascending limb of the loop of Henle is correct. This particular cotransporter can be blocked with the diuretic furosemide, which binds to the Cl site of the cotransporter and results in one of the most powerful diuretics available.

D. Sodium is transported against a high gradient in the distal convoluted tubule is correct. The sodium concentration in this region of the nephron may be very low compared to that of plasma, but the mechanisms available to conserve sodium (aldosterone-induced changes) are very powerful.

E. Sodium concentrations are elevated above plasma in the thick ascending limb of the loop of Henle is incorrect. The loop of Henle is impermeable to water, but significant amounts of sodium chloride are removed so that near the end of the loop, the solute concentration is actually quite dilute—perhaps 100 mOsm/L concentration compared to 300 mOsm/L in plasma.

14. Ans E

A. Formation of concentrated urine is dependent on the collecting duct being **permeable** to water, not **impermeable** to water. Only when the collecting duct is permeable to water will water leave the urine space and go to the more concentrated interstitium. Only in this way will urine become concentrated.

B. Formation of concentrated urine is related to a high urea concentration in the renal **medulla,** not the renal **cortex.** Without high urea concentration (50% of the total solute in the medulla) in the medulla, there is little osmotic pressure to pull water out of the collecting duct and cause the urine to become concentrated.

C. Formation of concentrated urine is facilitated by a **very low vasa recta (medullary) blood flow and not a high vasa recta blood flow.** Increasing vasa recta blood flow will wash out the cortical-medullary concentration gradient.

D. Formation of concentrated urine is associated with a water anti-diuresis and not a water diuresis. Diuresis by definition means increased urine flow and is inconsistent with the formation of concentrated urine.

E. Formation of concentrated urine is dependent on a high solute concentration in the medullary interstitial space. This is true and this high solute concentration causes water in the urine space to leave, thus reducing the volume of the urine. Antidiuretic hormone must be present to cause the collecting duct to be permeable to water.

SECTION VIII

Acid-Base Disturbances

Acid-Base Disturbances

1

① check pH < ↑ alkalosis / ↓ acidosis
② check pCO_2 < ↑ acidosis / ↓ alkalosis — does pCO_2 account for this change?
③ check HCO_3
↳ luruunMr^tJai comp.

normal pH - 1-H
$pCO_2 = 40$
$HCO_3 = 24$
$pO_2 = 100$

INDIVIDUAL DISTURBANCES

What the USMLE Requires You to Know

- Diagnosis of the four primary disturbances
- Diagnosis of a combined disturbance
- Compensations for each primary disturbance
- Davenport diagram
- Anion gap

The Buffering Systems

Specific disturbances in the system regulating H+ can be illustrated by using the equation in Figure VIII-1, which represents the bicarbonate buffer system with all other buffer pairs represented as HBuf/Buf".

The purpose of the regulating system is to control the concentration of H^+ ions, and the concentrations of other elements are of importance only in how they affect H^+ concentration.

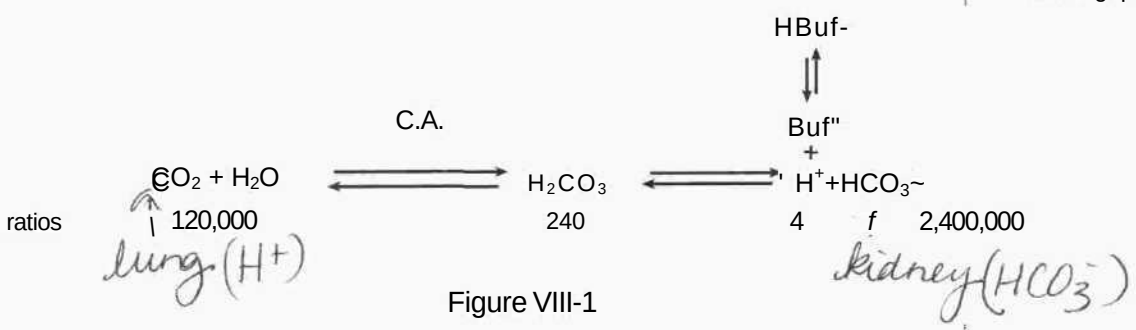


Figure VIII-1

To demonstrate the changes in the major variables during acid-base disturbances, the scheme can be simplified to the following:

pH = 7.35 ↓ ① acidosis
PO_2 = 95 ↓
HCO_3^- = 30 ↑
pCO_2 = 45 ↑ ② acidosis

Md), acidc^i^ UJ//HJ{. compensation

pH = 7.3 ↓
PO_2 = 80 ↓ resp. acidosis
HCO_3 = 18 ↓ combined
PCO_2 = 46 ↑

Reaction 1.

$$CO_2 \ll H^+ + HCO_3^- \quad \text{or} \quad H^+ \propto \frac{PCO_2}{HCO_3^-}$$

A disturbance causes a shift and, in doing so, affects the H^+ concentration, measured as a change in pH (increase H^+ = decrease pH).

THE FOUR PRIMARY DISTURBANCES

Four primary disturbances in the system are recognized, each of which results in an altered concentration of H^+. The basic deviations from normal can be either an acidosis (excess H^+) or an alkalosis (deficiency of H^+), which in either case may be caused by either a respiratory or a metabolic problem.

Respiratory Problems

Respiratory Acidosis

Caused by a decrease in alveolar ventilation relative to the total body production of CO_2 (hypoventilation). The result is an increase in PCO_2, which causes an increase in H^+ (or decrease in pH) and an increase in HCO_3~. Note that for every H^+ produced during the development of respiratory acidosis, one HCO_3~ is also produced. Some rise in HCO_3~ will always occur in uncompensated respiratory acidosis. But in most cases, the HCO_3~ will not rise out of its normal range.

Summary

cause: increase in $PaCO_2$

result: decrease in pH
slight increase in HCO_3~

Respiratory Alkalosis

Caused by an increase in alveolar ventilation relative to body production of CO_2 (hyperventilation). The decrease in CO_2 causes a decrease in H^+ (increased pH) and a decrease in HCO_3~. Note that for every H^+ consumed, one HCO_3~ is also consumed. Some decrease in HCO_3~ will always occur in uncompensated respiratory alkalosis.

Summary

cause: decrease in $PaCO_2$

result: decrease in H^+ (increased pH)
slight decrease in HCO_3~

Metabolic Problems

With the preceding respiratory problems, the cause originated with CO_2 on the left side of reaction 1. With a metabolic problem, the cause originates on the right side of reaction 1. However, the cause can be a consequence of a direct change in either H^+ or HCO_3~. A gain in H^+ as fixed acid (i.e., one not due to a respiratory effect) is equivalent to the direct loss of HCO_3~. Either change will produce the same overall effect on H^+ (or pH). This section looks at the consequences of a metabolic disorder as a gain or loss of H^+, but an equally correct approach would be looking at a loss or gain of HCO_3~.

Also, there is a greater change in HCO_3~ in an uncompensated metabolic disturbance than in an uncompensated respiratory disturbance.

Metabolic Acidosis

Caused by a gain in fixed acid. The increased H^+ forces the reaction to the left, decreasing HCO_3~. Forcing the reaction to the left will produce some CO_2, but, by convention, if there is no respiratory compensation for the metabolic problem, no significant change in arterial PCO_2 is considered to have taken place.

Summary

cause: gain in H^+ as fixed acid (or a loss in HCO_3~ via GI tract or kidney)

result: decrease in HCO_3~

Metabolic Alkalosis

Caused by a loss of fixed acid. The decreased H^+ forces the reaction to the right, increasing HCO_3~.

Summary

cause: loss in H^+ as fixed acid (or a gain in HCO_3~)

result: increase in HCO_3~

DIAGNOSING THE PROBLEM

Summary of the changes in the uncompensated state:

$$CO_2 \Leftrightarrow H^+ + HCO_3^- \quad \text{or} \quad H^+ \propto \frac{PCO_2}{HCO_3^-}$$

Table VIII-1. Summary of the Changes in the Uncompensated State

	CO_2	pH	HCO3-
1. Respiratory acidosis	⇑	⇓	⇑
2. Respiratory alkalosis	⇓	⇑	⇓
3. Metabolic acidosis	no change	⇓	⇓⇓
4. Metabolic alkalosis	no change	⇑	⇑⇑

Understanding the preceding is key to diagnosing an underlying disturbance. The disturbance should be determined first; then, compensatory mechanisms can be evaluated. A specific method of analyzing the data available must be developed. The following is one scheme that works well to determine the underlying disturbance(s).

Normal Systemic Arterial Values

pH = 7.400 PCO_2 = 40 mm Hg HCO3- = 24 mmol/L

Formulation of a Diagnosis

To formulate a diagnosis of the problem(s), one of the two possible pathways is followed, either acidosis or alkalosis.

	acidosis	alkalosis
pH	low	high

RespiratoryComponent

PCO_2	high	low

MetabolicComponent

HCO3-	low	high

Acidosis

If the pH is depressed, it is an acidosis.

If the CO_2 is elevated, there is a respiratory component to the acidosis (but it could also include a metabolic component).

If there is an acidosis and the CO_2 is not elevated, the only possible explanation is the presence of a metabolic acidosis (bicarbonate must be reduced).

If the CO_2 is elevated and the bicarbonate is depressed, it is a combined respiratory and metabolic acidosis.

Alkalosis

If the pH is elevated, it is an alkalosis.

If the CO_2 is depressed, there is a respiratory component to the alkalosis (but it could also include a metabolic component).

If there is an alkalosis and the CO_2 is not depressed, the only possible explanation is the presence of a metabolic alkalosis (bicarbonate must be elevated).

If the CO_2 is depressed and the bicarbonate is elevated, it is a combined respiratory and metabolic alkalosis.

CombinedDisturbances

If the CO_2 and HCO_3~ change in opposite directions, it is a combined disturbance. It is either a combined respiratory and metabolic acidosis or a combined respiratory and metabolic alkalosis.

COMPENSATORY MECHANISMS

Compensation can be via the respiratory system and/or the kidneys.

$CO_2 \Leftrightarrow H+ + HCO3-$

respiratory — renal

variable — variable

$$H^+ \propto \frac{PCO_2}{HCO_3^-}$$

Respiratory Compensation

This will occur only in a metabolic disturbance and can begin almost immediately.

Metabolic acidosis—compensation is a hyperventilation. The hyperventilation reduces CO_2, shifting the reaction to the left and consuming H^+.

Metabolic alkalosis—compensation is a hypoventilation. The hypoventilation increases CO_2, shifting the reaction to the right and producing H^+.

Renal Compensation

This can occur in a respiratory and/or metabolic disturbance. However, if the kidney is the source of the metabolic disturbance, only respiratory compensation will be significant. The kidney has the ability to change plasma bicarbonate. To lower plasma bicarbonate, the kidney excretes HCO_3~ in the urine. To raise plasma bicarbonate, the kidney has the capability to generate new HCO_3~ (distal tubule collecting duct) and secrete it into the general circulation. Renal compensation is slower than respiratory compensation, taking days to fully develop.

Acidosis—compensation is HCO_3~ production by the kidney and its secretion into the circulation. This will shift the reaction to the left and consume H^+. During renal compensation, plasma HCO_3~ should slowly increase.

For every HCO_3~ produced by the kidney, one H^+ will be excreted in the urine (acid urine)

Alkalosis—compensation is HCO_3~ excretion (alkaline urine). This will shift the reaction to the right and generate H^+. During renal compensation, plasma HCO_3~ should slowly decrease.

EXAMPLES OF DISTURBANCES

1.	Arterial	pH	7.3	metabolic acidosis
		PCO_2	30 mm Hg	
		PO_2	95 mm Hg	
	Serum	HCO_3-	14 mEq/L	

A decrease in CO2 below 40 means respiratory compensation via hyperventilation.

If the kidneys are functioning, they would be manufacturing HCO3~ and secreting it into the plasma, and the individual would be forming a very acid urine.

2.	Arterial	pH	7.6	respiratory alkalosis
		PCO_2	20mmHg	
		PO_2	95 mm Hg	
	Serum	HCO_3~	18 mEq/L	

If the kidneys are functioning, they would be dumping HCO_3~ in the urine, and the individual would be forming an alkaline urine.

3. Arterial $_pH$ 7.2 respiratory acidosis
   PCO_2 80 mm Hg
   PO_2 70 mmHg
   Serum HCO3- 30 mEq/L

   If the kidneys are functioning, they would be manufacturing HCO3" and secreting it into the plasma, and the individual would be forming a very acid urine.

4. Arterial pH 7.6 metabolic alkalosis
   PCO_2 48 mm Hg
   PO_2 70 mm Hg
   Serum HCO3- 44 mEq/L

   An increase in CO_2 above 40 means respiratory compensation via hypoventilation.

   If the kidneys are functioning, they would be dumping HCC>3~ in the urine, and the individual would be forming an alkaline urine.

5. Arterial PCO_2 55 mm Hg combined respiratory and metabolic acidosis
   Serum HCO_3- 20 mEq/L

   The only possible compensation would be via the kidney. If the kidneys are functioning, they would be manufacturing HCC>3~ and secreting it into the plasma, and the individual would be forming a very acid urine.

GRAPHICAL REPRESENTATION

The quantitative changes that occur in the acid-base homeostatic system can be represented graphically by the Davenport diagram. The pH units are plotted on the x axis, and HCO_3~ concentration on the y axis. Any point on this graph representing a given pH and HCO_3~ has a fixed value of PCO_2. This can be easily seen by referring to the Henderson-Hasselbalch equation.

$$pH = {}_pK + \log \frac{[HCO3\text{-}1}{aPCO_2}$$

pK = 6.10 [HCO3-] in mmol/L

a = 0.0301 PCO_2 in mmHg

When two variables are known, the third is fixed and can be calculated:

For example, if pH = 7.400 and HCO_3~ = 24 mmol/L, then PCO_2 must be 40 mm Hg. All points can be found on the graph at which the PCO_2 must be 40 mm Hg. All points lying on the locus will form a line referred to as the PCO_2 40 mm Hg isobar. Other isobars can be drawn for other values of PCO_2.

Understanding the graph in Figure VIII-2 will permit the diagnosis of all the primary disturbances.

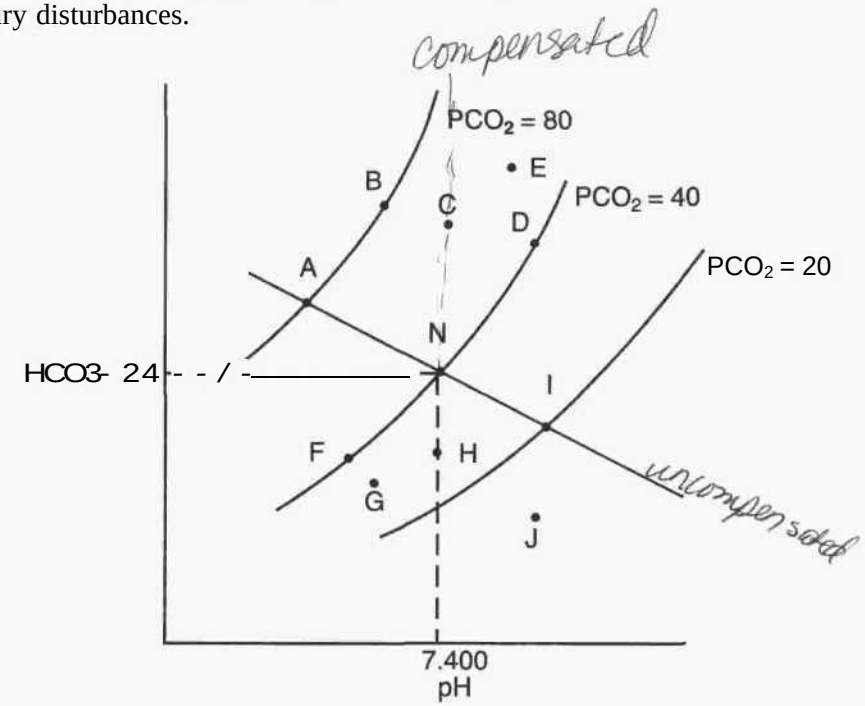


Figure VIII-2

A = uncompensated respiratory acidosis, or acute hypoventilation
B = partially compensated respiratory acidosis
C = completely compensated respiratory acidosis or completely compensated metabolic aikalosis
D = uncompensated metabolic alkalosis
E = partially compensated metabolic alkalosis
F = uncompensated metabolic acidosis
G = partially compensated metabolic acidosis
H = completely compensated metabolic acidosis or completely compensated respiratory alkalosis, or someone who has been living at a high altitude for several weeks
I = uncompensated respiratory alkalosis or acute hyperventilation, or someone who just arrived at a high altitude
J = partially compensated respiratory alkalosis or someone in the process of acclimatization at high altitude

ANION GAP

The total cation charges in the plasma always equal the total anion charges present. However, only major ions are measured when calculating the anion gap. The anion gap is simply due to unmeasured anions.

Cations are estimated as the plasma concentration of the major cation, Na+.

Anions are estimated as the plasma Cl~ and HCO3~.

$[Na\ K] - (HCO_3^- + Cl) = 0 - 12$

Normal Values

Na+ = 140 mEq/L

Cl- = 108 mEq/L

HCO3- = 24 mEq/L

This leads to a normal anion gap of about 5-11 mEq/L. The negative charges on the protein anions account for most of the anion gap. Thus, the normal anion gap must be adjusted downward in hypoalbuminemia.

The anion gap is most useful in diagnosing the cause of a metabolic acidosis. The anion gap will increase initiates in which the acidosis is accompanied by the accumulation of organic anions, e.g., lactic acidosis, ketoacidosis (diabetes), and the ingestion of salicylate.

pH = 7.35
PCO_2 = 35
HCO_3 = 18
AG = 25
most likely
a. DKA
b lactic acidosis
c uremia
d tubular necrosis

LA- MUD PIE

Chapter Summary

Diagnosing the Problem

If the pH is depressed, it is an acidosis.

If the CO_2 is elevated, there is a respiratory component to the acidosis (but it could also include a metabolic component).

If there is an acidosis and the CO_2 is not elevated, the only possible explanation is the presence of a metabolic acidosis (bicarbonate must be reduced).

If the CO_2 is elevated and the bicarbonate is depressed, it is a combined respiratory and metabolic acidosis.

If the pH is elevated, it is an alkalosis.

If the $C0_2$ is depressed, there is a respiratory component to the alkalosis (but it could also include a metabolic component).

If there is an alkalosis and the CO_2 is not depressed, the only possible explanation is the presence of a metabolic alkalosis (bicarbonate must be elevated).

If the $C0_2$ is depressed and the bicarbonate is elevated, it is a combined respiratory and metabolic alkalosis.

Compensation

Respiratory compensation is immediate, but renal compensation is slower, often taking days to fully develop.

The respiratory response to a metabolic acidosis is hyperventilation.

The respiratory response to a metabolic alkalosis is hypoventilation.

The renal response to an acidosis is the excretion of acid and the generation of new bicarbonate.

The renal response to an alkalosis is the excretion of bicarbonate.

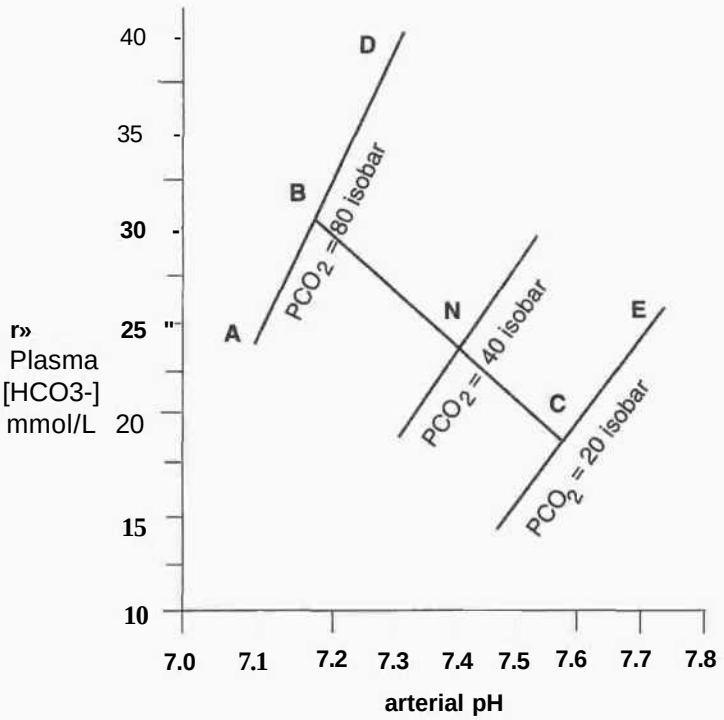
A widening of the anion gap occurs when organic anions accumulate during a metabolic acidosis.

ACID-BASE

Review Questions

Questions 1-6: Select the one best answer.

Question 1.



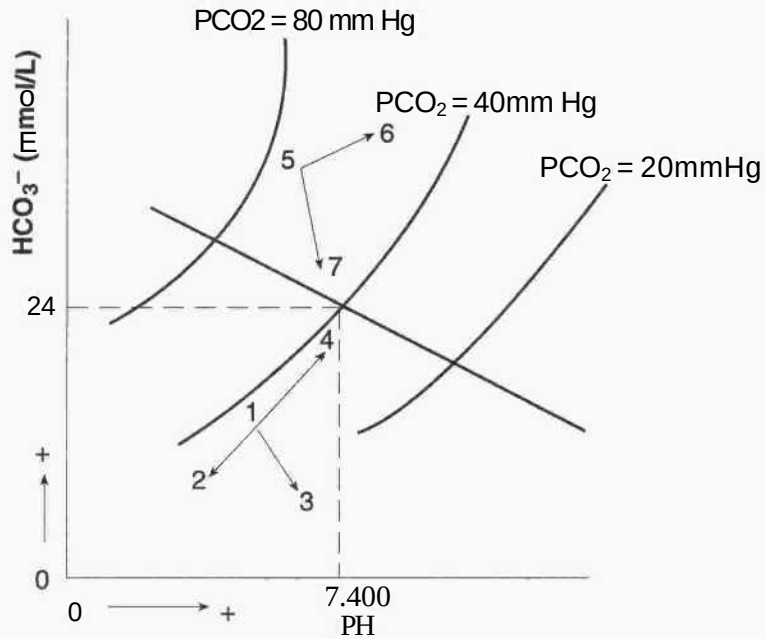
1. From the above graph use letters A-E to answer the following:

   Immediately after a dog's lddneys were surgically removed, his arterial pH, HCO_3~ and PCO_2 correspond to point N on the above graph. The dog is then artificially ventilated for 30 minutes at 50% of his normal respiratory minute volume. To what point on the graph will the dog's HCO_3~ and pH values move?

2. In noncompensated respiratory acidosis:

   A. the usual cause is chronic hyperventilation
   B. the pH of the blood may be normal
   C. blood PCO_2 will be elevated; total blood CO_2 will be elevated
   D. blood PCO_2 will be low; total blood CO_2 will be elevated
   E. blood PCO_2 will be elevated; total blood CO_2 will be low

Question 3



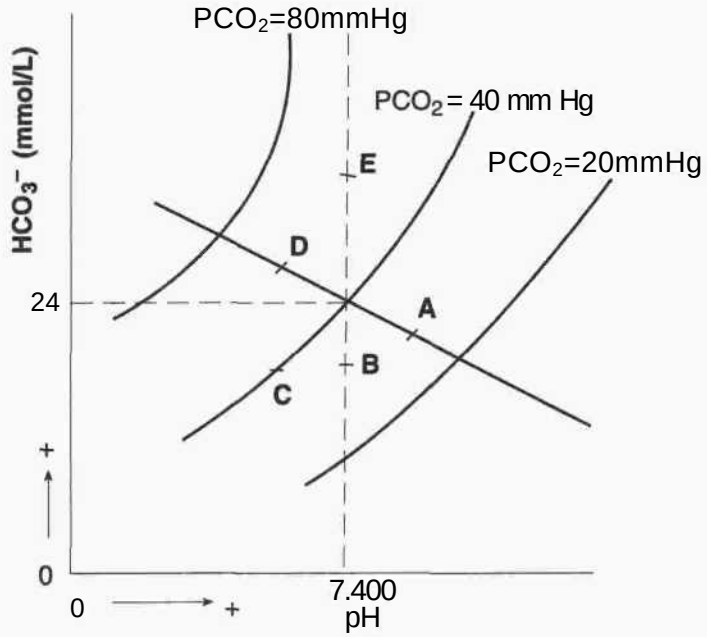
3. Which arrow on the above graph could represent the change in status of an individual with metabolic acidosis who was then given an intravenous injection of sodium bicarbonate?

   A. points 1 to 2
   B. points 1 to 3
   C. points 1 to 4
   D. points 5 to 6
   E. points 5 to 7

4. Partially compensated metabolic alkalosis would be characterized by (systemic arterial blood):

   A. PCO_2>40mmHg
   B. pH>7.40
   C. HCO_3~ > 24 mmol/L
   D. all of the above

Question 5



5. Which point on the above graph would most likely represent the systemic arterial blood of a mountain climber after several weeks at high altitude?

6. An analysis of arterial blood from a patient provides the following data:

   pH = 7.310
   PCO_2 = 35mmHg
   HCO_3- = 17mEq/L

   You can conclude from this information that the individual has:

   A. uncompensated respiratory alkalosis
   B. uncompensated metabolic acidosis
   C. partially compensated respiratory alkalosis
   D. partially compensated metabolic acidosis
   E. combined metabolic and respiratory acidosis

Questions 7-8. Select all the correct answers.

7. In which of the following would you expect plasma bicarbonate to be above normal (>24 mmol/L)?

   A. uncompensated respiratory acidosis
   B. completely compensated respiratory acidosis
   C. uncompensated metabolic alkalosis
   D. uncompensated respiratory alkalosis

8. In which of the following would you expect systemic arterial PCO_2 to be below normal (<40 mm Hg)?

   A. incompletely compensated metabolic acidosis
   B. uncompensated respiratory acidosis
   C. uncompensated respiratory alkalosis
   D. incompletely compensated metabolic alkalosis

Answers

1. AnsB — If ventilation is reduced below normal (hypoventilation), the animal will be in a state of respiratory acidosis. The purpose of removing the kidneys is that renal compensation will not be considered in the answer. Even if they were not removed, it should be remembered that renal compensation has a time period on the order of days. From our discussions in class, the animal would simply move up the buffer line to B in which the PCO_2 doubles, corresponding to a 50% decrease in alveolar ventilation. If the kidneys remained intact, the animal would slowly move from B toward D. Point C would represent acute hyperventilation and respiratory alkalosis.

2. AnsC — Noncompensated respiratory acidosis represents acute hypoventilation. The PCO_2 and the total CO_2 will be elevated. The pH of the blood because of CO_2 retention will definitely be reduced (more acid). If compensation occurred via kidneys, pH would slowly increase toward normal.

3. AnsC — The initial point for the metabolic acidosis is either 1 or 5. Point 5 is an acidosis with an elevated PCO_2 and thus is a respiratory acidosis. Point 1 is in the area for metabolic acidosis and is the correct starting point. The injection of bicarbonate would raise the pH. Point 2 shows a decrease in pH and thus point 1 to point 2 is not correct. Moving to points 4 or 3 shows an increase in pH but moving to point 3 shows a decrease in PCO_2, which means an increase in ventilation was the cause in the pH rise. Also, moving toward point 2 shows a decrease in bicarbonate and if a bicarbonate injection was given, bicarbonate would increase. The only correct possibility is to move from point 1 toward 4 where both pH and bicarbonate levels are increasing.

4. AnsD — In a metabolic alkalosis pH will be elevated (the alkalosis) and characteristically bicarbonate will also be elevated. Partial compensation means the pH is decreasing but is still above 7.4. The respiratory compensation will be a hypoventilation and a PCO_2 above 40 mm Hg. Thus all 3 variables listed will be above normal.

5. AnsB — Going to a high altitude will produce a hyperventilation and acute respiratory alkalosis. The source of the hyperventilation is the low systemic arterial PO_2 stimulating the peripheral chemoreceptors. If the question was the acute problem the correct answer would be A. Over the 2 weeks, however, the kidneys will completely compensate for the problem by dumping bicarbonate in the urine. As a result, the pH will return to normal, point B.

6. **Ans** D

The low pH demonstrates an acidosis. If it was a respiratory acidosis, the PCO_2 would be elevated. Since it is not, the cause cannot be respiratory, therefore the origin must be metabolic. The low bicarbonate confirms that it is metabolic acidosis. The respiratory compensation is a hyperventilation and a decrease in PCO_2. This occurred to a slight extent, and because the pH is not in the normal range, the compensation was only partial or incomplete.

7. **Ans** A, B,C

Bicarbonate will be elevated in any state of respiratory acidosis or metabolic alkalosis. The compensation for respiratory acidosis is for the kidney to raise plasma bicarbonate by absorption in the distal nephron regions. Thus, during the compensation the bicarbonate level will go even higher. Metabolic acidosis is characterized by a decrease in plasma bicarbonate.

8. **Ans** A **and** C

The PCO_2 will be below normal in any state where the individual is hyperventilating. In a metabolic acidosis the pH will be depressed. Respiratory compensation will be to hyperventilate to lower the PCO_2 and raise the pH toward normal. In respiratory alkalosis the cause of the alkalosis is a hyperventilation and the low PCO_2. In uncompensated metabolic acidosis, ventilation remains normal and thus PCO_2 remains close to normal. In metabolic alkalosis the pH is elevated. The respiratory compensation will be hypoventilation and CO_2 retention. This will decrease pH back toward normal.

SECTION IX

Endocrinology

Mechanism of Hormone Action

Note: Hormonal action is such a pervasive subject that information is presented in several chapters and books. As might be expected, this chapter emphasizes the physiological action of the endocrine hormone. In contrast, the molecular action of hormones is emphasized in the biochemistry book. The properties and actions of the endocrine and other hormones can also be found in the discussion of relevant systems throughout these books.

What the USMLE Requires You to Know

- The differences between lipid-soluble and water-soluble hormone systems
- What normally determines hormone activity and the consequences of receptor down-regulation
- The concept of permissive action

GENERAL CHARACTERISTICS

Lipid- versus Water-Soluble Hormones

Figure DC-1-1 demonstrates several major differences between the lipid-soluble hormones and the water-soluble hormones.

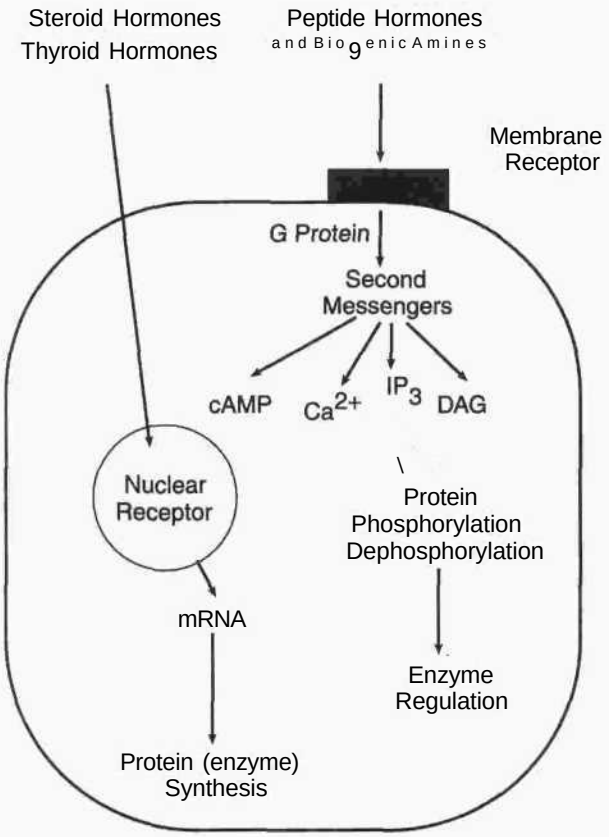
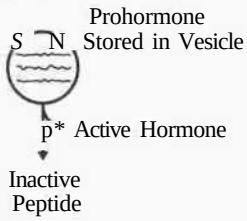


Figure 1X-1-1

Table IX-1-1. A Summary of the Differences Between the Two Major Classes of Hormones

	Lipid-Soluble Hormones (steroids, thyroid hormones)	Water-Soluble Hormones (peptides, proteins)
Receptors	Inside the cell, usually in the nucleus	Outer surface of the cell membrane
Intracellular action	Stimulates the synthesis of specific new proteins	Production of second messengers, e.g., cAMP Insulin does not utilize cAMP, instead activates membrane-bound tyrosine kinase Second messengers modify action of intracellular proteins (enzymes)
Storage	Synthesized as needed Exception: thyroid	Stored in vesicles Prohormone stored in vesicle along with an enzyme that splits off the active hormone 
Plasma transport	Attached to proteins that serve as carriers Exceptions: adrenal androgens	Dissolved in plasma (free, unbound)
Half-life	Long (hours, days) « to affinity for protein carrier	Short (minutes) « to MW

Protein-Bound and Free Circulating Hormones

The liver produces proteins that bind lipid-soluble hormones, e.g.,

Cortisol-binding globulin

Thyroid-binding globulin

Estrogen/testosterone-binding globulin

Equilibrium

Most of the lipid-soluble hormones circulating in plasma are bound to protein, in equilibrium with a small amount of free hormone. It is the free form that is available to the tissues, and thus the free unbound form normally determines the plasma activity. It is the free form that also creates negative feedback. This equilibrium is shown in Figure IX-1-2.

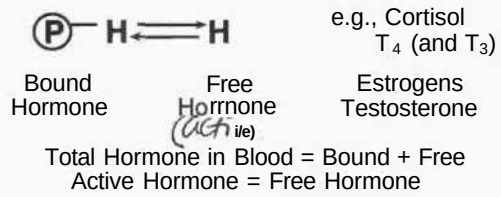


Figure IX-1-2. Transport of Lipid-Soiuble Hormones

The Role of the Liver

If the liver changes its production and release of binding proteins, the circulating level of **j^Qund_hojmfinewill change.** However, under most conditions the level of **free hormonewill remain constant.**

Modulation

Liver dysfunction and androgens can decrease and estrogens can increase the circulating level of binding proteins. For example, a rise in circulating estrogen causes the release of more binding protein by the liver, which binds more free hormone. The transient decrease in free hormone reduces negative feedback to the hormone-secreting tissue. The increased secretion of free hormone quickly returns the plasma free hormone to normal.

This explains why duringpiggjiaacy-arulother states with a rise ir^estroggaieyels:

- Total plasma lipid-soluble hormone increases.
- Free plasma hormone remains constant at a normal level; thus, the individual does not show signs of hyperfunction.

PROPERTIES OF RECEPTORS

Hormone Specificity

A hormone affects only cells that possess receptors specific to that particular hormone.

For example, adrenocorticotropic hormone (ACTH) and luteinizing hormone (LH) both increase the secretion of steroid hormones. However, ACTH does so only in the adrenal cortex and LH only in gonadal tissue.

Hormone Activity

Under normal conditions, receptors are not saturated; that is, extra receptors exist. Therefore:

- Normally, the number of hormone receptors is not rate-limiting for hormone action.
- Plasma concentration of free hormone is usually indicative of activity.

Chronic high circulating levels of a hormone can cause the number of receptors on a hormone's target cell to decrease (a phenomenon known as down-regulation, or tissue resistance).

- In this situation, the number of receptors can dictate hormonal activity, such as in type 2 (maturity onset) diabetes mellitus.
- Once saturated, it is the number of receptors that determines activity.

Permissive action: A phenomenon in which ongjype of hormone must be present before another hormone can act; for example, to prevent hypoglycemia, cor ; tisol must be present fqr_glucagonjojarr)^out glycogenolysis.

we always have extra receptors so they are not rate limiting the concent. of hormone is rate limiting.

Chapter Summary

Lipid-soluble endocrine hormones: Receptors are inside cells. Because they must be synthesized as needed and must generate new proteins to carry out their actions, they represent slow-acting systems. The total plasma level does not necessarily provide an index of activity because most is bound. It is the free hormone that determines activity.

Water-soluble hormones: Receptors are on the membrane surface. Second messengers carry out intracellular action. Because they are stored in vesicles and need only to modify proteins to carry out their actions, they are fast-acting systems.

Normally, receptors are not saturated. It is the plasma level of free hormone that determines activity.

The Hypothalamic-Anterior Pituitary System

2

Which of foll. not synthesized in ventromedial arcuate nuclei?
gonadotropin releasing hormone (preoptic nuclei)

JA

GENERAL FEATURES

The hormones in this system are all water-soluble. The hypothalamic hormones are synthesized in the neuron cell body, packaged in vesicles, and transported down the axon to be stored and released from the nerve terminals. The major hypothalamic hormones and their targeted pituitary hormones are summarized in Figure IX-2-1.

What the USMLE Requires You to Know

- Site of synthesis, storage, and release of neurohormones
- The hypothalamic hormones that regulate anterior pituitary function
- The consequences of pituitary stalk damage versus an inherent hypofunctioning anterior pituitary
- The functional implications of the pulsatile nature of this system

The Major Hypothalamic Hormones and Their Targeted Pituitary Hormones

Pre^tg, Region

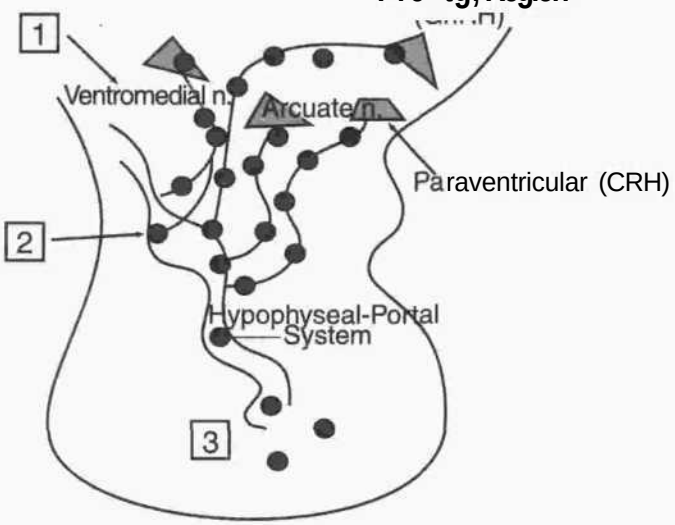


Figure IX-2-1

A yg. woman was brought into ER for headache & MRI shows [illegible] in brain. Menstrual irreg., popliteal edema

1. The hypothalamic hormones, thyrotropin-releasing hormone (TRH), corticotropin-releasing hormone (CRH), growth hormone releasing hormone (GHRH), somatostatin, and prolactin-inhibiting factor (PIF) are synthesized in neuronal cell bodies in the ventromedial, arcuate, and paraventricular nuclei; gonadotropin-releasing hormone (GnRH)is synthesized in the preoptic nucleus.
2. The nerve endings all come together in the median eminence region of the hypothalamus. The hormones are then secreted into the hypophyseal-portal system and transported to the anterior pituitary.
3. Hypothalamic hormones bind to receptors on cells of the anterior pituitary and modify the secretion of thyroid-stimulating hormone (TSH) (thyrotropin), corticotropin (ACTH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), growth hormone (GH), and prolactin.

thyroid hormones are non pulsatile

The Effect of Each Hypothalamic Hormone on the Anterior Pituitary

A 3rd yr. neurosurgical resident severed the
What would you expect?
you are removing inhibition of PIF so ↑ Prolactin

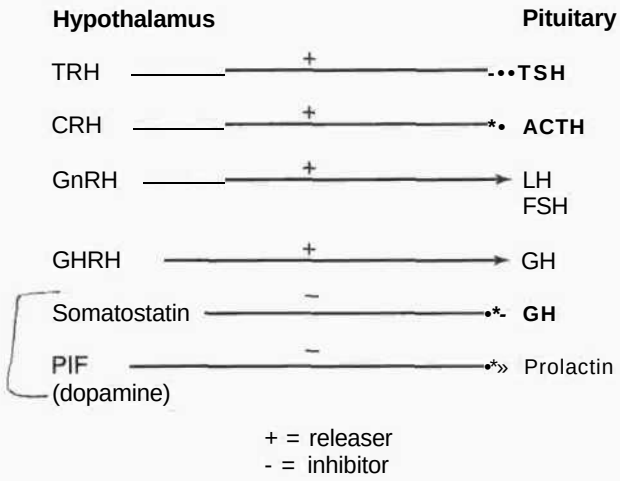


Figure IX-2-2

TRH = thyrotropin-releasing hormone
TSH = thyroid-stimulating hormone or thyrotropin
CRH = corticotropin-releasing hormone
ACTH = adrenocorticotropic hormone or corticotropin
GnRH = gonadotropin-releasing hormone
LH = luteinizing hormone
FSH = follicle-stimulating hormone
GHRH = growth hormone releasing hormone
GH = growth hormone
PIF = prolactin-inhibiting factor

DAMAGE TO THE PITUITARY STALK

When the connection between the hypothalamus and the anterior pituitary is severed (e.g., damajge_tg_jhe_pitjutajxjtalk)> secretion of all anterior pituitary hormones decreases, except prolactin, which increases. The secretion of prolactin increases because a chronic source of inhibition (PIF) has been removed.

The fact that growth hormonejdeciease^demonstrates that the main factor regulating the release of growth hormone is the releasing factprGHRH.

GONADOTROPH DOWN-REGULATION

In the hypothalamic-anterior pituitary system, hormonal release is mainly pulsatile. A possible exception is the thyroid system.

The pulsatile release of GnRH prevents down-regulation of its receptors on the gonadotrophs of the anterior pituitary. Axgnstant infusion of GnRH will cause a decrease in the release of both LH and FSH.

Chapter Summary

Hypothalamic hormones affecting the pituitary are synthesized in the ventromedial, arcuate, and preoptic nuclei but are stored and released from the median eminence.

Anterior pituitary hormones are regulated primarily by hypothalamic releasing hormones, except prolactin, which is mainly under the influence of PIF, an inhibiting hormone.

The pulsatile release of GnRH prevents down-regulation of gonadotroph receptors.

Clinical Correlate

Sheehan's Syndrome

The pituitary in pregnancy is enlarged and therefore more vulnerable to infarction.

Sometimes when delivery is associated with severe blood loss, the ensuing shock causes arteriolar spasm in the pituitary with subsequent ischemic necrosis*

Some degree of hypopituitarism has been reported in 32% of women with severe postparlum hemorrhage.

Symptoms vary, depending on the extent and location of pituitary damage.

Clinical Correlate

Hyperprolactinemia

May result from medications (dopamine antagonists) or diseases affecting hypothalamus or pituitary stalk, such as prolactin-secreting adenomas in the anterior pituitary.

In women, produces amenorrhea (suppresses normal pulsatile pattern of GnRH. release and prevents positive feedback effects of estrogen and subsequent LH surge and sometimes gajaslooJiea (inappropriate production of milk). Serum levels of estradiol are usually decreased.

In men, may produce galactorrhea, decreased libido, impotence, and hypogonadism. Serum levels of testosterone are usually decreased.

Treatment includes surgical removal of tumor or medical treatment with_brornocriptine (dopamine agonist).

Adrenal Hormones

3

LAYERS OF THE ADRENAL CORTEX AND THEIR ROLE IN HORMONE FORMATION

Anatomy

General Features

Figure IX-3-1 summarizes each adrenal region.

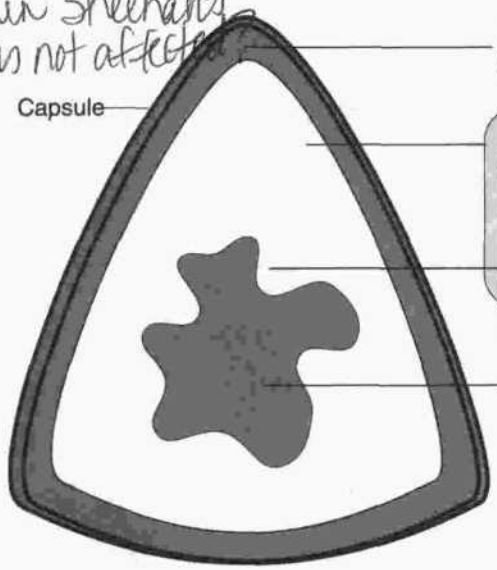
ACTH controls the release of both cortisol and adrenal androgens.

Although a separate hormone that affects adrenal androgens has been proposed, it has not been characterized.

Also, the main factor regulating aldosterone secretion is angiotensin II.

What the USMLE Requires You to Know

- The consequences of the loss of each adrenal region
- The loss of adrenal function versus the loss of anterior pituitary function
- The major congenital enzyme deficiencies in steroid hormone synthesis
- The actions and regulation of glucocorticoids
- Primary and secondary disorders of glucocorticoid secretion
- The major physiological actions of aldosterone
- The renin-angiotensin-aldosterone system as a major long-term regulator of blood pressure
- Primary disorders of mineralocorticoid secretion
- Venous congestion as an example of secondary hyperaldosteronisrfi



REGION	HORMONES	CONTROLLED BY
Zona Glomerulosa	Aldosterone	Angiotensin II, $[K^+]$
Zona Fasciculata	Cortisol	ACTH
Zona Reticularis	Androgens	ACTH
Medulla	Epinephrine	Autonomic Nervous System

(LH has no effect on the production of adrenal androgens)

Figure IX-3-1

Consequences of the Loss of Regional Adrenal Function

Zona glomerulosa: The absence of the mineralocorticoid, aldosterone, results in:

- Loss of Na^+
- Decreased volume of the ECF
- Low blood pressure
- Circulatory shock
- Death (Mineralocorticoid is generally required for survival.)

Zona fasciculata, zona reticularis: The **absence of the** glucocorticoid, **cortisol,**

- Circulatory failure, because without cortisol, catecholamines do not exert their normal vasoconstrictive action.
- An inability to readily mobilize energy sources (glucose and free fatty acids) from glycogen or fat. Under normal living conditions, this is not life-threatening; however, under stressful situations, severe problems can arise. For example, fasting can result in fatal hypoglycemia.

Medulla: The **absence of the** catecholamine, **epinephrine** (the major hormone of the adrenal medulla):

- Decreases the capacity of the individual to mobilize glycogen or fat during exercise or cold exposure; however, the adrenal medulla is not essential for survival.

Note: If problems develop with anterior pituitary secretion, glucocorticoid secretion may be affected, but the mineralocorticoid system remains intact.

BIOSYNTHETIC PATHWAYS OF STEROID HORMONE SYNTHESIS

The Synthetic Pathways

Overview

Figure IX-3-2 shows a composite of the synthetic pathways in all steroid hormone-producing tissues. A single tissue has only the pathways necessary to produce the hormones normally secreted by that particular tissue. For example, the zona glomerulosa has only the pathways of the first column because the main output of the zona glomerulosa is aldosterone.

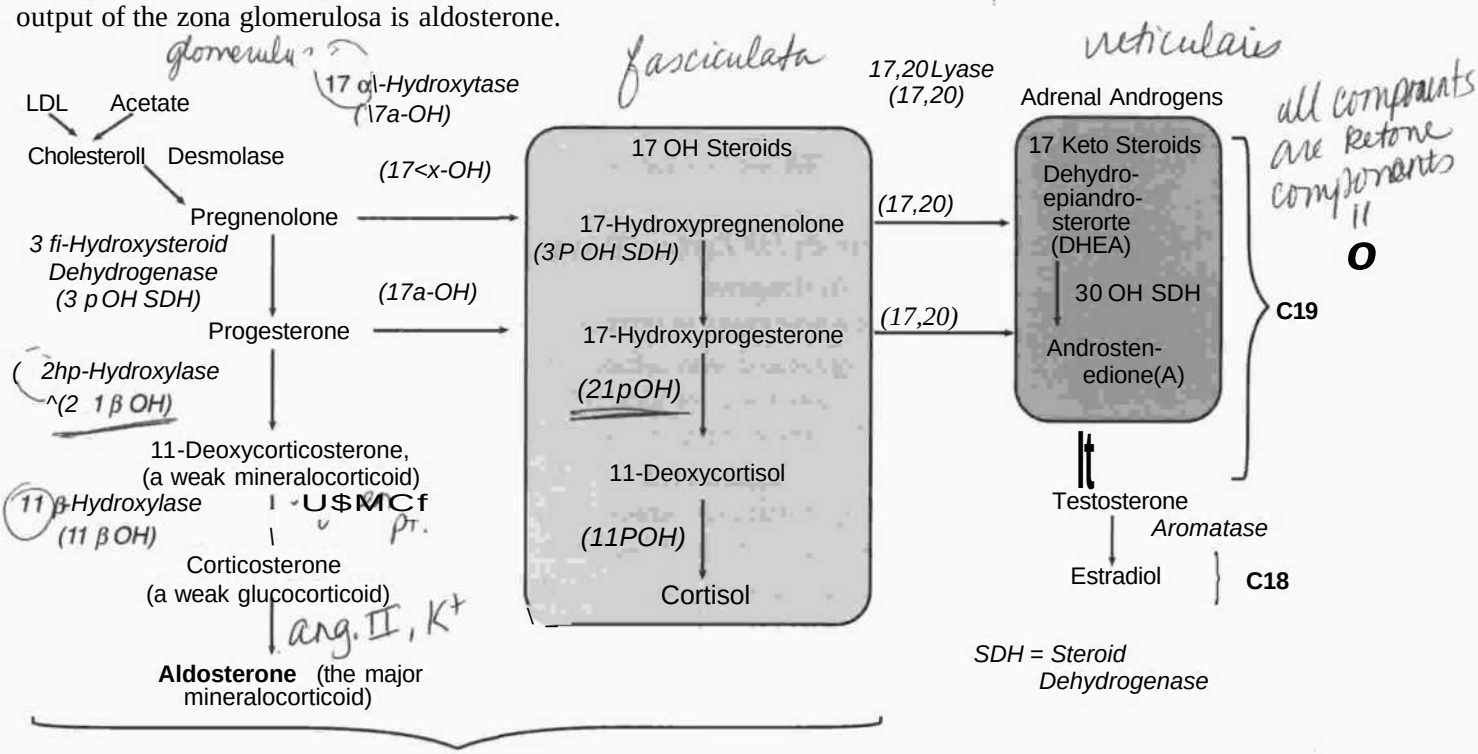


Figure IX-3-2

C21 Steroids (21 Carbon Atoms)

C21 steroids with an OH at position 17 are called 17-hydroxysteroids. The only 17 OH steroid with hormonal activity is cortisol.

The lipid-soluble 17 OH steroids are metabolized to water-soluble compounds before they are filtered and excreted in the urine. The pathway for cortisol is shown in Figure IX-3-3.

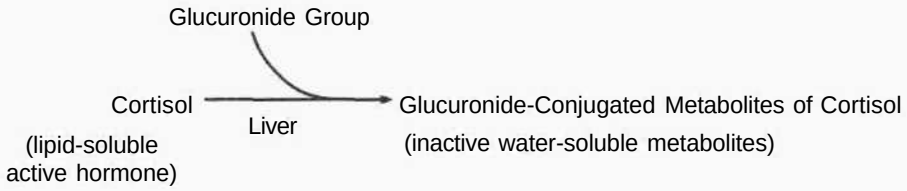


Figure IX-3-3

Urinary 17 OH steroids are usually an index of cortisol secretion.

C19 Steroids (19 Carbon Atoms)

Adrenal Androgens

Have a keto group at position 17 and therefore are called 17-ketosteroids.

Are conjugated with sulfate in the adrenal cortex, making them water soluble. As water-soluble metabolites, they circulate in the bloodstream, are filtered by the kidney, and are excreted in the urine.

The major secreted form is dehydroepiandrosterone (DHEA), a weak androgen that masculinizes only when secreted in excessive amounts in women or in prepubertal males.

Although adrenal androgen is the precursor of the potent androgen testosterone, normally little is produced in the adrenals because the enzymes necessary for the conversion are not present. For the same reason, estradiol secretion by the adrenal is small.

Testosterone

Produced mainly by the Leydig cells of testes.

The active hormone is lipid-soluble and not a 17-ketosteroid.

When metabolized, it is converted to a 17-ketosteroid and conjugated to become water soluble. In this form, it is filtered and excreted by the kidney.

Urinary Excretion

Urinary 17-ketosteroids are an index of all androgens, adrenal and testicular.

In females and prepubertal males, urinary 17-ketosteroids are an index of adrenal androgen secretion.

In adult males (postpuberty), urinary 17-ketosteroids are 2/3 adrenal, 1/3 testicular, and thus mainly an index of adrenal secretion.

C18Steroids—Estrogens(e.g.,Estradiol)

Aromatase converts androgen into estrogen.

Regional Synthesis

ConversionofCholesteroltoPregnenolone

The starting point in the synthesis of all steroid hormones is the conversion of cholesterol to pregnenolone.

The enzyme catalyzing this conversion is desmolase. This is a rate-controlling step in all steroid hormone synthesis.

SynthesisintheZonaGlomerulosa

Figure IX-3-4 represents the pathways present in the zona glomerulosa. Angiotensin II is the main stimulus to the zona glomerulosa, which produces aldosterone, the major mineralocorticoid.

Note

Remember that in each steroid-producing tissue only the enzymatic-catalyzed pathways necessary for the synthesis of its normally secreted hormones are present.

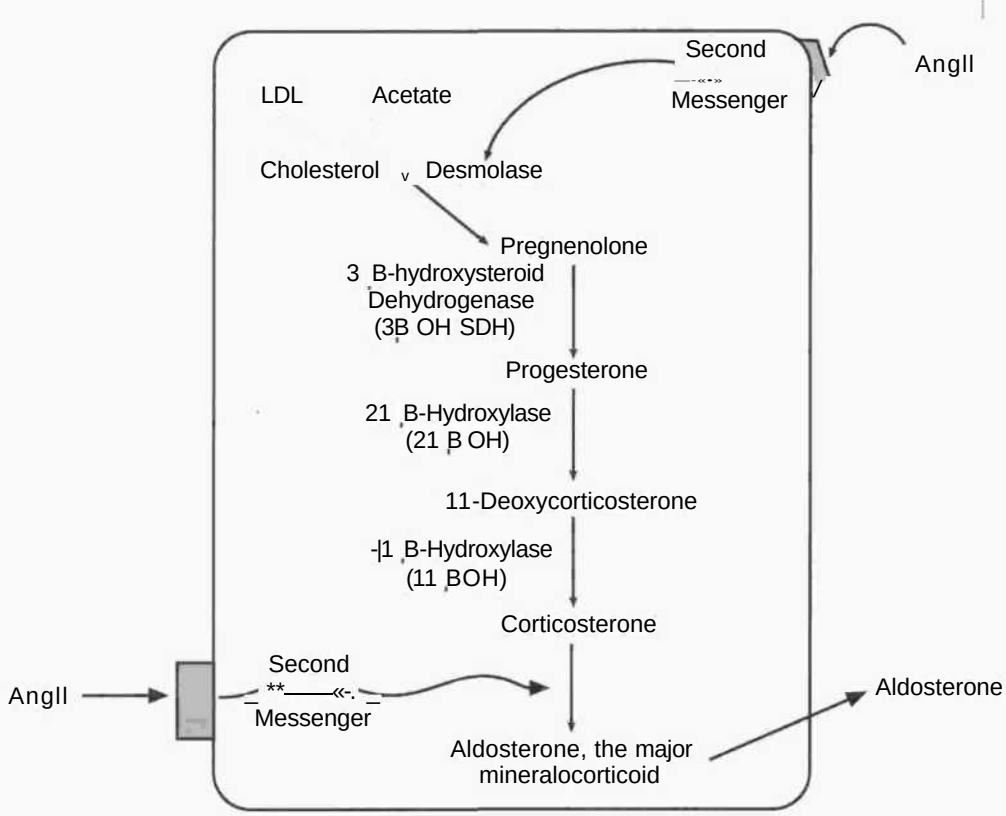


Figure IX-3-4

Synthesis in the Zona Fasciculata and the Zona Reticularis

Figure IX-3-5 represents the control of steroid hormone synthesis in the zona fasciculata and the zona reticularis.

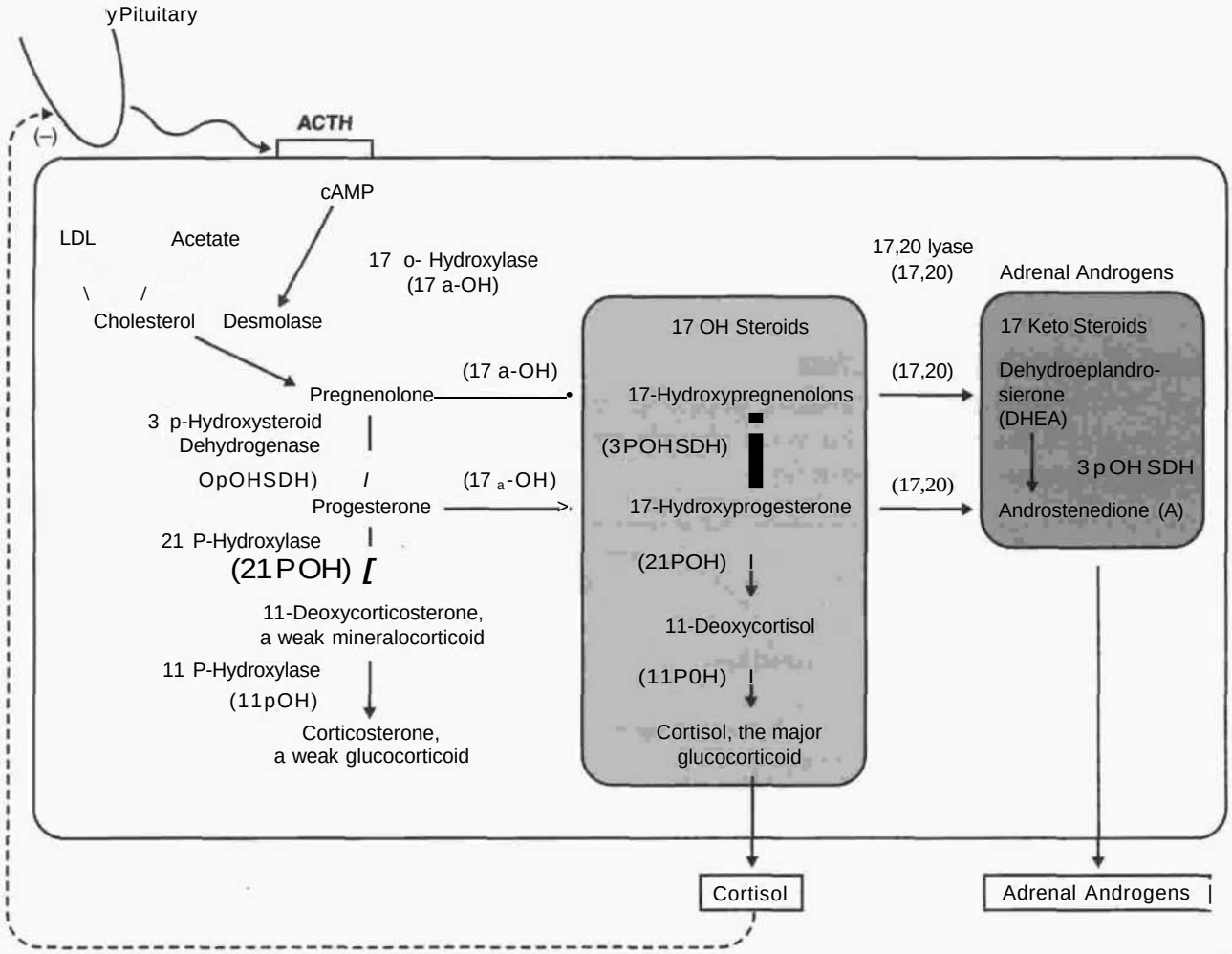


Figure IX-3-5

Note

3 p OH steroid dehydrogenase (SDH), 2ip-hydroxylase (21 p OH), and lip-hydroxylase (11 p OH) are required for conversions in the first and second columns.

Normal hormonal output consists of the following:

11-Deoxycorticosterone: Under normal conditions, this weak mineralocorticoid is not important. Almost all mineralocorticoid activity is due to aldosterone.

Corticosterone: Also not important under normal conditions. Almost all glucocorticoid activity is due to cortisol.

Adrenal androgens: These weak water-soluble androgens represent a significant secretion; however, they produce masculinizing characteristics only in women and prepubertal males when secretion is excessive.

Cortisol: Main glucocorticoid secreted by the adrenal cortex, responsible for most of the hypothalamic and anterior pituitary negative feedback control of ACTH secretion.

ENZYME DEFICIENCIES

Single enzyme defects can occur as congenital "inborn errors of metabolism." Congenital defects in any of the enzymes leads to **deficient cortisol secretion** and the syndrome called *congenital adrenal hyperplasia.* In all of the following examples, assume the deficiency is significant to the extent that it affects normal hormonal production but not a complete blockade.

21 (3-Hydroxylase Deficiency

Tissues affected: zona glomerulosa, zona fasciculata, zona reticularis.

Effect in the Zona Glomerulosa

Blockade Point

Figure IX-3-6 illustrates the blockade point in the zona glomerulosa.

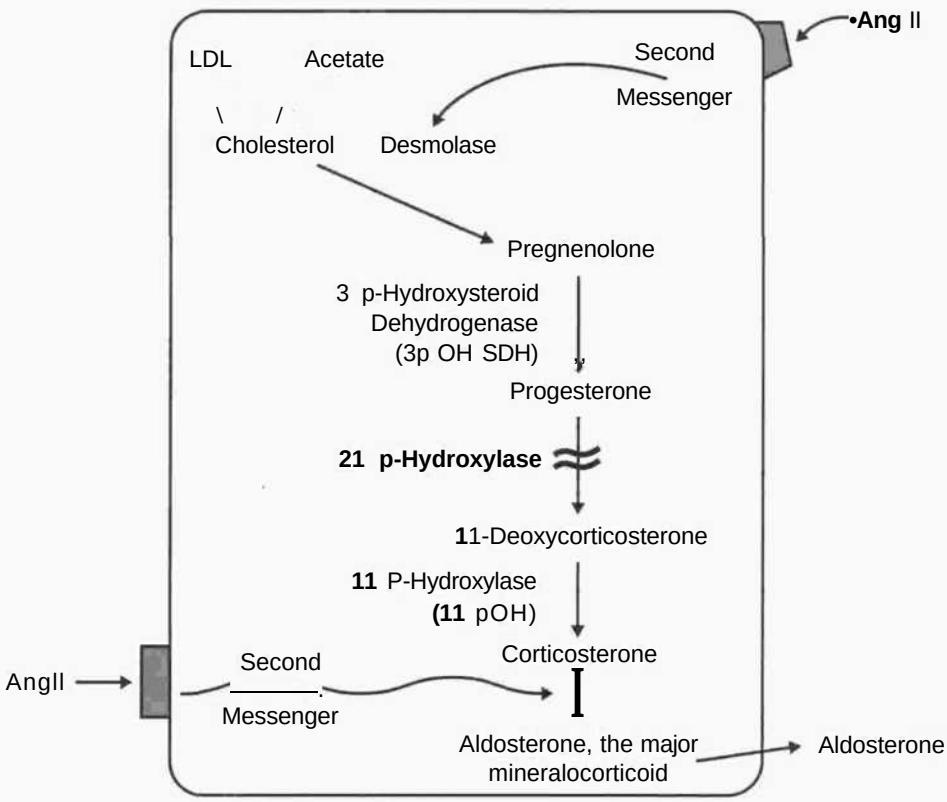


Figure IX-3-6

Consequence

The result is decreased production of aldosterone, the main mineralocorticoid.

21 β Hydroxylase def.
↓ mineralocorticoid
= ↓ bp hypotension
= ↑ hr ↑ androgens
↓ cortisol
↑ ACTH

Effect in the Zona Fasciculata and Zona Reticularis

Blockade Points

Figure IX-3-7 shows the two blockade points (wavy lines) in the zona fasciculata and zona reticularis.

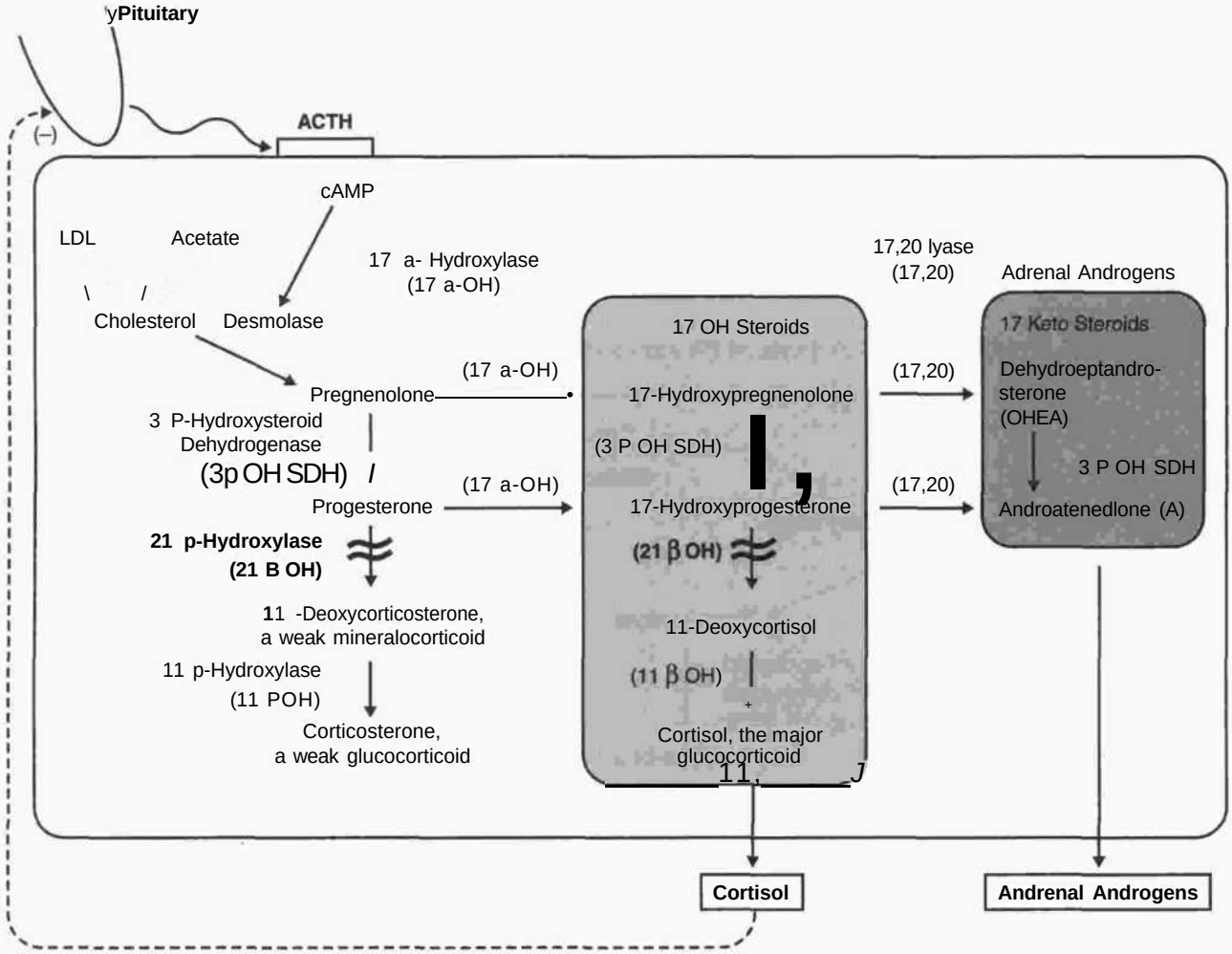


Figure IX-3-7

Consequences

Decreased production of 11-deoxycorticosterone, a weak mineralocorticoid. Therefore, a major problem with this disorder is **mineralocorticoid** deficiency, which results in the following:

- Loss of Na^+
- Decrease in the extracellular volume
- Decreased blood pressure

Increased renin secretion by the kidney and increased circulating angiotensin II.

Decreased production of corticosterone, a weak glucocorticoid, and cortisol, the main glucocorticoid. Therefore, another problem is **glucocorticoid deficiency.**

Loss of feedback on the pituitary by cortisol, which causes:

- Increased secretion of ACTH
- Increased stimulation of the adrenals, producing hyperplasia
- Excessive production of steroids above the blockade, including androgens
- **Excessive adrenal** androgen production leads to the virilizing syndrome in females and effects on prepubertal males.

11 p-Hydroxylase Deficiency

Tissues affected: zona glomerulosa, zona fasciculata, zona reticularis.

Effect in the Zona Glomerulosa

Blockade Points

Figure IX-3-8 illustrates the blockade point in the zona glomerulosa.

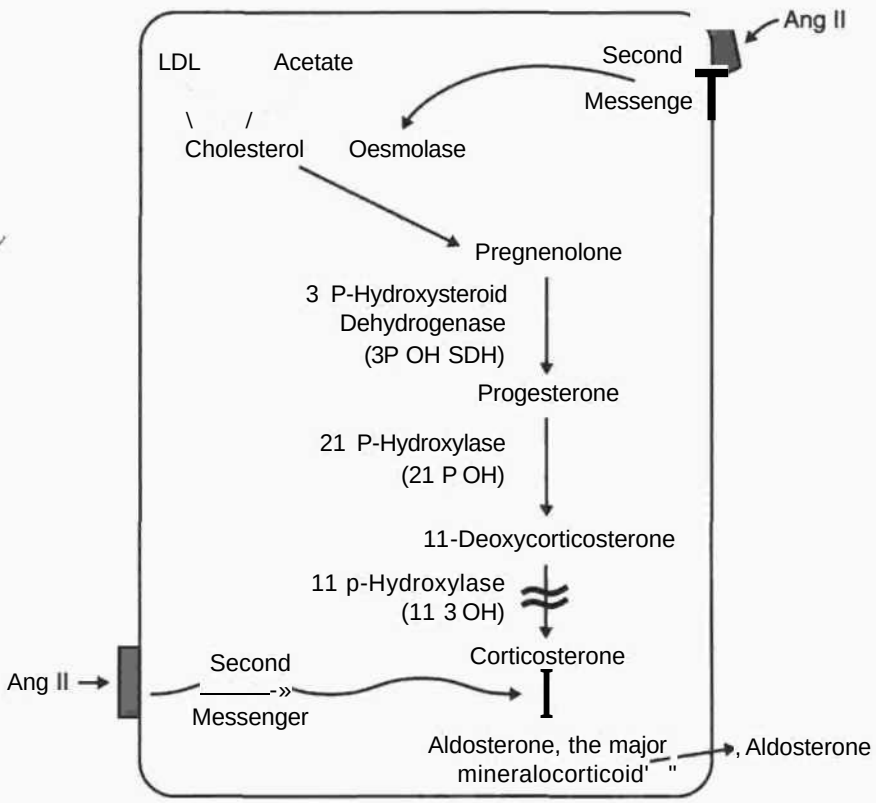


Figure IX-3-8

Consequence

A decreased ability to produce aldosterone, the main mineralocorticoid.

***Effect in the Zona** Fascicutata **and Zona** Reticularis*

Blockade

Figure IX-3-9 illustrates the blockade in the zona fasciculata and zona reticularis.

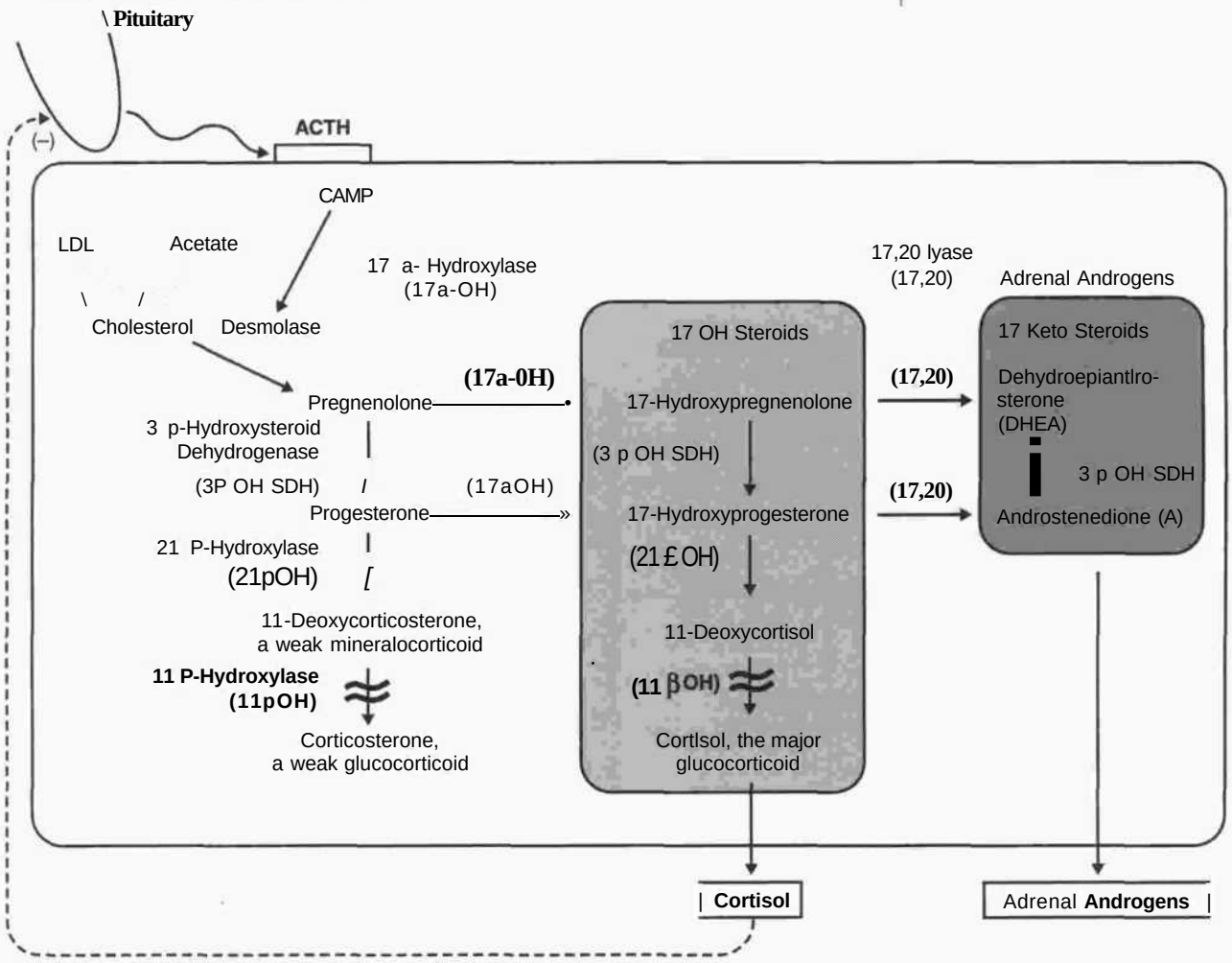


Figure IX-3-9

Consequence

Decreased production of corticosterone, a weak glucocorticoid, and cortisol, resulting in increased secretion of ACTH due to loss of feedback on the pituitary. The excess ACTH induces increased stimulation of the adrenals, producing hyperplasia and excessive production of steroids above the blockade, including:

11-Deoxycorticosterone, normally a weak mineralocorticoid. Excessive mineralocorticoid leads to Na^+ retention, increased volume of ECF, and a **rise in blood pressure.** The rise in blood pressure reduces plasma renin and angotensin II.

Androgens. **Excessive adrenal androgen** production leads to virilizing syndrome in females and effects on prepubertal males.

17 a-Hydroxylase Deficiency

Blockade in the Adrenal Zona Fasciculata and the Zona Reticularis

Figure IX-3-10 illustrates the blockade points in the zona fasciculata and zona reticularis.

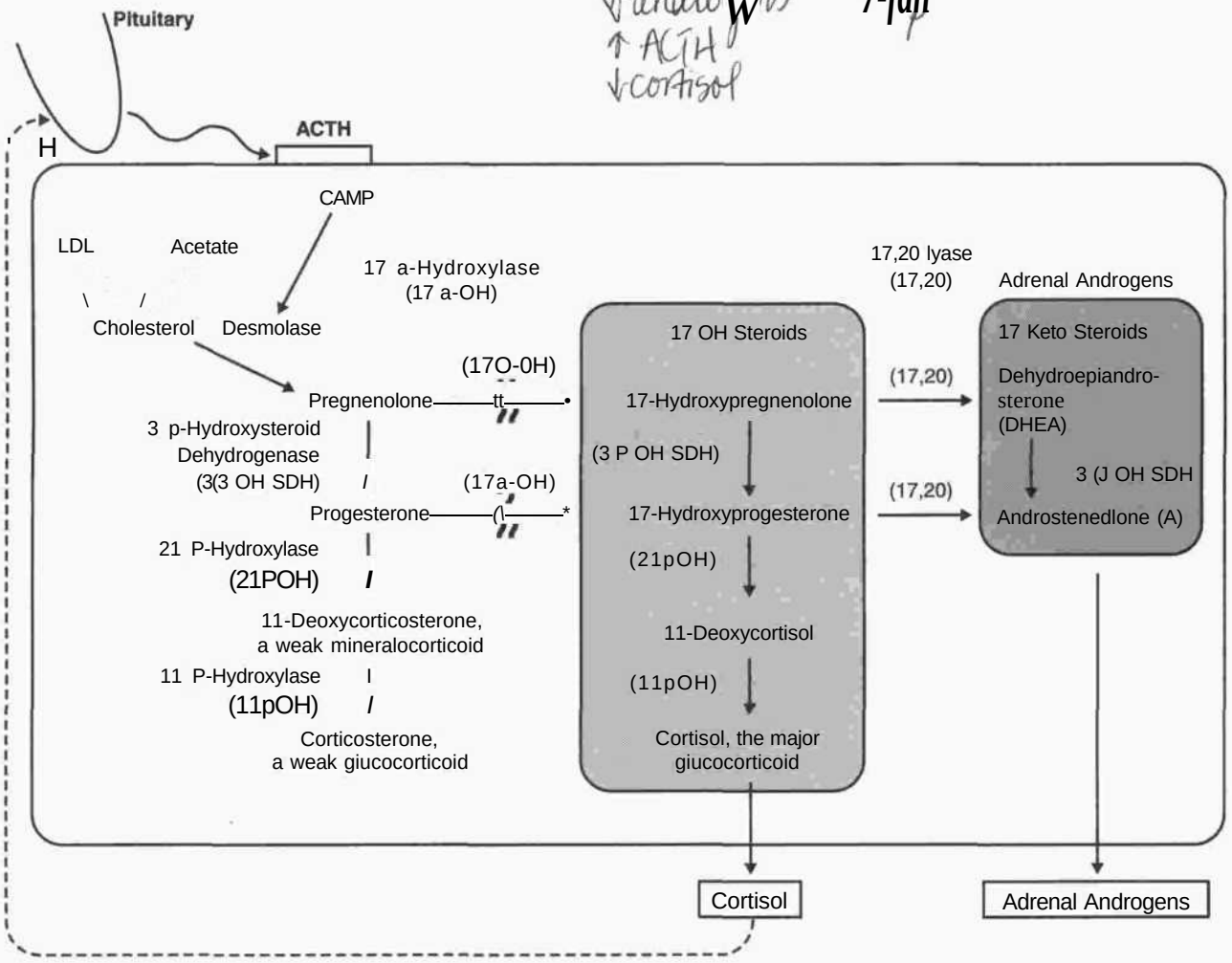


Figure IX-3-10

Consequence

Decreased production of cortisol and adrenal androgens, resulting in increased secretion of ACTH due to loss of feedback on the pituitary.

The excess ACTH increases stimulation of the adrenals, producing hyperplasia and excessive production of steroids before the blockade. These steroids include:

11-Deoxycorticosterone: Although normally a weak mineralocorticoid, excessive production of mineralocorticoid leads to Na^+ retention, increased

volume of ECF, and a **rise in blood pressure.** The rise in blood pressure reduces plasma renin and angiotensin II levels.

Corticosterone, which helps replace the loss of glucocorticoid activity.

Effect in the Testes

Blockade Points

Figure IX-3-11 illustrates the blockade points in the testes.

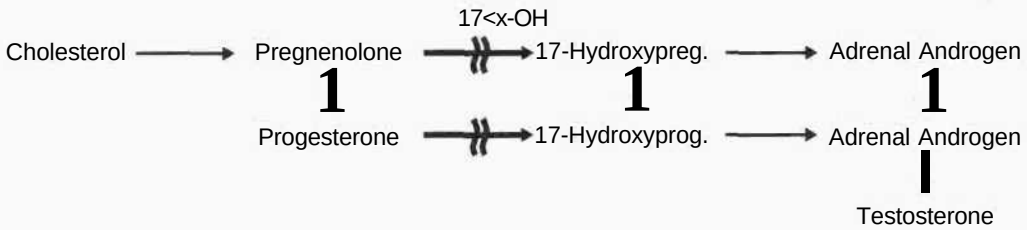


Figure IX-3-11

Consequence

Decreased production of testosterone.

Note: If the loss of androgen is severe, the male fetus will develop female internal and external structures (see male reproductive chapter for further information).

Effect in the Ovaries

Blockade Points

Figure IX-3-12 illustrates the blockade points in the ovaries.

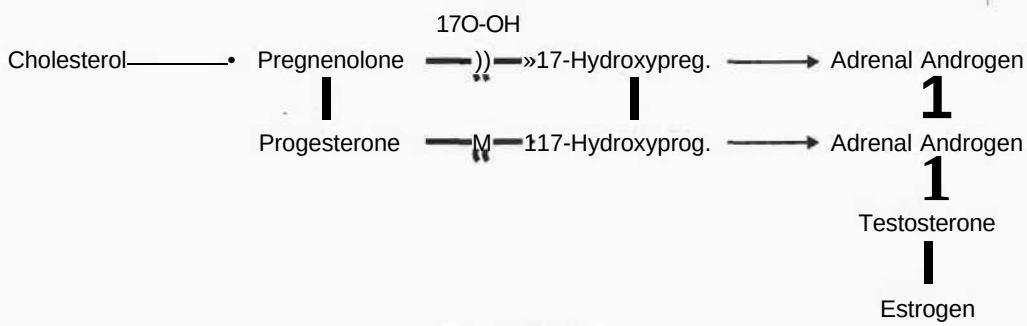


Figure IX-3-12

Consequence

Decreased production of estrogens.

Table IX-3-1. Summary of Enzyme Deficiencies

Deficiency	Glucocorticoid	ACTH	Blood Pressure	Mineralocorticoid Aldo	Mineralocorticoid DOC	Androgen	Estrogen
21pOH	⇓	t	⇓	⇓	⇓	adrenal	-
11 pOH	I	it	ir	li	ir	tr adrenal	-
17 a OH	⇓	tr	Ir	ii	ir	adrenal & testicular	li

Note: In all three disorders, there will be a deficiency in cortisol and an increase in circulating ACTH. The ACTH is responsible for the adrenal hyperplasia.

PHYSIOLOGICAL ACTIONS OF GLUCOCORTICOIDS

Stress (Includes States Such as Trauma, Exposure to Cold, Illness, Starvation, and Exercise)

The capacity to withstand stress is dependent on adequate secretion of the glucocorticoids.

Stress hormones usually act to mobilize energy stores. The stress hormones are:

Growth hormone: mobilizes fatty acids by increasing lipolysis in adipose tissue *f t^CTOd 'yitm^*

Glucagon: mobilizes glucose by increasing liver glycogenolysis

Cortisol (does not increase in starvation): mobilizes fat, protein, carbohydrate (see below]

Epinephrine, in some forms of stress such as exercise: mobilizes glucose via glycogenolysis and fat via lipolysis

Insulin tends to decrease in stress because it mainly promotes the storage of the products of digestion.

Metabolic Actions of Cortisol

Cortisol promotes the mobilization of energy stores, specifically:

1. Protein: Cortisol promotes degradation and increased delivery of amino acids.
2. Lipids: Cortisol promotes lipolysis and increased delivery of free fatty acids and glycerol.
3. Carbohydrate: Cortisol raises blood glucose, making more glucose available for nervous tissue. Two mechanisms are involved:

   Cortisol inhibits glucose uptake in most tissues (muscle, lymphoid, and fat).

   Cortisol increases hepatic output of glucose via gluconeogenesis from amino acids in particular (not from liver glycogenolysis).

↑ cortisol then ↑ a.a.
↑ cortisol then ↑ F.A.
↑ cortisol then ↑ glucose ↓ absorption ↑ synthesis

(3C) pyruvate
Pyruvate CO_2
OAA
(tO

Permissive Actions of Cortisol

Cortisol enhances the capacity of glucagon and catecholamines, hence the adjective *permissive* aptly describes many of the actions of cortisol.

Glucagon

Promotes glycogenolysis in the liver (some lipolysis from adipocytes as well). Without cortisol, fasting hypoglycemia rapidly develops.

Catecholamines

Promote glycogenolysis and lipolysis in liver and muscle. Promote vasoconstriction and bronchodilation. Without cortisol, blood pressure decreases.

Control of Adrenocorticotropin (ACTH) and Cortisol Secretion

General Features of the Primary Controlling Factors

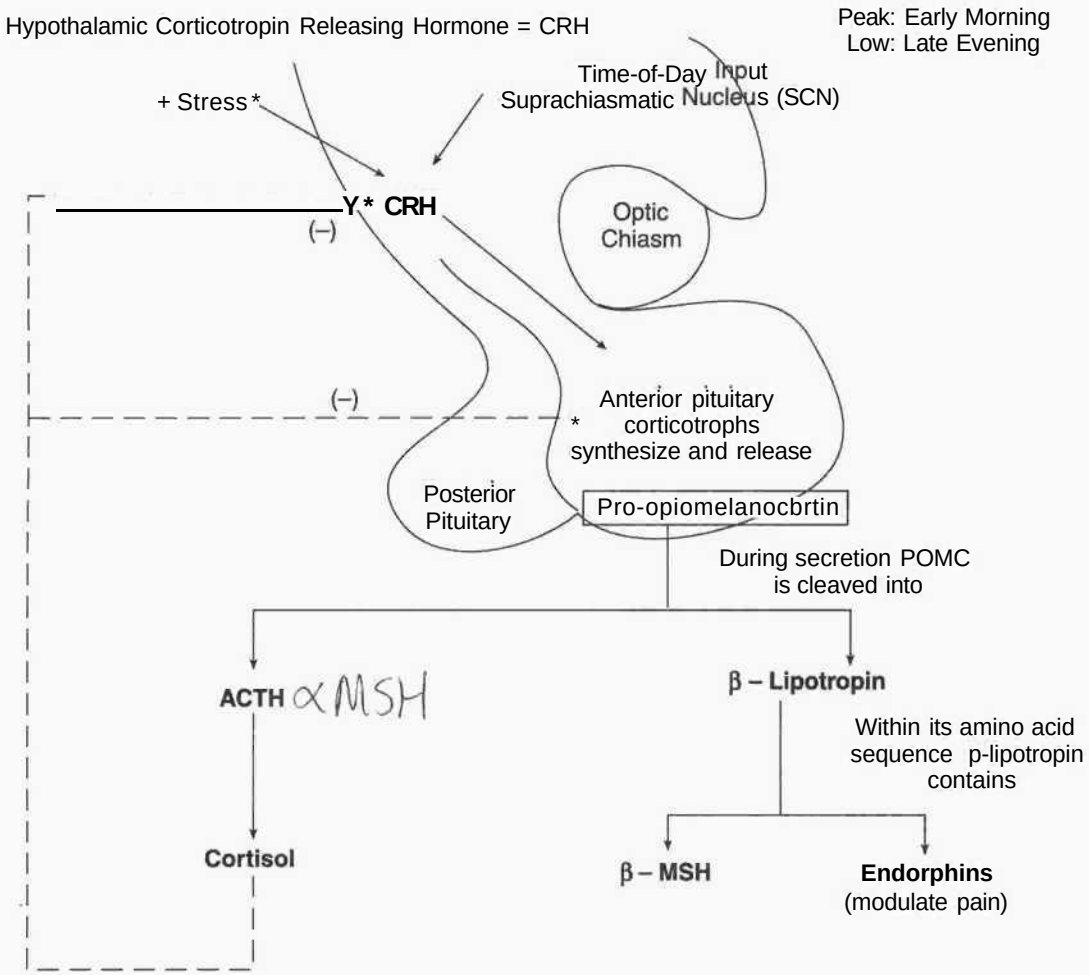


Figure IX-3-13

Role of the Specific Modulators

Corticotropin-Releasing Hormone (CRH)

Secretion of CRH increases in response to stress in the early morning:

Peak cortisol secretion occurs early in the morning between the 6th and 8th hours of sleep. Secretion then declines slowly during the day and reaches a low point late in the evening.

CRH promotes the synthesis and release of pro-opiomelanocortin (POMC), a prohormone. During secretion, POMC is cleaved into ACTH and P-lipotropin.

ACTH
Stimulates the secretion of cortisol (and adrenal androgens) of adrenal cortex. Cortisol suppresses the release of ACTH by acting on the hypothalamus and anterior pituitary.

Excessive secretion of ACTH (e.g., Addison's disease) causes darkening of the skin. This is due to the melanocyte-stimulating hormone (a-MSH) sequence within the ACTH molecule, and the P-melanocyte-stimulating hormone activity of (3-lipoprotein.

|3-Lipotropin
Role not well understood.

Precursor to p-MSH and endorphins. Endorphins may modulate the perception of pain.

PATHOPHYSIOLOGICAL CHANGES IN CORTISOL SECRETION

The Disorders of Cortisol Secretion

Table IX-3-2. The Primary and Secondary Disorders of Cortisol Secretion

	Plasma Cortisol	Plasma ACTH
Primary hypercortisolism*	tr*	⇓
Secondary hypercortisolism (pituitary)	tr	tr
Primary hyrxKortisolism (Addison's disease)	⇓	trt
Secondary hypocortisolism (pituitary)	⇓	⇓

^Exogenous administration of glucocorticoids produces similar results. There is a suppression of ACTH release, which causes adrenal atrophy. Sudden withdrawal of glucocorticoid treatment can cause plasma levels to decrease to extremely low levels. Therefore, it is better to withdraw treatment gradually.

*I High circulating ACTH can cause darkening of the skin.

Cushing's Syndrome

Cushing's syndrome is synonymous with hypercortisolism.

Secondary hypercortisolism originating in the pituitary is also often called Cushing's disease.

Characteristics of Hypercortisolism (Cushing's Syndrome)

- Protein depletion as a result of excessive protein catabolism
- Inhibition of inflammatory response and poor wound healing
- Hyperglycemia leads to hyperinsulinemia and insulin resistance.
- Hyperlipidemia
- Bone dissolution and osteoporosis
- Thinning of the skin with wide purple striae located around abdomen and hips
- Increased adrenal androgens, when present in women, can result in acne and mild hirsutism.
- Mineralocorticoid effects of the high level of glucocorticoid lead to salt and water retention (hypertension), potassium depletion, and a hypokalemic alkalosis.
- Redistribution of body fat. Extremities are thin, but fat collects in the abdominal wall and upper back (buffalo hump).

For characteristics of hypofunction, adrenal insufficiency, see Addison's disease in mineralocorticoid section.

PHYSIOLOGICAL ACTIONS OF ALDOSTERONE

General Features

1. The primary target tissue for aldosterone is the kidney, where its most important action is to increase Na^+ reabsorption by the principal cells of the kidney's collecting ducts. Because water is reabsorbed along with the Na^+, aldosterone can be considered to control the amount of Na^+ rather than the concentration of Na^+ in the ECF.
2. Aldosterone also promotes the secretion of H^+ by the intercalated cells of the collecting duct, and K^+ secretion by the principal cells.
3. The Na^+-conserving action of aldosterone is also seen in salivary ducts, sweat glands, and the distal colon.
4. Figure IX-3-14 shows the overall effects of aldosterone. This is a generalized representation of the effect of aldosterone on the renal distal tubule/collecting duct region.

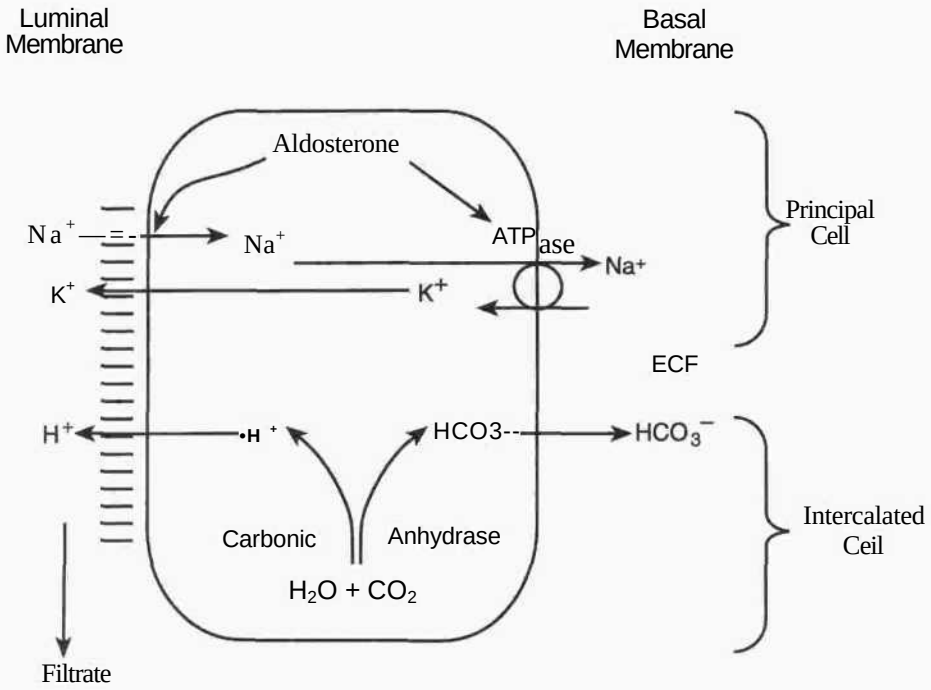


Figure IX-3-14

Specific Actions of Aldosterone

1. Aldosterone promotes the activity of Na/K-ATPase-dependent pump that moves Na^+ into the renal ECF in exchange for K^+.

   Because the lumen is somewhat impermeable to NaCl, aldosterone also increases the number of Na^+ channels in the luminal membrane, thus increasing the passive movement of Na^+ from the filtrate into the cell.

   The net effect is to remove Na^+ from the filtrate and pump it into the ECF. Generally, water is retained with the sodium, and little change is seen in sodium concentration of the extracellular fluid.

2. A consequence of the above action is that the tubule lumen becomes more negatively charged than the ECF.

   This negative charge attracts K^+. Thus, aldosterone facilitates K^+ secretion into the distal tubule/collecting duct.

   The negative charge also attracts H^+ and therefore facilitates H^+ secretion into the distal tubule/collecting duct and its loss in the urine.

   Whenever a H^+ is secreted, a HCO3- moves into the ECF. This represents new HCO3- created by the body stores.

Control of Aldosterone Secretion

ControllingFactors

ACTH is of minor importance in the control of aldosterone secretion. It can stimulate aldosterone secretion, but this is a transient effect. Physiologically, aldosterone is largely under the control of the renin-angiotensin system.

Sensory Input—The Juxtaglomerular Apparatus

The main sensory cells are the juxtaglomerular cells. They are modified smooth muscle cells that surround and directly monitor the pressure in the afferent arteriole. They are also innervated and stimulated by sympathetic neurons.

Additional sensory input is from the macula densa cœD of the distal tubule. They perceive sodium delivery to the distal nephron and communicate with the juxtaglomerular cells.

The juxtaglomerular apparatus is represented in Figure IX-3-15.

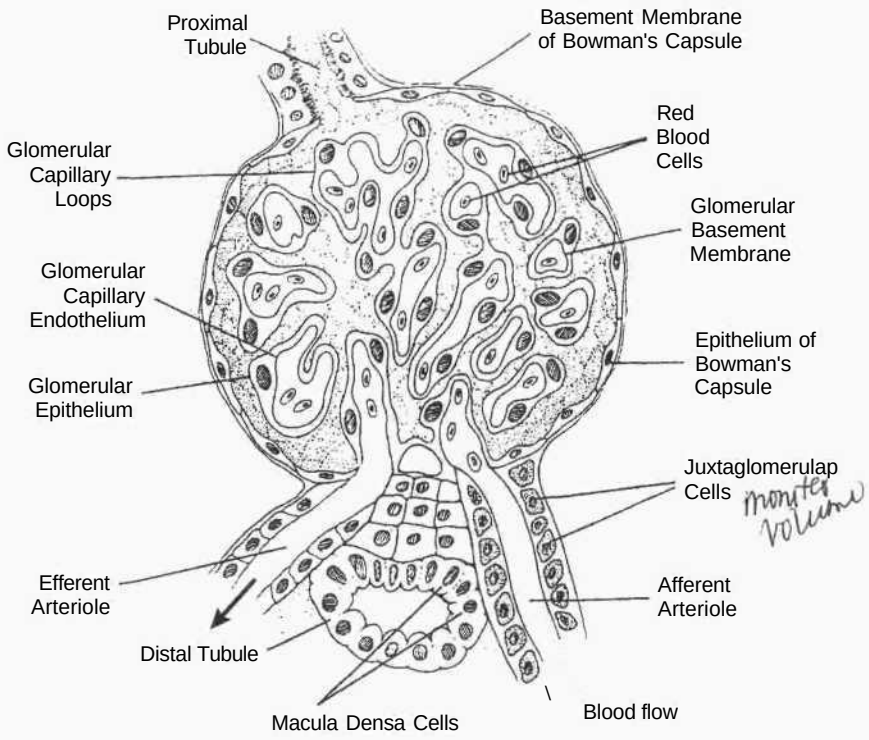


Figure IX-3-15. Renal Corpuscle and Juxtaglomerular Apparatus

Regulation of the** Renin-Angiotensin-Aldosterone **System

This system represents long-term regulation of blood pressure. Details are illustrated in Figure IX-3-16.

Any system that regulates blood pressure must monitor the pressure (juxtaglomerular apparatus), compare that pressure to a set point value, and, if they do not match, modify cardiac output and total peripheral resistance to bring pressure back toward the set point value.

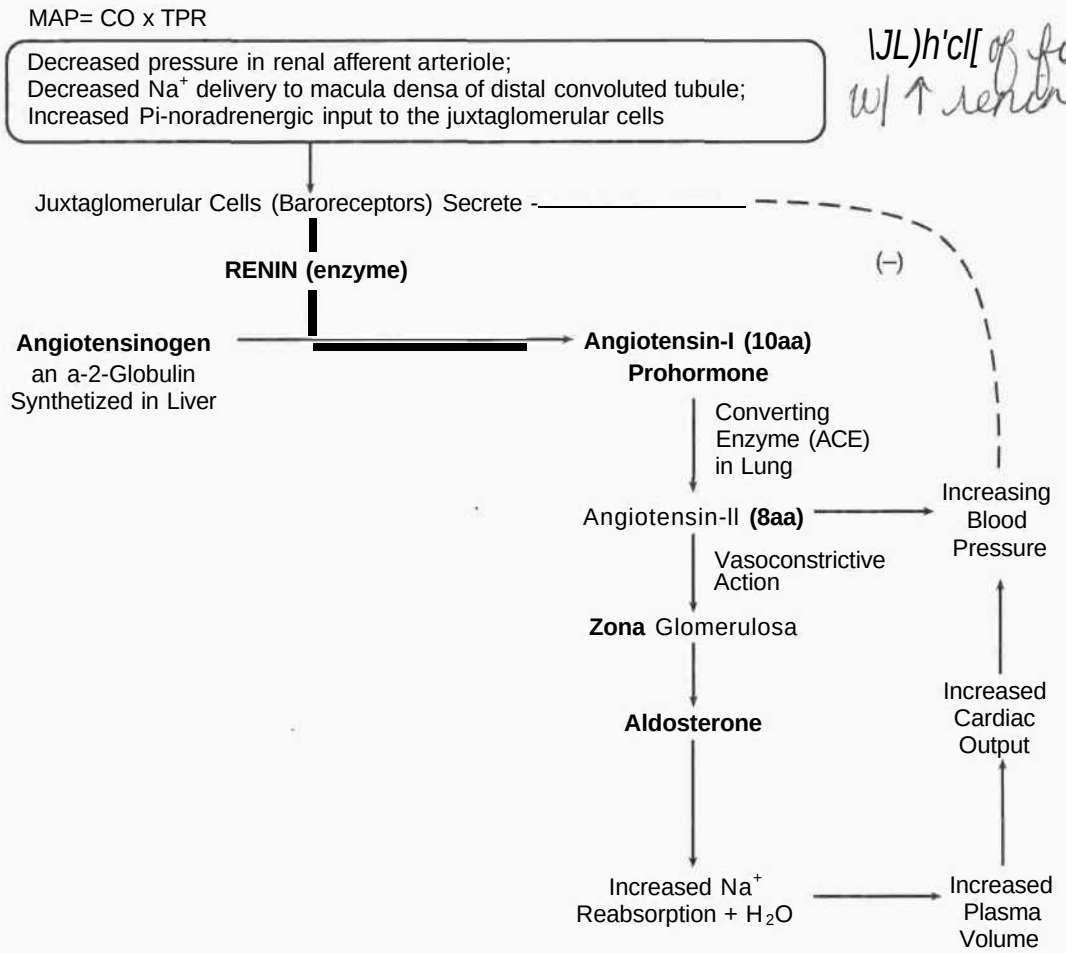


Figure IX-3-16. The Long-Term **Regulation of Blood Pressure**

Any of the three stimuli listed at the top of the figure will produce an increase in the secretion of renin and circulating angiotensin II. Angiotensin II raises blood pressure by two independent actions:

The direct vasoconstrictive effects of angiotensin II increase total peripheral resistance.

It stimulates the adrenal cortex to secrete aldosterone, resulting in increased reabsorption of Na^+.

As Na^+ reabsorption is increased, so also is water. This increases the volume of the ECF, the plasma, and the blood, thus raising cardiac output and blood pressure.

An increase in blood pressure will suppress the renin-angiotensin-aldosterone system. This decrease in angiotensin II will decrease total peripheral resistance. Reduced activity of aldosterone will cause a urinary loss of sodium and water, lowering cardiac output.

Potassium Effect

In addition to the preceding system, elevated plasma K^+ (hyperkalemia) increases the secretion of aldosterone by directly stimulating the zona glomerulosa.

A small increase in the plasma potassium level can cause a several-fold increase in aldosterone secretion.

↑ renin associated only w/ Na^+ + volume

Physiological Changes in Aldosterone Secretion

Increased Aldosterone Secretion: Any condition that decreases pressure in the renal artery (e.g., hemorrhage, prolonged sweating, going from a lying-down position to a standjng r2osition) will activate the renin-angiotensin system, increase aldosterone secretion, and increase sympathetic stimulation to return blood pressure toward normal.

Decreased Aldosterone Secretion: Any condition that increases blood pressure in the renal artery. *'f bp \j/ AJMUA.,*

This includes weightlessness, because blood no longer pools in the extremities when the individual is standing or sitting. A large portion of the redistributed blood ends up in the atria and large veins of the chest and abdomen. The increased distention of these vessels stimulates baroreceptors located there. Signals from these baroreceptors reach the vasomotor center, where they inhibit sympathetic output, including sympathetic signals that normally promote renin secretion by the juxtaglomerular cells. As a result, less renin, angiotensin II, and aldosterone are secreted, causing individuals to lose Na^+ and ECF volume.

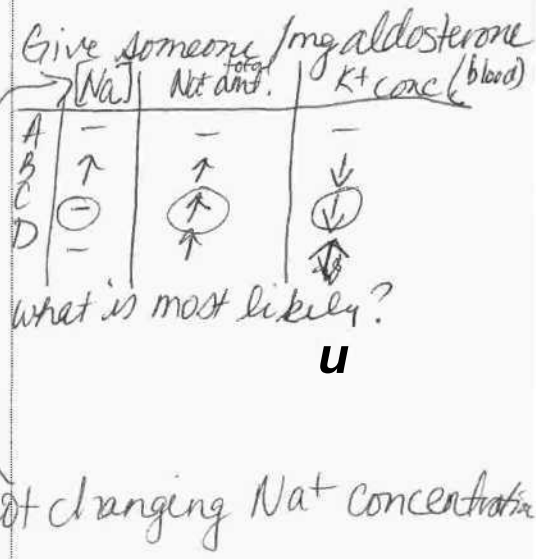
Pathophysiological Changes in Aldosterone Secretion

Primary hypoaldosteronism is an important part of the overall problems in Addison's disease.

Table IX-3-3. Important Changes in the Primary Disorders

	Primary Hyperaldosteronism (Conn's syndrome)	Primary Hypoaldosteronism
1. Total body sodium	ft	*
2. ECF volume	ft	⇓
3. Plasma volume	f	⇓
4. Blood pressure	ll	u 1
5. Plasma potassium concentration	⇓	⇈
6. Blood (plasma) pH	t	⇓
7. Edema*	no	no <A-
8. Plasma renin & angiotensin II activity	li	⇑

* A major increase in Na^+ and water retention is prevented by "Na^+ escape" in primary hyperaldosteronism. Although the mechanism is not well understood, evidence exists that atrial natriuretic peptide plays a role.



Addison's Disease (Primary Adrenal Insufficiency)

High circulating ACTH and hyperpigmentation.

Hypotension from two sources:

Insufficient mineralocorticoid leads to loss of salt and water, which reduces blood volume and cardiac work.

Insufficient glucocorticoid reduces vascular reactivity to catecholamines.

Hypotension produces increased plasma renin and angiotensin II.

Insufficient mineralocorticoid impairs renal secretion of potassium and H^+, leading to hyperkalemia and metabolic acidosis.

Insufficient adrenal androgens in women lead to loss of body hair (male still has testosterone).

Insufficient glucocorticoids lead to hypoglycemia and an inability of the kidney to excrete a water load (hyponatremia).

Other symptoms include weakness, nausea, vomiting, and diarrhea.

Increased secretion of ADH from neurosecretory neurons terminating in the posterior pituifary.

Secondary Hyperaldosteronism

Etiology

Sequestration of blood on the venous side of the systemic circulation is a common cause of secondary hyperaldosteronism. This results in decreased cardiac output, and thus decreased blood flow and pressure in the renal artery. The following conditions produce secondary hyperaldosteronism through this mechanism:

Congestive heart failure

Constriction of the vena cava

Hepatic cirrhosis

Summary of the Preceding Concerning Secondary Hyperaldosteronism

The cause in all cases is a **decrease** in blood pressure.

1.	Plasma renin & angiotensin II activity The increased angiotensin-II activity will drive the secondary hyperaldosteronism.	ft
2.	Total body sodium	ft
3.	ECF volume	ft
4.	Plasma volume	ft
5.	Edema*	yes

→ 1° condition not related to aldosteron

*Na^+ escape prevents peripheral edema in primary but not secondary hyperaldosteronism. Also note that the increased ECF volume remains mainly on the venous side of the circulation, accentuating the venous congestion and preventing a return of circulating blood volume to normal.

Renal arterial stenosis will also produce secondary hyperaldosteronism. But in this case, circulating blood volume will increase, and the result is hypertension.

Chapter Summary

Loss of mineralocorticoid function causes severe hypotension and can be fatal. Lack of glucocorticoids is not life-threatening under normal conditions, but stressful situations (e.g., fasting) cause severe problems.

Congenital enzyme deficiencies in steroid hormone synthesis decrease cortisol, and the accompanying increase in ACTH produces adrenal hyperplasia. 21 p OH is associated with hypotension and 1113 OH with hypertension. Both increase adrenal androgen secretion. 17 a OH deficiency produces hypertension but a reduction in androgens and estrogen.

Cortisol is one of several stress hormones that mobilize substrates. Specifically, cortisol breaks down triglycerides and protein and raises blood glucose by decreasing its peripheral uptake.

Primary versus secondary cortisolism can be distinguished by the response to ACTH.

Aldosterone increases the reabsorption of sodium and water by the kidney and thus regulates whole-body sodium rather than sodium concentration. However, aldosterone does closely regulate potassium concentration.

The renin-angiotensin-aldosterone system represents a long-term regulation of blood pressure. The juxtaglomerular cells represent the main sensory input and monitor blood pressure inside the kidney.

Venous congestion is a common cause of secondary hyperaldosteronism.

Antidiuretic Hormone (ADH) and Regulation of Osmolarity and Extracellular Fluid (ECF)

4

CONTROL OF ADH SECRETION

Osmolarity and ECF Volume

ADH is a major controller of water excretion and ECF volume. ADH also controls osmolarity.

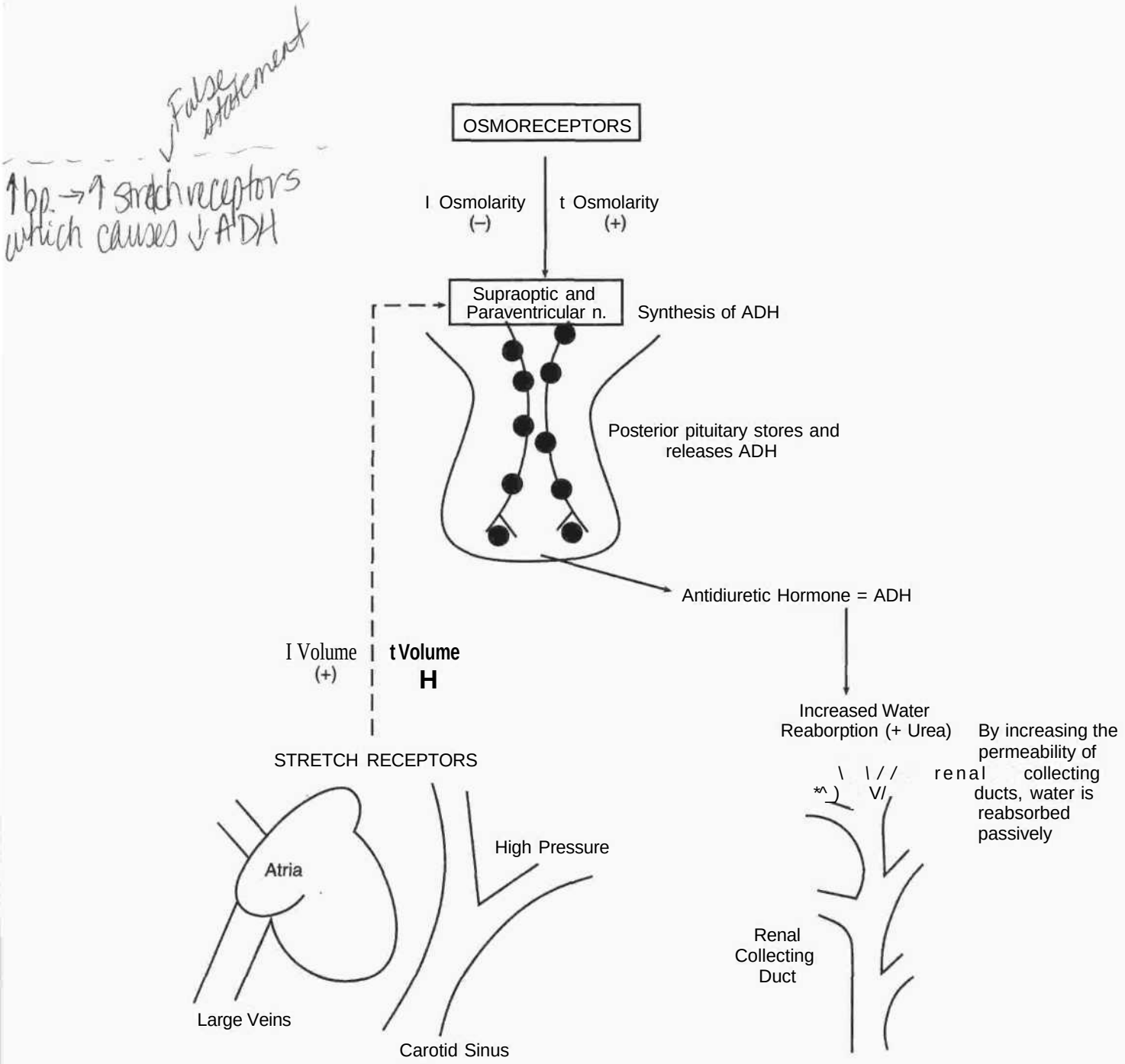
The osmoreceptors are very sensitive. However, with volume depletion, osmoregulation is secondary to volume regulation; a return of circulating volume will occur even as osmolarity decreases.

General Features Concerning the Control and Actions of **ADH**

Figure IX-4-1 illustrates the control and actions of ADH. In the figure, solid lines represent stimulation, and dashed lines inhibition.

What the USMLE Requires You to Know

- The site of synthesis versus the storage and release site for ADH
- The effect of ADH on the renal collecting duct
- Regulation of the release of ADH with changing ECF volume and osmolarity
- Primary polydipsia versus diabetes insipidus versus syndrome of inappropriate secretion of antidiuretic hormone (SIADH)
- The source and major stimuli that release atrial natriuretic peptide (ANP)
- The actions of ANP on the kidney



(+) Increases Release of ADH, (-) Decreases Release of ADH

Figure IX-4-1

Synthesis and Release of ADH

ADH is synthesized in the hypothalamus, but it is stored and released from the posterior pituitary. Loss of posterior pituitary function may result in only a transient deficiency in ADH if hypothalamic function (cell bodies that synthesize ADH) remains intact.

Action of ADH

The main target tissue is the renal collecting duct.

ADH increases the permeability of the duct to water by placing water channels in the membrane.

Water is reabsorbed passively, drawn across the membranes by the higher osmolarity of the interstitium.

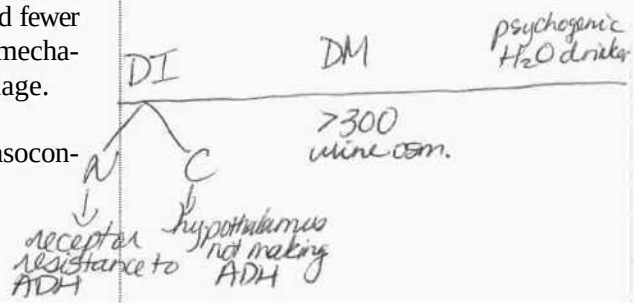
Urea can pass with the water, but electrolytes cannot.

Regulation of ECF Volume and Osmolarity

Volume Regulation

Stimuli arising from stretch receptors act to chronically inhibit ADH secretion. Decreases in blood volume cause venous and arterial stretch receptors to send fewer signals to the CNS, decreasing chronic inhibition of ADH secretion. This mechanism is especially important for restoring ECF volume following a hemorrhage.

In humans, ADH is arginine vasopressin (AVP). Although AVP also has vasoconstrictive activity, this effect is probably not important.



Osmoregulation

An increase of only 1% in the osmolality of the ECF bathing the hypothalamic osmoreceptors will evoke an increased rate of ADH secretion. A similarly sized decrease in osmolality will decrease ADH secretion. In this manner, ECF osmolality is kept very close to 300 mOsm/L.

PATHOPHYSIOLOGICAL CHANGES IN ADH SECRETION

Diabetes Insipidus

All the consequences can be explained on the basis of the lack of an effect of ADH on the renal collecting ducts.

Central Neurogenie Diabetes Insipid us

Sufficient ADH is not available to affect the renal collecting ducts.

Nephrogenic Diabetes Insipidus

Due to the inability of the kidneys to respond to ADH.

Syndrome of Inappropriate ADH Secretion (SIADH)

Excessive secretion of ADH causes an excessive reabsorption of water in the renal collecting duct.

Table IX-4-1. A Summary of the Effects of Primary Polydipsia, Diabetes Insipidus, and SIADH

	Primary Polydipsia	Central Neurogenie Diabetes Insipidus	SIADH
1. Permeability of collecting ducts to H_2O	Ji	a	rr
2. Urine flow	t	ir	I
3. Urine osmolarity	⇓ <300	⇓ <300	ft >300
4. ECF volume	u	⇓	ft
5. ECF osmolarity (Na concentration)	⇓	rr	⇓
6. ICF volume	it	$	ti
7. ICF osmolarity	n	ft	⇓

ATRIAL NATRIURET1C PEPTIDE (ANP)

ANP is the hormone secreted by the heart. ANP is found throughout the heart but mainly in the right atrium. The stimuli that release ANP (two peptides are released) are:

- Stretch, an action independent of nervous involvement
- Increased salt intake

ANP increases sodium loss (natriuresis) and water loss by the kidney because of, in part, an increase in glomerular filtration rate due to:

- ANP-mediated dilation of the afferent arteriole
- ANP-mediated constriction of the efferent arteriole

ANP also increases sodium loss (natriuresis) and water loss (diuresis) by the kidney because of an inhibition of the reabsorption of sodium and water in the collecting duct.

Clinical Correlate

Differential Diagnosis of Diabetes Inslpidus

In diabetes insipidus, the individual continues to form large quantities of glucose-free dilute urine in spite of an elevated extracellular osmolarity. This is now considered diagnostic for diabetes insipidus. An injection of ADH will reduce urine flow in the central form but not the nephrogenic form of the disease.

With a water deprivation test, the patient with primary polydipsia will soon reduce urine flow, whereas with complete diabetes insipidus the individual will continue to form a large volume of dilute urine.

In SIADH, the individual becomes hyposmotic but continues to form a concentrated urine.

Effect of Alcohol and Weightlessness on ADH Secretion

Ingesting ethyl alcohol or being in a weightless environment suppresses ADH secretion. In weightlessness, there is a net shift of blood from the limbs to the abdomen and chest. This results in greater stretch of the volume receptors in the large veins and atria, thus suppressing ADH secretion.

The physiological importance of ANP is not known because it has not been possible to identify or produce a specific deficiency state in humans. However, ANP secretion increases in weightlessness (submersion to the neck in water) while renin, aldosterone, and ADH secretion decrease. Thus, along with other hormones, it may play a role in normal regulation of the ECF osmolality and volume.

ANP tends to antagonize the effects of angiotensin II and ADH.

Chapter Summary

ADH is synthesized in the hypothalamus but is stored and released from the posterior pituitary.

The major action of ADH is the passive reabsorption of water and urea, but not electrolytes, in the renal collecting duct.

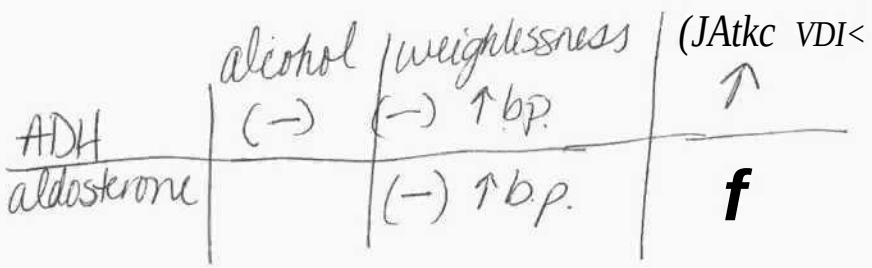
Reduced input from the low-pressure stretch receptors is a strong stimulus for the release of ADH.

Osmoreceptors are very sensitive and normally maintain osmolarity in a very narrow range.

Primary polydipsia and diabetes insipidus are characterized as states forming a large volume of dilute urine. However, primary polydipsia is a hyposmolar state, whereas diabetes insipidus is a hyperosmolar state. SIADH is a hyposmolar state with a small volume of concentrated urine.

ANP, found mainly in the tissue of the right atrium, is released in response to stretch.

The major action of ANP is diuresis and natriuresis.



The Endocrine Pancreas

5

ORGANIZATION AND SECRETION OF THE ISLETS OF LANGERHANS

The location and proportion of each major hormone-secreting cell type of the islets of Langerhans are shown in Figure IX-5-1. The local (paracrine) action of each islet hormone is shown by bold solid arrows (if facilitatory) and bold dashed arrows (if inhibitory). The diameter of each circle approximately represents the proportion of that cell type present in the islets.

What the USMLE Requires You to Know

- Organization and paracrine effects in the islets of Langerhans
- Regulation of the peripheral uptake of glucose
- The actions of insulin on carbohydrate, protein, and fat metabolism
- The main promoters and inhibitors of insulin secretion
- Pathophysiology of diabetes mellitus
- The actions of glucagon on the liver
- The regulation of glucagon secretion

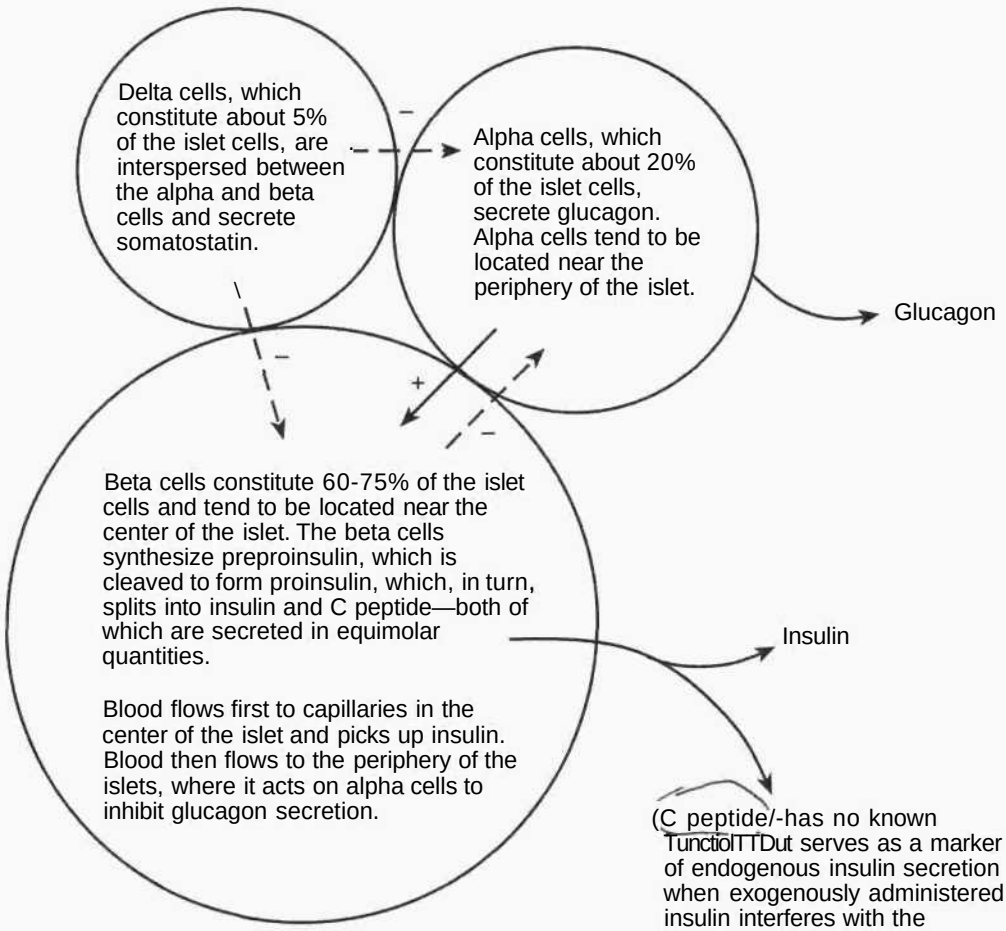


Figure IX-5-1a

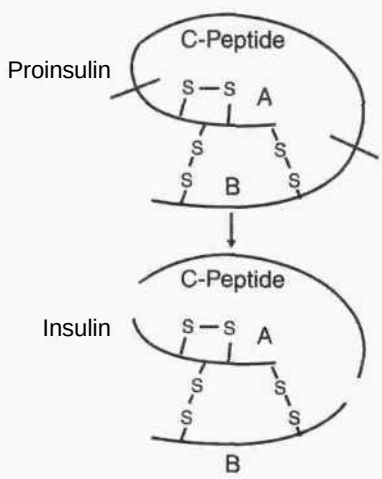


Figure IX-5-1b. Insulin

ACTIONS OF INSULIN

The Insulin Receptor

The portion of the insulin receptor that faces externally has the hormone-binding domain.

The portion of the insulin receptor that faces the cytosol has tyrosine kinase activity.

When occupied by insulin, the receptor phosphorylates itself and other proteins.

Peripheral Uptake of Glucose

Glucose is taken up by peripheral tissues by facilitated transport (a passive transport not linked to sodium). Insulin facilitates this uptake in some tissues. Typically the insulin receptor causes the insertion of glucose transporters in the membrane.

exercisin wuocteocbrwt require insulin for uptake of glucose

Tissues that require insulin for effective uptake of glucose are:

Adipose tissue

Resting skeletal muscle (although glucose can enter working muscle without the aid of insulin)

Tissues in which glucose uptake is not affected by insulin are:

2° active transport mechanism

Nervous tissue

Kidney tubules

Intestinal mucosa

Red blood cells

p-cells of pancreas

Insulin accelerates but is not required for glucose uptake by the liver. It does this by enhancing glucose metabolism, not by inserting new transporters into the membrane.

Metabolic Actions of Insulin

Insulin is a major anabolic hormone, which is secreted in response to a carbohydrate- and/or protein-containing meal.

Anabolic hormones tend to promote protein synthesis (increase lean body mass).

Other anabolic hormones include:

Thyroid hormones

Growth hormone/IGF I

Sex steroids (androgens)

Effects of Insulin on Carbohydrate Metabolism

Insulin increases the uptake of glucose and its metabolism in muscle and fat. By increasing glucose uptake in muscle, glucose use, i.e., metabolism to carbon dioxide and water, is increased.

Insulin increases glycogen synthesis in liver and muscle. The activity of enzymes which promote glycogen synthesis (glucokinase and glycogen synthetase) is increased. The activity of those enzymes which promote glycogen breakdown (phosphorylase and glucose-6-phosphatase) is decreased.

Glucokinase and glucose-6-phosphatase are expressed by the liver but not by muscle.

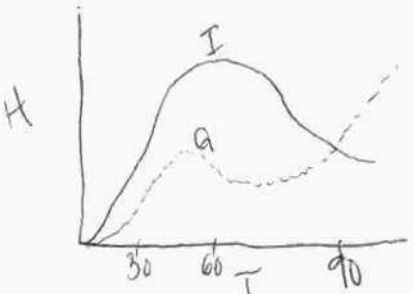
Effects of Insulin on Protein Metabolism

Insulin increases amino acid uptake by muscle cells.

Insulin increases protein synthesis.

Insulin decreases protein breakdown (deficiency of insulin results in a breakdown of protein).

response to meal { ↑ insulin, ↑ glucagon



Type I DM	Type II DM
1. ↓ insulin	↑ insulin
2. ↑ prot. breakdown → ketones	↑ prot. synth.
3. thin	↑ fat (obese)
4. HSL(+) LPL(-)	LPL(+) HSL(-)
5. ↑ FFA	↓ FFA
6. β oxidation → energy, ketone bodies	
7. hyperKalemia	hypoKalemia

Effects of Insulin on Fat Metabolism

Insulin increases:

Glucose uptake by fat cells (increases membrane transporters). By increasing glucose uptake, insulin also makes triose phosphates available for triglyceride synthesis in adipose tissue.

Triglyceride uptake by fat cells. It increases the activity of lipoprotein lipase (also called extracellular or clearing factor lipase). Lipoprotein lipase is located on the endothelium of capillaries and clears VLDL and chylomicrons from the blood.

Triglyceride synthesis (lipogenesis) in adipose tissue and liver by stimulating the rate-limiting step, namely the carboxylation of acetyl CoA to malonyl CoA. In other words, insulin stimulates the conversion of carbohydrate into fat.

These relationships are shown schematically in Figure IX-5-2.

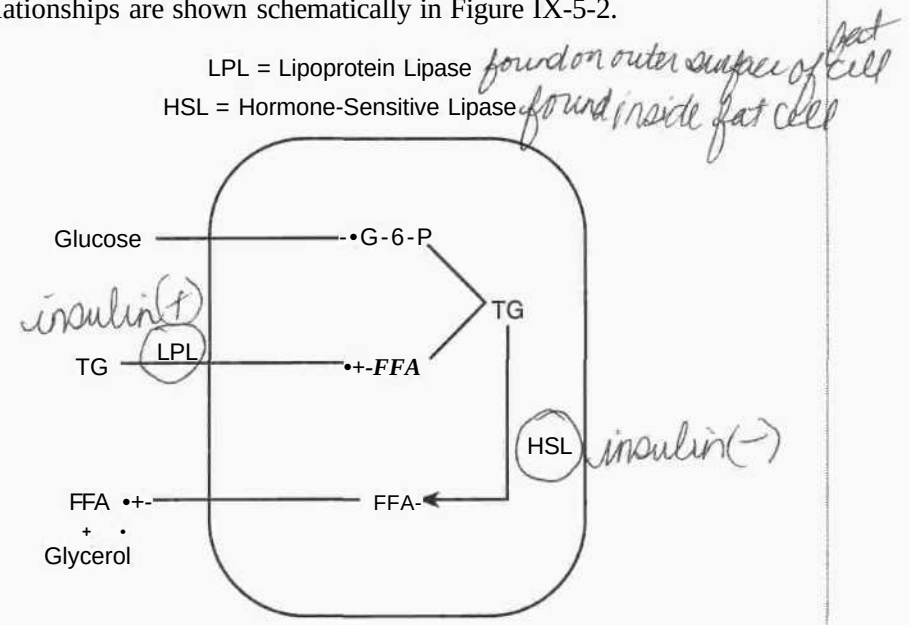


Figure IX-5-2

Insulin Decreases:

Triglyceride breakdown (lipolysis) in adipose tissue by decreasing the activity of hormone-sensitive lipase. This enzyme is activated by stress hormones (i.e., cortisol, growth hormone, epinephrine [glucagon]).

Formation of ketone bodies by the liver.

Summary of Insulin's Effects on Carbohydrate (CHO), Lipid, and Protein Metabolism

In type I DM li^Wf/h *Kfl \\fl [A$$U4*
a pyruvate dehydrogenase
b. transcarbonyl phosphatase
is rate limiting

Insulin is secreted after a CHO and/or protein meal.

Its major overall effects are to increase body stores of protein, fat, and CHO.

It also decreases the catabolism of amino acids and fatty acids.

It accelerates the metabolism of glucose to CO_2 and H_2O.

Insulin Effects on Potassium

Insulin pumps K^+ into cells. Although the overall process is not well understood, insulin increases the activity of Na/K-ATPase in most body tissues.

This K+-lowering action of insulin is used to treat acute, life-threatening hyperkalemia. For example, sometimes hyperkalemia of renal failure is successfully lowered by the simultaneous administration of insulin and glucose. (The glucose is given to prevent severe insulin-induced hypoglycemia from developing.)

Summary of the Major Actions of Insulin

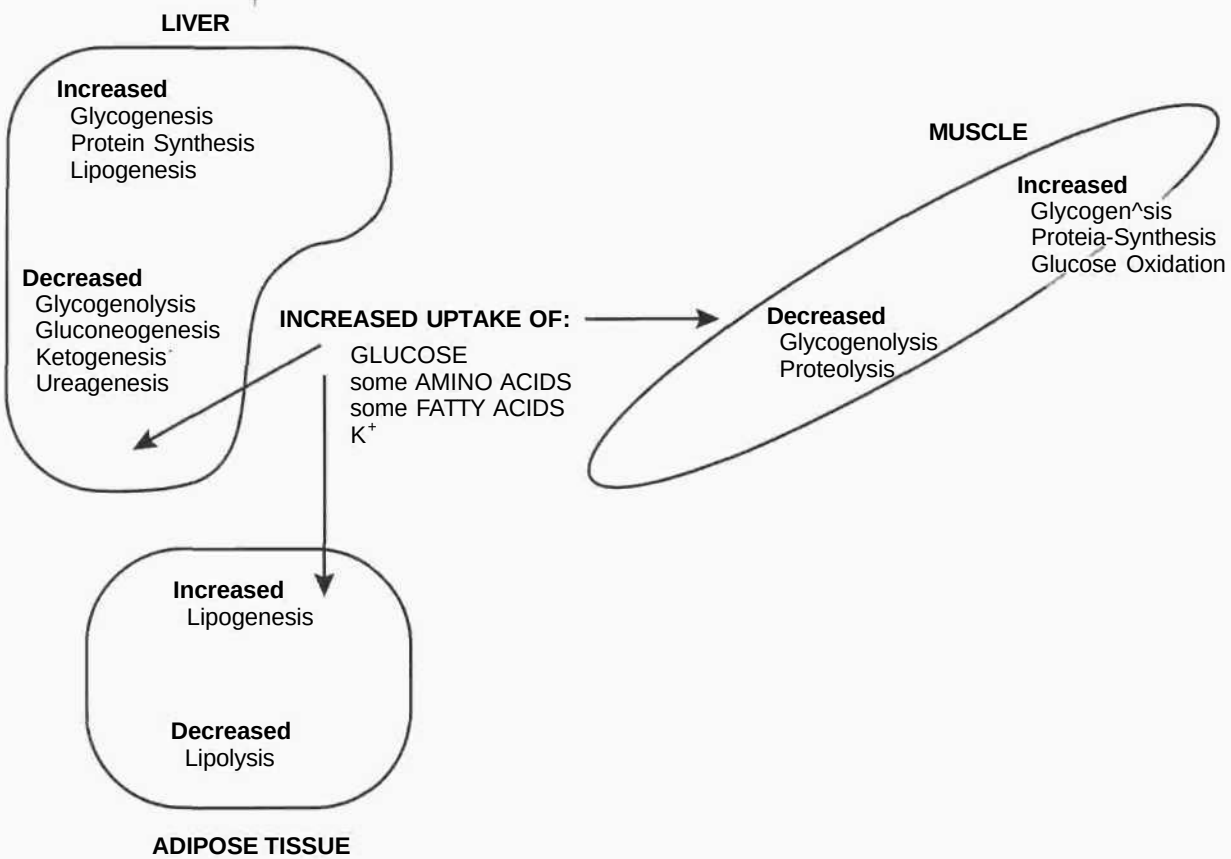


Figure IX-5-3

Control of Insulin Secretion

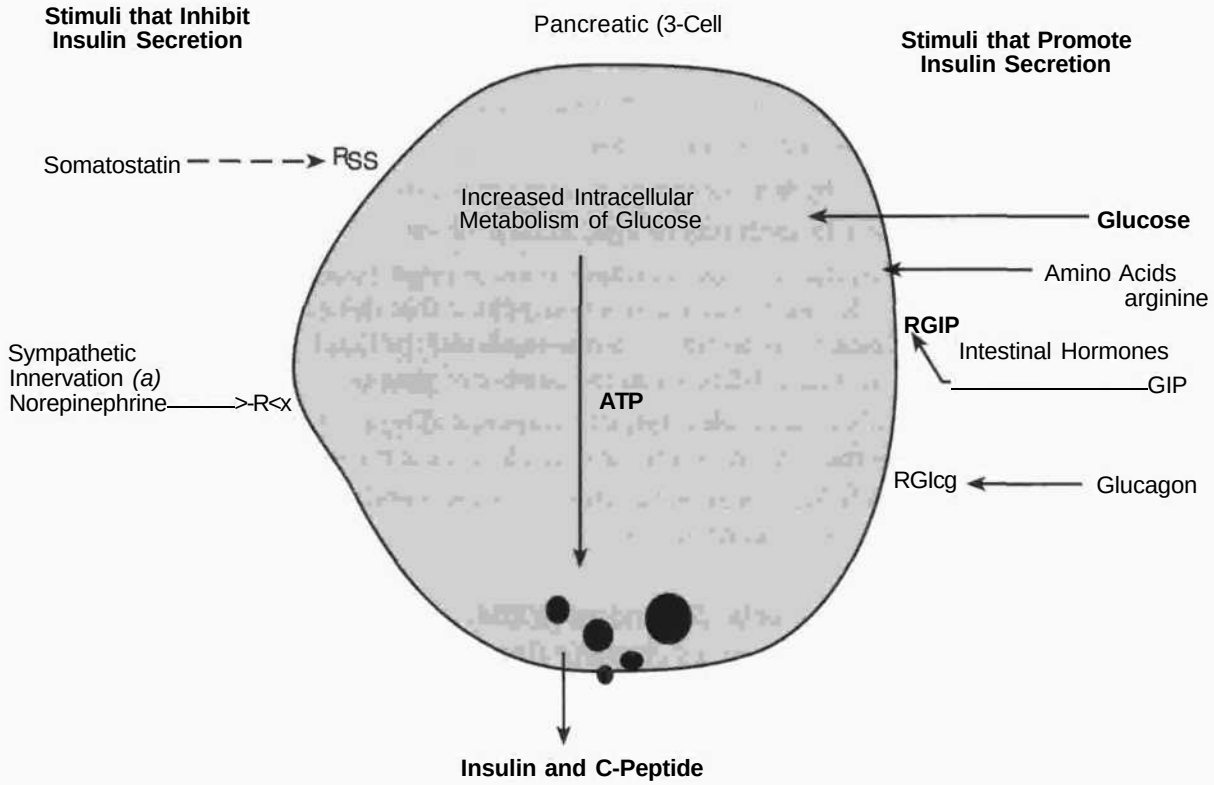


Figure IX-5-4

GeneralFeatures

The most important controller of insulin secretion is plasma glucose. Above a threshold of 100 mg%, insulin secretion is directly proportional to plasma glucose.

For glucose to promote insulin secretion, it must not only enter the P-cell but also be metabolized, so as to increase intracellular ATP concentration.

All of the hormones or neurotransmitters named in Figure IX-5-4 attach to the membrane receptors (R). In contrast, the metabolic substrates, glucose and amino acids, enter the p-cell.

surgery - increase insulin if person is going into exercise ↓ insulin amt. if diabetic take

Pathological States Associated with Insulin

Type 2 or Non-Insulin-Dependent (NIDDM)
(Formerly Called Maturity-Onset)

Accounts for about 90% of all the cases of diabetes

Body build is usually obese.

Usually, but not always, middle-aged or older

Insulin levels may be high, normal, or low

Resistance to insulin action in major target tissues: The mechanism is not well understood, but one possibility is that chronically elevated plasma insulin has decreased (down-regulated) the number of insulin receptors, creating a deficiency in the number of glucose transporters.

With a controlled diet, the symptoms of type 2 diabetes often disappear without the necessity for pharmacological therapy.

Individuals tend to be ketosis resistant. (With some insulin activity, there will be no ketoacidosis.)

Type 1 or Insulin-Dependent (IDDM)
(Formerly Known as Juvenile Onset)

Body build usually lean

Usually, but not always, prepubertal in onset

Due to an absence of insulin production

Increased glucagon secretion also generally occurs.

Metabolic Effects in Insulin-Deficient Individuals

CHO

Increased blood glucose concentration

Increased glycogen breakdown

Decreased peripheral glucose use

Protein

Increased protein breakdown

Increased catabolism of amino acids

Increased gluconeogenesis

Increased ureagenesis

Decreased protein synthesis

Fat

Increased triglyceride breakdown

Increased level of circulating free fatty acids

Increased ketosis, resulting in ketoacidosis (metabolic acidosis)

Decreased fatty acid synthesis

Decreased triglyceride synthesis

Potassium Ion

Intracellular concentration is low.

Hydrogen ions move intracellularly to be buffered, and potassium ions leave the cell.

There is a lack of the normal insulin effect of pumping potassium ion into cells.

Plasma levels may be increased, normal, or even decreased, depending in part on the renal handling of potassium.

Sudden insulin replacement can produce severe hypokalemia.

Pulmonary System

Hyperventilation and reduced PCO_2 level as a compensation for the metabolic acidosis.

Renal System

The failure to reabsorb all the filtered glucose in the proximal tube also prevents normal water and electrolyte reabsorption in this segment, resulting in the loss of electrolytes along with the water and glucose. This includes both sodium and potassium. Thus, there is increased excretion of sodium and potassium, even though urine concentration of electrolytes is low.

A major determinant of urine osmolarity is glucose.

Individual becomes dehydrated and hyperosmotic. Because of the high levels of plasma glucose, sodium is not a good index of ECF osmolarity.

In the distal tubule, there are:

Increased hydrogen ion secretion and the formation of an acid urine as a compensation for the ketoacidosis. The hydrogen ion secretion will tend to diminish potassium secretion, but the higher than normal tubular flow will promote potassium secretion. Even if potassium secretion is diminished, failure to reabsorb potassium in earlier segments, due to the diuresis, will tend to produce an overall increase in potassium excretion.

Increased bicarbonate reabsorption.

A deficiency in a counterregulatory hormone will make the individual more prone to episodes of hypoglycemia.

Counterregulatory hormones include growth hormone, cortisol, glucagon, epinephrine, and norepinephrine.

Table IX-5-1. **Summary of Insulin-Related** Pathophysiological **States**

	Glucose	Insulin	C peptide	Ketoacidosis
Type 2 diabetes	ft	⇑,⇔	⇑,⇔	—
Type 1 diabetes	ft	*I*	ll	+
Insulinoma	a	ft	ft	-
Factitious hypoglycemia (self-injection of insulin)	I	ft	I	—

ACTIONS OF GLUCAGON

Overview

Glucagon is a peptide hormone.

Glucagon is secreted by the a-cells of the pancreatic islets. The primary target for glucagon action is the liver hepatocyte, where its action is mediated by an increase in the concentration of cAMP. The cAMP activates protein kinase A, which, by catalyzing phosphorylation, alters the activity of enzymes mediating the actions given below.

Note: Skeletal muscle is not a target tissue for glucagon.

Specific Actions of Glucagon on the Liver

↑ blood sugar

1. Increases liver glycogenolysis.

   Glucagon activates glycogen phosphorylase, breaking down glycogen to glucose-1-phosphate.

   Glucagon inactivates glycogen synthetase, preventing the glucose-1-phosphate from being recycled back into glycogen.

2. Increases liver gluconeogenesis. deamination

   Glucagon promotes the conversion of pyruvate to phosphoenolpyruvate.

   Glucagon increases the conversion of fructose-1, 6-biphosphate to fructose-6-phosphate.

3. Increases liver ketogenesis and decreases lipogenesis.

   Glucagon inhibits the activity of acetyl CoA carboxylase, decreasing the formation of malonyl CoA. When the concentration of malonyl CoA is low, ketogenesis is favored over lipogenesis.

Acetyl CoA
4 ——— 7 malonyl CoA
Acety CoA
4 AccKj CoA
palmitic acid

4. Increases ureagenesis.

   By increasing the production of glucose from pyruvate, glucagon indirectly stimulates the transamination of alanine to pyruvate. The amino group is eliminated as urea.

5. Increases insulin secretion.

   The amino acid sequence of glucagon is similar to that of the duodenal hormone, secretin.

   Like secretin (and most other gut hormones), glucagon stimulates insulin secretion.

6. Increases lipolysis in the liver.

   Glucagon activates hormone-sensitive lipase in the liver, but because the action is on the liver and not the adipocyte, glucagon is not considered a major fat-mobilizing hormone.

Mr. Jones brought into ER comatose. Blood sugar 860.
He has been on insulin for 5-10 yrs. He has ketoacidosis.
What is first line of defense
rehydrate

70 yr. old man many yrs. (30 yrs)
Type II diabetic → changes to Type I diabetic b/c of # of years he had had diabetes.

Somoghi effect when morning glucose level is high before you change insulin levels you should give pt. a midnight snack

Control of Glucagon Secretion

Major factors that control glucagon secretion are summarized in Figure IX-5-5. Stimuli that promote glucagon secretion are depicted on the right, and those that inhibit on the left. R designates a surface receptor for the particular hormone or neurotransmitter.

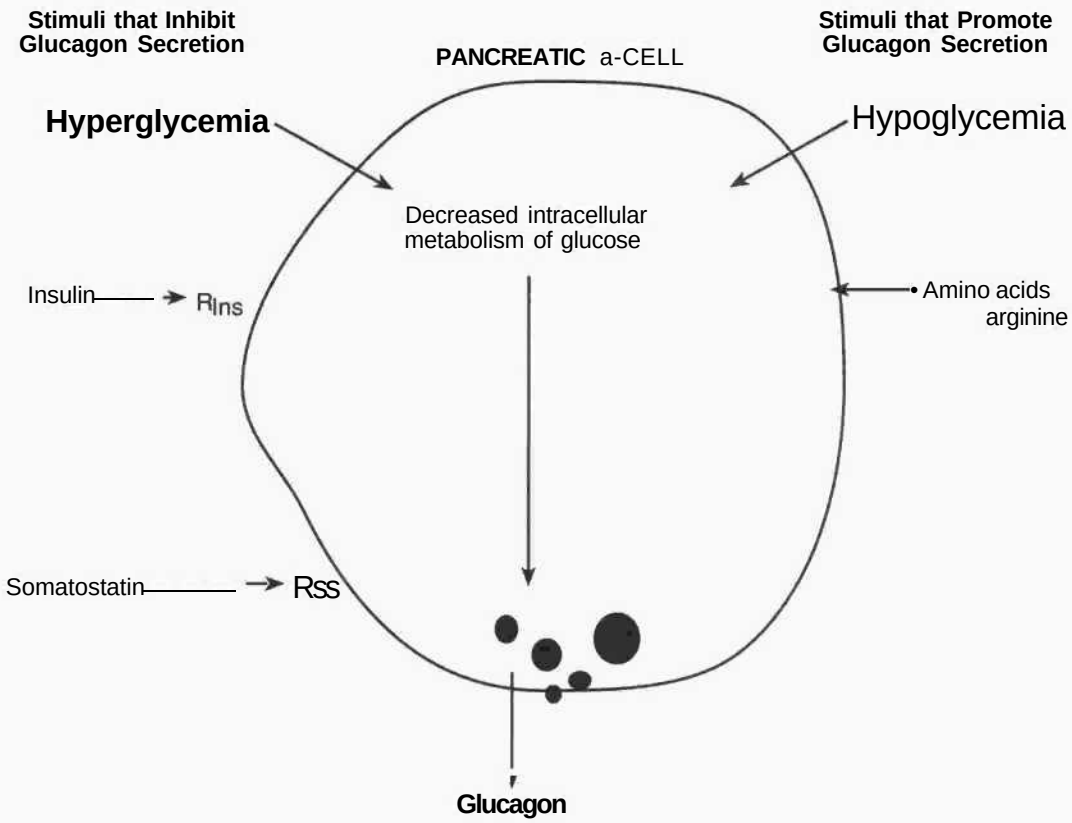


Figure IX-5-5

FurtherInformation

Low plasma glucose (hypoglycemia) is the most important physiological promoter for glucagon secretion, and elevated plasma glucose (hyperglycemia) the most important inhibitor.

Amino acids, especially dibasic amino acids (arginine, lysine), also promote the secretion of glucagon. Thus, glucagon is secreted in response to the ingestion of a meal rich in proteins.

Chapter Summary

Locally within the islets, glucagon stimulates the release of insulin, but insulin inhibits the release of glucagon.

C-peptide secreted in conjunction with insulin is an index of endogenous insulin secretion.

The peripheral uptake of glucose is via facilitated transport. In some tissues, such as adipose and resting skeletal muscle, the number of functioning transporters is regulated by insulin.

Insulin facilitates the metabolism of glucose to carbon dioxide and water and also its conversion to glycogen in liver and muscle.

Insulin promotes protein synthesis and decreases protein breakdown.

Insulin promotes lipogenesis. It inhibits lipolysis by decreasing the activity of hormone-sensitive lipase.

Hyperglycemia is the major promoter of insulin secretion.

Type 2 diabetes shows tissue resistance to insulin, whereas a lack of insulin is the problem in type 1 diabetes.

The major target tissue for glucagon is the liver, where its primary action is glycogenolysis and increased glucose output.

Hypoglycemia is the main promoter and hyperglycemia the main inhibitor of glucagon secretion.

Growth Hormone

6

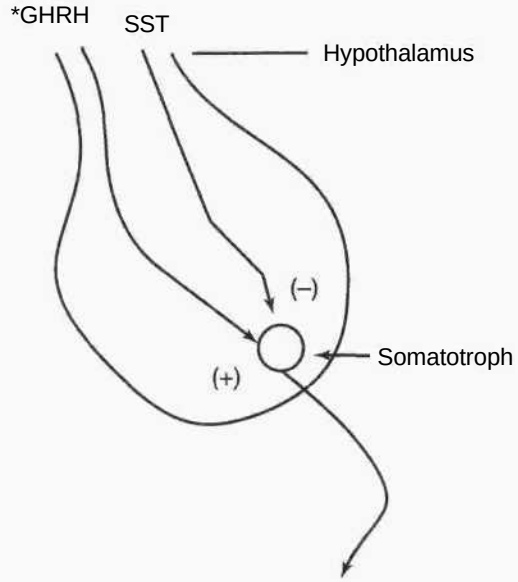
GH has both anabolic and catabolic properties

GENERAL FEATURES

Growth hormone is a major growth-promoting hormone, but all anabolic hormones (i.e., growth hormone, insulin, thyroid hormones, and androgens) are required for normal growth. The major catabolic and anabolic actions of growth hormone are shown in Figure IX-6-1. This figure shows that most of the direct actions of growth hormone are consistent with its actions as a stress or catabolic hormone. A direct anabolic action is that it promotes the entry of amino acids into cells, thus making them more available for protein synthesis. However, most of the anabolic actions of growth hormone are indirect via the production of growth factors.

What the USMLE Requires You to Know

- The stress effects of growth hormone (catabolic) versus the growth-promoting (anabolic) effects
- Insulin-like growth factor-I (IGF-I) (also called *somatomedin C)* as a major growth factor and its regulation by growth hormone
- The stress factors that regulate the secretion of growth hormone
- Factors initiating the pubertal increase in growth hormone secretion



Growth Hormone
—Peptide Hormone

Direct Catabolic Effects	Direct Anabolic Effects (growth)	Indirect Anabolic Effects (growth)
1. Decreases uptake of glucose in fat and muscle ∴ raises blood glucose	—Increased uptake of a.a. into cells	—Via growth factors
2. Mobilizes fats by increasing the activity of hormone sensitive lipase ∴ raises free fatty acids		
—In growth hormone deficiency, body fat increases		

GHRH—Growth Hormone Releasing Hormone
SST—Somatostatin
*dominant hypothalamic factor

Challenge test:
you take blood glucose level
then make hypoglycemic and
take blood glucose

Figure IX-6-1

INDIRECT ANABOLIC ACTIONS OF GROWTH HORMONE

Most of the anabolic actions of growth hormone are an indirect result of increased production of growth factors, which are called *somatomedins,* or *insulin-like growth factors* (IGFs). A major growth factor is somatomedin C, also called *IGF-I.*

The steps in the production and release of IGF-I are shown in Figure IX-6-2.

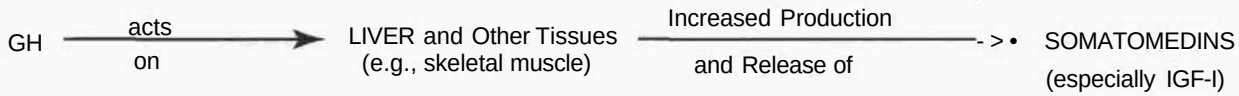


Figure IX-6-2

Specific Properties of the IGFs

IGF-I is a major anabolic growth factor. It:

- Is a circulating peptide growth factor similar in structure to proinsulin, and it has some insulin-like activity.
- Circulates in the blood tightly bound to a large protein, whose production is also dependent on growth hormone. Being bound to a protein, the plasma half-life is very long (20 hours).

Because it has a long half-life, plasma IGF-I serves as a reflection of 24-hour GH secretion. Growth hormone secretion is difficult to measure directly because it is secreted in pulses and mainly at night.

The major known anabolic effect of IGF-I is that it increases the synthesis of cartilage (chondrogenesis) in the epiphyseal plates of long bones; thereby increasing bone length.

It is also hypothesized that circulating IGFs increase lean body mass. The decreased lean body mass of aging may, in part, be due to the concomitant decrease in IGFs. IGFs also decrease in catabolic states, especially protein-calorie malnutrition.

IGF-II is another somatomedin, the importance of which is not well understood.

CONTROL OF GROWTH HORMONE (GH) SECRETION

GH secretion is pulsatile. The secretory pulses are much more likely to occur during the night in stages III and IV (non-REM) of sleep than during the day.

Pulses of GH are more frequent in pubertal adolescents than in younger children or in adults.

This increased GH secretion is facilitated by the pubertal increase in androgen secretion. At puberty, the increased androgen secretion is a major drive for increased GH secretion.

In males, the increased androgen arises from the testes. In females, it arises from the adrenal cortex.

Secretion of GH requires the presence of normal plasma levels of thyroid hormones. GH secretion is markedly reduced in hypothyroid individuals.

During the sixth decade of life and later, GH secretion diminishes considerably in both men and women. What initiates this decrease is unknown.

hypoglycemia promotes GH
exercise promotes GH
certain a.a. promotes GH

hyperglycemia inhibits GH

The main acute factors that control the secretion of GH are summarized in Figure IX-6-3.

The factors listed on the left inhibit GH secretion, and those on the right promote GH secretion. Each of the inhibitors could act by increasing SST (somatostatin) secretion, decreasing GHRH (growth hormone releasing hormone), or both.

Each of the promoters could act by increasing GHRH secretion, decreasing SST secretion, or both.

Notice that most of the factors that regulate growth hormone secretion are identical to those that regulate glucagon (except for those boxed). These factors are consistent with their shared role as stress hormones.

The inhibitory effect of IGF-I represents a negative feedback loop to the hypothalamus.

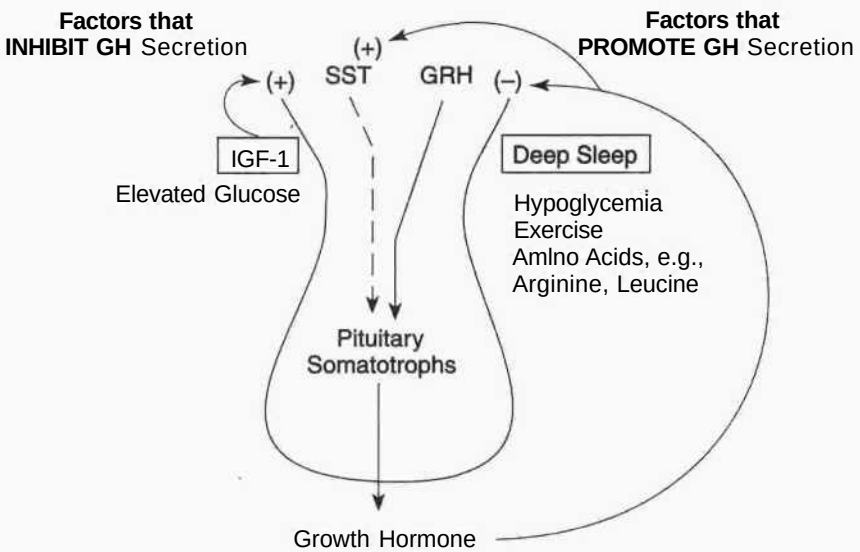


Figure IX-6-3

PATHOPHYSIOLOGICAL CHANGES IN GROWTH HORMONE SECRETION

Growth Hormone or IGF-I Deficiency

Prepuberty

Results in dwarfism. Normal growth hormone but decreased IGF-I results in Laron syndrome (Laron dwarfism), which is due to growth hormone insensitivity.

Postpuberty

A growth hormone deficiency is not a major problem and is very treatable.

Such individuals are more sensitive to insulin-induced hypoglycemia.

The most reliable, although not the safest, test for hypo-GH in adults is insulin-induced hypoglycemia. Determinations of the basal levels of growth hormone and IGF-I are not as reliable.

Hypersecretion of Growth Hormone

Prepuberty

Results in giantism.

Postpuberty

Results in acromegaly. This is an insidious, chronic, debilitating disease associated with bony and soft tissue overgrowth. The following represent the major characteristics:

Enlargement of the hands and feet (acral parts)

Protrusion of the lower jaw (prognathism), along with overgrowth of the facial bones, produces coarse facial features called *acromegalic fades.*

Increased amounts of body protein

Decreased amount of fat

Increase in the size of the visceral organs

Impaired cardiac function

Abnormal glucose tolerance curves

Chapter Summary

Most of the direct actions of growth hormone are consistent with its actions as a stress hormone; i.e., it decreases the peripheral uptake of glucose and promotes lipolysis.

Most of the anabolic actions of growth hormone are indirect via growth factors.

The most important growth factor is IGF-I, which increases the synthesis of cartilage in the epiphyseal plates of long bones.

The increased secretion of growth hormone during puberty is driven by a concurrent increase in androgen secretion.

The acute factors regulating growth hormone secretion are similar to those regulating glucagon and are consistent with their role as stress hormones.

Adrenal Medulla

7

GENERAL FEATURES OF ADRENAL MEDULLARY SECRETION

Normally 80% of the hormonal secretion of the adrenal medulla is epinephrine (adrenaline) and 20% is norepinephrine. The plasma half-life of the catecholamines is only about 2 minutes.

Removal of the adrenal medulla reduces plasma epinephrine to very low levels but does not alter plasma norepinephrine. This proves that the medulla is not an important source of norepinephrine.

Most circulating norepinephrine arises from postganglionic sympathetic neurons.

Because many of the actions of epinephrine are also mediated by norepinephrine, the adrenal medulla is not essential for life.

The vasoconstrictive action of norepinephrine is essential for the maintenance of normal blood pressure, especially when an individual is standing. Plasma norepinephrine levels double when one goes from a lying to a standing position. People with inadequate production of norepinephrine suffer from orthostatic hypotension.

The secretion of epinephrine by the adrenal medulla rapidly increases in response to:

Exercise

Emergencies

Exposure to cold

Severe hypoglycemia, which is a stimulus that causes a rise in all stress hormones (i.e., cortisol, growth hormone, glucagon, and epinephrine).

What the USMIE Requires You to Know

- The origin of plasma epinephrine versus plasma norepinephrine
- The major factors affecting the secretion of epinephrine from the adrenal medulla
- The effects of circulating epinephrine on carbohydrate and lipid metabolism
- Pheochromocytoma

MAJOR METABOLIC ACTIONS OF EPINEPHRINE

Mobilization of Substrates

Epinephrine acts to mobilize substrates; specifically:

Epinephrine enhances the breakdown of carbohydrate (glycogen) and fat (triglyceride). Thus, increased metabolic substrates are delivered to peripheral tissues. -$$40 f biwdAuMA^

Epinephrine does not induce the breakdown of protein.

Metabolic Rate

Epinephrine increases the metabolic rate. This will not occur without thyroid hormones or the adrenal cortex.

Actions Mediated by Binding of Epinephrine to the (3-Adrenergic Receptors

Specific Metabolic Actions of Epinephrine

CHO: Epinephrine increases the activity of liver and muscle phosphorylase, promoting glycogenolysis. This increases glucose output by the liver.

Because muscle lacks glucose-6-phosphatase, glucose cannot be released by skeletal muscle; instead, it must be metabolized at least to lactate before being released into the circulation.

Lactate produced by muscle in response to epinephrine can be metabolized in many tissues, including the liver.

The liver also can recycle lactate back to glucose. Through this cycle (the Cori cycle), the lactate arising from muscle glycogenolysis becomes a source of plasma glucose.

Triglyceride (TG): Epinephrine increases lipolysis in adipose tissue by increasing the activity of hormone-sensitive lipase. Glycerol from TG breakdown is a minor substrate for gluconeogenesis.

Permissive action of thyroxine and catecholamines
this explains tachycardia

Clinical Correlate
Pheochromocytomas

Tumors arising from sympathetic chromaffin tissue. Most release norepinephrine, but epinephrine or even dopamine can be secreted.

Hypertension, which may be episodic, is usually present. It is more severe in norepinephrine-secreting tumors.

Hyperglycemia, glucosuria, and side effects of the increased metabolic rate are often present.

Summary of the Metabolic Actions of Epinephrine on CHO and Fat

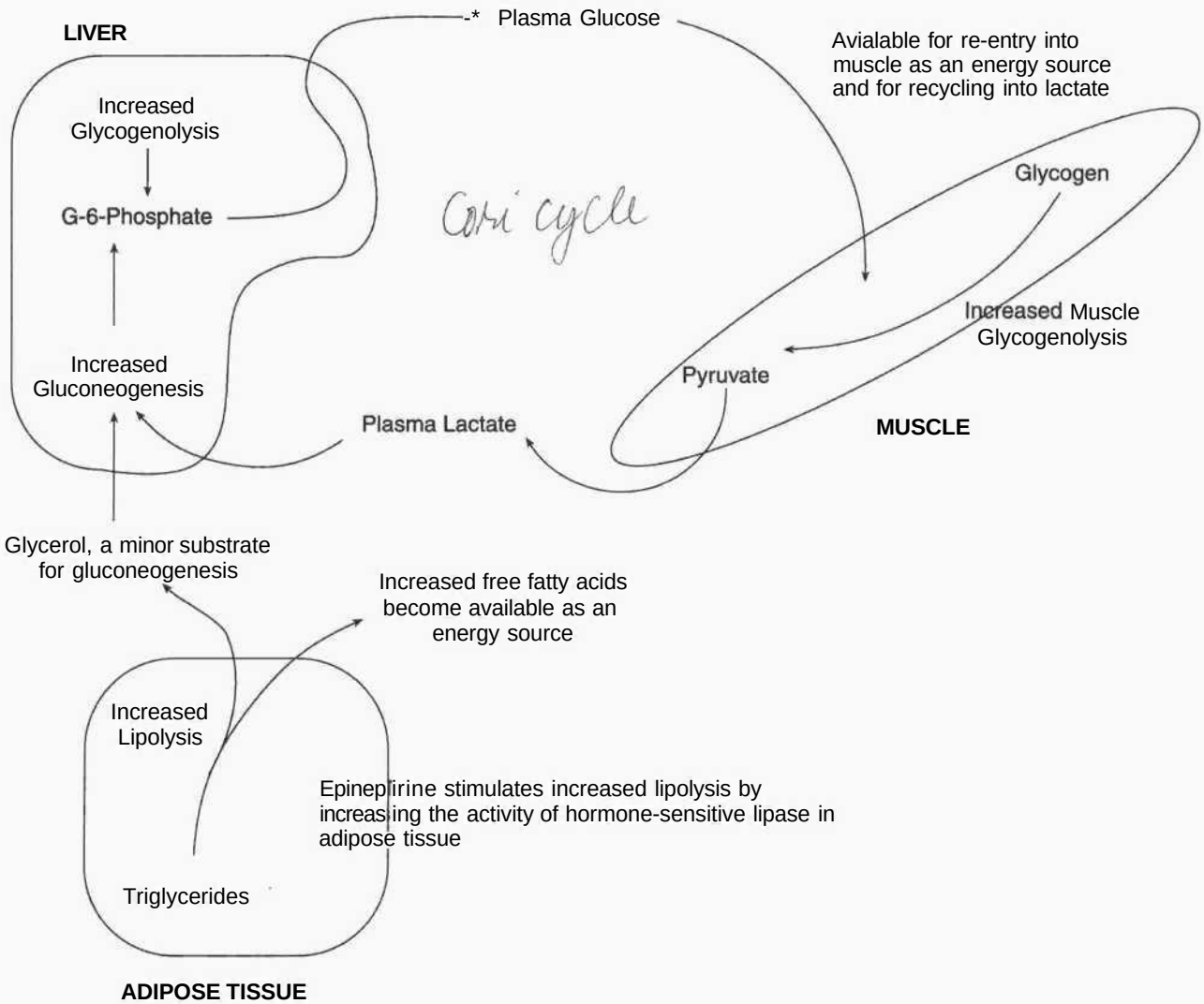


Figure IX-7-1

Chapter Summary

Circulating epinephrine originates mainly from the adrenals, whereas circulating norepinephrine arises mainly from sympathetic nerve endings.

Epinephrine is a stress hormone secreted in response to exercise, exposure to cold, and hypoglycemia.

Epinephrine increases blood glucose via liver glycogenolysis. It also stimulates muscle glycogenolysis, but muscle does not release glucose.

Epinephrine increases the release of fatty acids from adipose tissue by increasing the activity of hormone-sensitive lipase.

Pheochromocytomas are most consistently associated with hypertension.

Hormonal Control of Calcium and Phosphate

8

COMPARTMENTAUZATION OF CALCIUM IN THE BODY

The approximate percentage of the body's total calcium is given for each of the compartments in Figure IX-8-1. In addition, the fraction of Ca^{2+} is indicated. The Ca^{2+} concentration in the interstitial fluid is 10^3 to 10^4 higher than the intracellular Ca^{2+} concentration. The initiation of many cellular processes (secretion, movement of intracellular organelles, cell division) are linked to a sudden brief increase in intracellular (cytosolic) Ca^{2+}-

What the USMLE Requires You to Know

- The compartmentalization of calcium
- The relationship between free calcium and free phosphate
- The regulation of parathyroid hormone (PTH) secretion and its peripheral actions, which are the primary factors helping maintain constant plasma calcium levels
- The regulation and peripheral actions of calcitonin
- Primary and secondary disorders of PTH secretion
- The different forms of vitamin D and its peripheral actions, which help maintain plasma calcium and phosphate levels
- Vitamin D deficiency as an example of secondary hyperparathyroidism

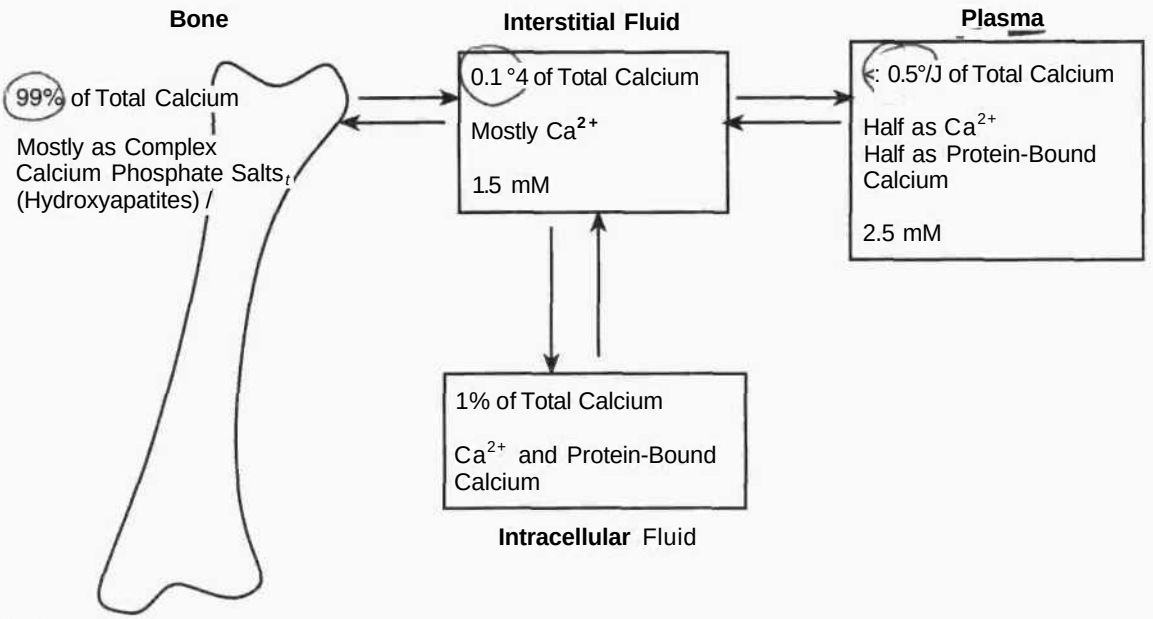


Figure IX-8-1

Body Monitors + Measures: Free ionized Ca^{2+}

Plasma Calcium

Of the Ca^{2+} in plasma, 40% is attached to protein and another 15% is associated with anions such as phosphate and citrate. The remaining 45% is ionized (free). As schematically shown in Figure IX-8-2, the free ionized and bound forms are in equilibrium. The free Ca^{2+} is the physiologically active and precisely regulated form. The ratio of free to bound Ca^{2+} is pH dependent. It decreases in alkalosis and increases in acidosis.

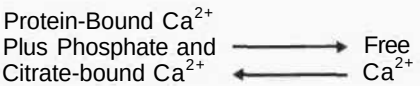


Figure IX-8-2

RELATIONSHIP BETWEEN CALCIUM AND PHOSPHATE

There is a chemical equilibrium between calcium and phosphate. Thus, calcium homeostasis cannot be considered without understanding the relationship between calcium and phosphate.

Bone is a complex precipitate of calcium and phosphate called *hydroxyapatite*, which is laid down in a protein (osteoid) matrix. Whether calcium and phosphate are laid down in bone (precipitate from solution) or are resorbed from bone (go into solution) depends on the product of their concentrations rather than on their individual concentrations.

When the product exceeds a certain number (solubility product or ion product), bone is laid down:

$[Ca^{2+}]$ X [PO4] > solubility product = bone deposition

Thus, an increase in the interstitial fluid concentration of either Ca^{2+} or phosphate increases bone mineralization.

For example, an increase in plasma phosphate would increase the product of their concentrations, promote precipitation, and lower free calcium in the intersitial fluid.

When the product is below the solubility product, bone is resorbed:

$[Ca^{2+}]$ X $[PO_4]$ < solubility product = bone resorption

Thus, a decrease in the interstitial concentration of either Ca^{2+} or phosphate promotes the resorption of these salts from bone (demineralization).

For example, a decrease in plasma phosphate alone would promote bone demineralization. Increasing renal excretion of phosphate by itself would promote bone demineralization and a rise in interstitial free calcium.

It is the free Ca^{2+}, not the phosphate, that is regulated so precisely. Hormonal control of free Ca^{2+} levels is almost entirely achieved via parathyroid hormone.

$Ca^{2+} + PO_4 < SP$ when $\downarrow Ca^{2+}$

PTH
1. immediately goes to kidney to reabsorb Ca^{2+}
2. dumps PO_4 into urine ($\downarrow Ca^{2+} \times PO_4 < SP$) reduces spurious
3. the falling of the SP causes osteoclasts to be activated (demineralize bone for Ca^{2+})
4. Activate vit. D (responsible for absorb Ca^{2+} in GI)

$Ca^{2+} + PO_4 > SP$
activates osteoblasts
osteoblasts deposit Ca^{2+} into bone

PARATHYROID HORMONE (PTH)

General Features of PTH and Its Action

PTH is a peptide hormone released from the parathyroids in response to lowered interstitial free Ca^{2+}. **In fact, the only important physiological signal regulating release of PTH is free Ca^{2+}.**

The function of PTH is to raise free Ca^{2+}, which it does by several mechanisms. Some are fast acting, whereas others are slower to take effect.

Actions of Parathyroid Hormone That Raise Free Ca^{2+}

Rapid Actions of PTH

PTH increases Ca^{2+} reabsorption in the distal tubule of the kidney and decreases phosphate reabsorption in the proximal tubule. By decreasing renal phosphate reabsorption, PTH lowers plasma phosphate. This causes the product of the Ca^{2+} and phosphate concentrations to be less than the solubility product. This, in turn, promotes the resorption of these ions from bone and raises their concentration in the circulating blood.

Bone is immersed in a saturated aqueous solution of calcium and phosphate ions (the bone's interstitial fluid). This pool of calcium is separated from but readily exchanges with the ECF via the osteocytes and osteoblasts. The exchange process is summarized in Figure IX-8-3.

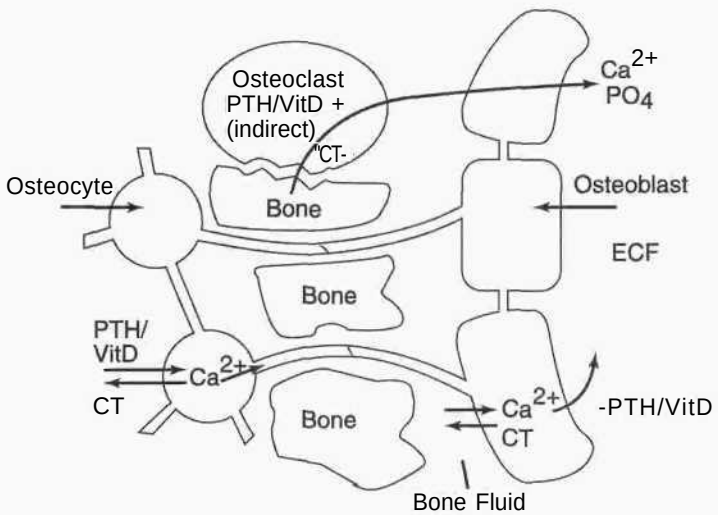


Figure IX-8-3

Slower Actions of PTH

PTH slowly increases the formation and activity of osteoclasts, which resorb bone, releasing Ca^{2+}.

PTH increases the formation of 1,25 di-OH D_3 (active vitamin D) in the proximal tubules of the kidney, which leads to increased absorption of Ca^{2+} and phosphate from the small intestine.

CALCITONIN

General Features

Calcitonin (CT) is a peptide hormone secreted by the parafollicular cells (C cells) of the thyroid gland. It is released in response to elevated free calcium.

Calcitonin lowers plasma calcium by decreasing the activity of osteoclasts, thus decreasing bone resorption.

Calcitonin is not a major controller of Ca^{2+} in humans.

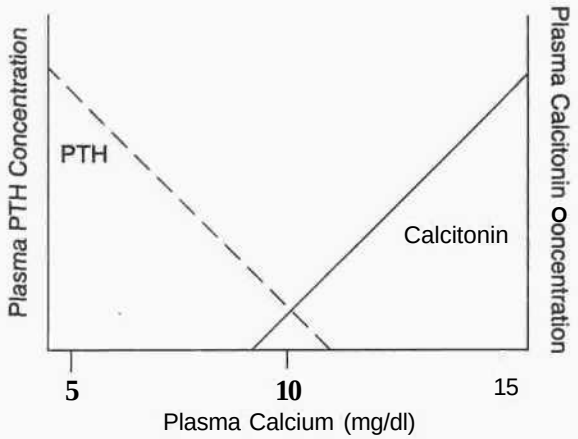


Figure IX-8-4

At a normal plasma calcium concentration (10 mg/dl), both PTH and calcitonin are secreted and PTH secretion is inversely related to the plasma concentration of ionized calcium (Ca^{2+}). Calcitonin secretion is directly related to Ca^{2+} concentration.

Note

Bone Cells

Osteoblasts (deposit bone) arise from osteoprogenitor cells of mesenchymal origin.

Osteocytes: Osteoblasts become entrapped in mineralized bone during bone growth or remodeling. They then differentiate into osteocytes.

Osteoblasts located on the surface of bone differentiate into the spindle-shaped cells that line the inner surface of bone (the endosteum).

Osteoclasts (resorb bone) arise from monocytes that migrate to bone. Several monocytes fuse to form the multinucleated osteoclasts.

The receptors for parathyroid hormone are actually on the osteoblasts, not the osteoclasts. Thus, there must be communication between these cells, and they can be considered a functional unit.

FUNCTION OF BONE CELLS IN THE REMODELING OF BONE

Bone Remodeling

Bone is undergoing continual remodeling throughout life, although the turnover is faster in younger individuals. As many as 300,000 bone-remodeling sites are active in a normal person.

More remodeling occurs in cancellous (trabecular or low-density) bone than in cortical (compact or high-density) bone. The remodeling sites are depicted in Figure IX-8-5.

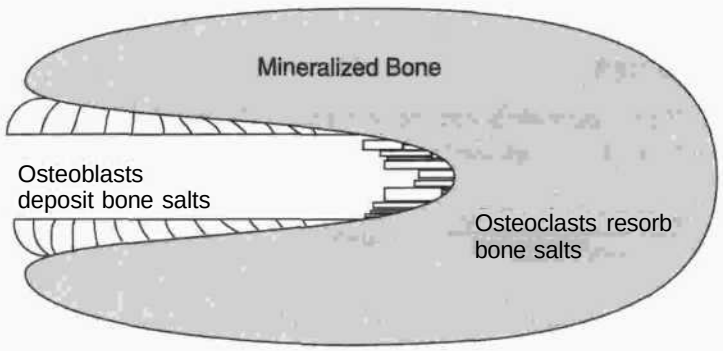


Figure IX-8-5

Active remodeling sites can be envisioned as advancing columns of bone-resorbing osteoclasts, followed by rows of osteoblasts, which lay bone down again. Upon mineralization, these remodeling sites become the basic structural units of bone (i.e., the osteons or Haversian systems). When surrounded by mineralized bone, the osteoblasts differentiate into osteocytes.

Weight-Bearing Stress

Though poorly understood, weight-bearing stress increases the mineralization of bone.

The absence of weight-bearing stress (being sedentary, bedridden, or weightless) promotes the demineralization of bone. Under these conditions:

- Plasma Ca^{2+} tends to be in the upper region of normal.
- Plasma PTH decreases.
- Urinary calcium increases.

Indices

Indices can be utilized to detect excess bone demineralization and remodeling:

- Increased serum alkaline phosphatase, an enzyme associated with osteoblastic activity
- Increased urinary excretion of hydroxyproline, a breakdown product of collagen

PRIMARY PATHOLOGICAL CHANGES IN PTH SECRETION

Signs of Primary Hyperparathyroidism

In primary hyperparathyroidism, the initiating factor is hypersecretion of PTH, usually by a tumor of the parathyroid gland or by ectopic parathyroid tissue. Excess PTH elicits:

Increased plasma calcium and decreased plasma phosphate. Even though phosphate is mobilized from bone plasma, phosphate decreases due to PTH inhibiting phosphate reabsorption in the proximal tubule and producing phosphaturia.

Polyuria and calciuria. Even though PTH increases calcium reabsorption by the kidney, the filtered load of calcium can greatly exceed T_M and calcium excretion increases.

Increased serum alkaline phosphatase and increased excretion of cAMP (second messenger for PTH in kidney), and hydroxyproline

Muscle weakness and easy fatigability

Signs of Primary Hypoparathyroidism

In primary hypoparathyroidism, the initiating factor is inadequate secretion of PTH by the parathyroid glands. Usually it is caused when parathyroid tissue is inadvertently removed during thyroid surgery.

PTH Deficiency Results in

Decreased plasma Ca^{2+} and increased plasma phosphate. Even though less phosphate is resorbed from bone, plasma phosphate increases because the normal action of PTH is to inhibit phosphate reabsorption and increase excretion by the kidney. Therefore, without PTH, more of the filtered load is reabsorbed.

Tetany (uncontrollable muscular contractions). Hypocalcemic tetany is due to an increased excitability of motor neurons.

Predictive Indices for a Primary Disorder

When plasma calcium and phosphate levels are changing in opposite directions, the cause is usually a primary disorder.

An exception maybe chronic renal failure. This state is not a primary disorder but is usually associated with hypocalcemia and hyperphosphatemia.

Clinical Correlate

Pseudohypoparathyroidism

This is a rare familial disorder characterized by target tissue resistance to parathyroid hormone. The defect is due to the deficiency of the Gs protein.

It presents with the same signs and symptoms as primary hypoparathyroidism, except plasma levels of PTH are increased.

It is usually accompanied by developmental defects: mental retardation, short and stocky stature, one or more metacarpal or metatarsal bones missing (short 4th or 5th finger).

Lab results
$Ca^{2+} = 14.5$
PTH 4-5

SECONDARY PHYSIOLOGICAL AND PATHOLOGICAL CHANGES IN PTH SECRETION

Because the only physiologically significant signal affecting PTH secretion is free calcium, changes in PTH secretion and secondary parathyroidism can be predicted from expected changes in circulating Ca^{2+}.

Secondary Hyperparathyroidism

In all of the following situations, there is a decrease in plasma Ca^{2+}, which elicits an increase in PTH secretion.

A diet deficient in vitamin D

Poor absorption of fat, thus decreased absorption of fat-soluble vitamin D

Inability to synthesize 1,25 di-OH D_3, as in severe kidney disease

Increased demand for Ca^{2+}, as in pregnancy or lactation

Thus, all of the above result in secondary hyperparathyroidism, which in these cases is characterized by:

Increased plasma PTH

Decreased plasma Ca^{2+} and a decreased Ca^{2+} excretion

Decreased plasma phosphate but often normal or increased phosphate excretion

Even though the elevated PTH increases phosphate resorption from bone, PTH also inhibits phosphate reabsorption by the kidney, thereby promoting phosphate excretion and a drop in plasma phosphate.

Secondary Hypoparathyroidism

In the case where there is excessive intake of vitamin D, there will be an increase in plasma Ca^{2+}, which will elicit an decrease in PTH secretion.

Vitamin D increases absorption of Ca^{2+} in the gut and resorption of Ca^{2+} from bone.

This is an example of secondary hypoparathyroidism and is characterized by:

- Decreased plasma PTH
- Increased plasma Ca^{2+} and increased Ca^{2+} excretion
- Increased plasma phosphate but often a normal or decreased phosphate excretion

Because PTH increases the excretion of phosphate by inhibiting reabsorption in the proximal tubule, decreased PTH will cause increased reabsorption of phosphate and drive plasma levels higher.

Predictive Indices for a Secondary Disorder

When the plasma calcium and phosphate are changing in the same direction, the origin is usually a secondary disorder.

- Secondary hyperparathyroidism: both decrease
- Secondary hypoparathyroidism: both increase

Ca = 14.5 ↑
PO_4 = 3.5 ↓

1. Check Ca^{2+} & PO_4 level are they moving in same or opposite direction
   Same → 2° pathology
   opp → 1° pathology
2. In 1° pathology the $[Ca^{2+}]$ parallels the physiology so if ↑ Ca^{2+} hyper ↓ Ca^{2+} hypo
3. In 2° pathology the $[Ca^{2+}]$ is antiparallel to the physiology.
   So if ↑ Ca^{2+} hypo ↓ Ca^{2+} hyper

ROLE OF VITAMIN D_3 (CHOLECALCIFEROL) IN CALCIUM HOMEOSTASIS

Sources of Cholecalciferol and Synthesis of 1,25 di-OH D3

Vitamin D_2 is a vitamin. It is a normal dietary component. A slightly different form, vitamin D_3, is synthesized in the skin. Its active form (1,25 di-OH D_3) is a hormone secreted by cells of the kidney's proximal tubule. The synthesis of 1,25 di-OH D_3 is outlined in Figure IX-8-6.

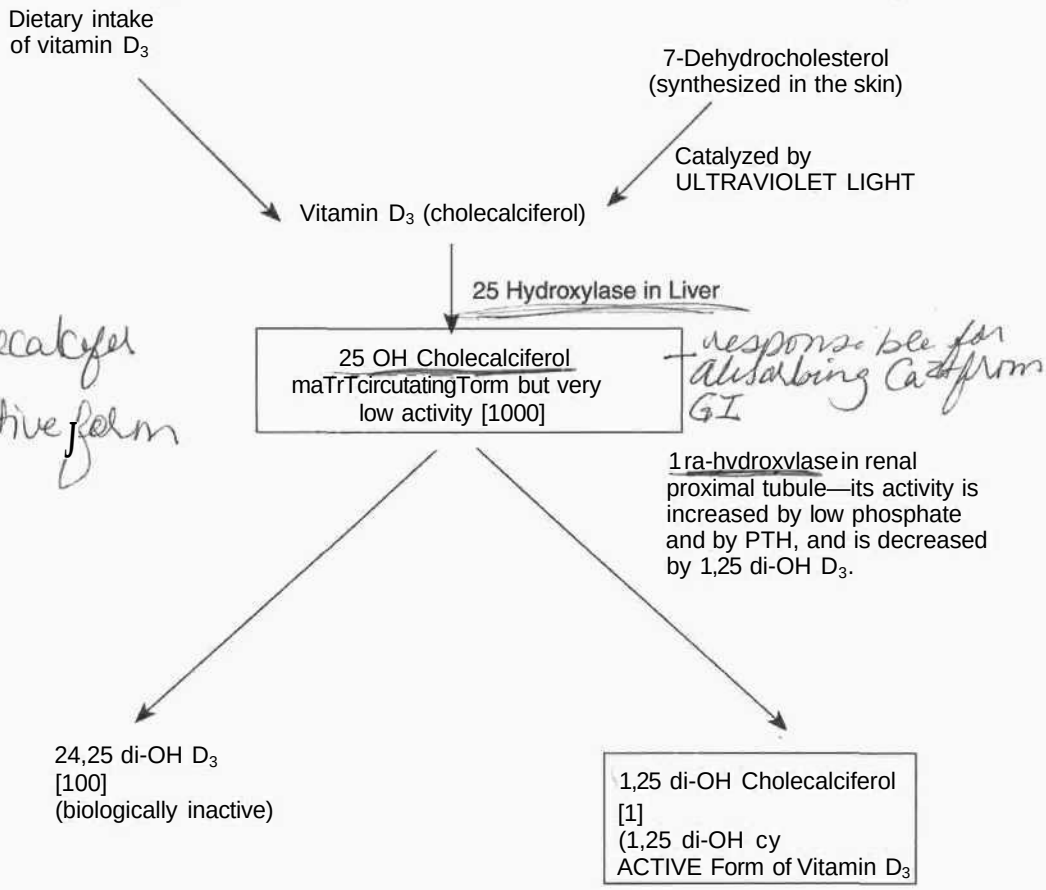


Figure IX-8-6

The synthesis of 1,25 di-OH D_3 occurs sequentially in the skin => liver => kidney. The relative numbers of molecules of each of the hydroxylated forms of D_3 present in the blood of a normal person are given in brackets. After its conversion to the 25 OH form in the liver, it can be stored in fat tissue. The serum levels of 25 OH vitamin D represent the best measure of the body stores of vitamin D when a deficiency is suspected. Most of the 25 OH form, which is the immediate precursor of 1,25 di-OH D_3, is converted to the inactive metabolite, 24,25 di-OH D_3- Ultraviolet (UV) light also evokes skin tanning, decreasing the penetration of UV light, and thus decreases the subsequent formation of D_3. This mechanism may prevent overproduction of D_3 in individuals exposed to large amounts of sunlight.

Actions of 1,25 di-OH D3

Under normal conditions, vitamin D acts to raise plasma Ca^{2+} and phosphate. Thus, vitamin D promotes bone deposition. This is accomplished by:

1,25 di-OH D_3 increases the absorption of Ca^{2+} and phosphate by the intestinal mucosa by increasing the production of Ca^{2+}-binding proteins. The details of this process are poorly understood.

The resulting high concentrations of Ca^{2+} and phosphate in the extracellular fluid exceed the solubility product, and precipitation of bone salts into bone matrix occurs.

1,25 di-OH D_3 increases the reabsorption of Ca^{2+} by renal distal tubule.

At abnormally high activity levels 1,25 di-OH D_3 increases bone resorption and release of Ca^{2+} and phosphate from bone. Receptors for 1,25 di-OH D_3 are on the nuclear membranes of osteoblasts. Through communication from osteoblasts, activated osteoclasts carry out the bone resorption. 1,25 di-OH D_3 requires the concurrent presence of PTH for its bone-resorbing action.

Effects of 1,25 di-OH D3 Deficiency on Bone

Bone decalcification (rickets in children, osteomalacia in adults) develops because vitamin D deficiency results in decreased absorption of Ca^{2+} and phosphate in the gut. As a result, the plasma concentrations of these ions never exceed the solubility product, and bone salts cannot be laid down into the matrix.

Decalcification with concomitant loss of bone matrix also occurs because the inadequate Ca^{2+} absorption lowers plasma Ca^{2+} slightly. This stimulates secretion of PTH (secondary hyperparathyroidism), which promotes bone reabsorption with liberation of calcium into the plasma. Serious hypocalcemia (tetany) is prevented at the expense of bone integrity.

Effects of 1,25 di-OH D3 Excess on Bone

Although vitamin D increases the intestinal absorption of calcium and phosphate, thereby increasing interstitial calcium and phosphate levels and promoting calcium deposition, the direct effect of vitamin D on bone is resorption, as mentioned above. Thus, excess vitamin D produces excess bone resorption, leading to osteoporosis.

Note that either a deficiency or an excess of vitamin D produces inadequate bone mineralization.

Clinical Correlate

Osteomalacia and Osteoporosis

In rickets, or osteomalacia, bone calcification fails to keep up with bone matrix formation, resulting in deformable, undermineralized bone.

In osteopenia, or osteoporosis, bone matrix formation fails to keep up with bone resorption, resulting in thin, fragile bones.

Chapter Summary

It is the free calcium in the interstitial fluid and plasma that is so precisely regulated. Free calcium is regulated mainly by PTH, which acts to raise calcium by both fast and slow actions.

Fast actions of PTH include increased calcium reabsorption in the renal distal tubule, inhibition of phosphate in the proximal tubule, and the transfer of free calcium from the interstitial fluid surrounding bone.

Slower actions include activation of osteoclasts to resorb bone and converting vitamin D to the active hormonal form.

In primary parathyroidism, plasma calcium and phosphate change in opposite directions, but they change in the same direction in secondary disorders.

The main circulating form of vitamin D is the 25-OH form, but the active physiological form is the 1,25 di-OH form.

Normally, vitamin D promotes bone deposition because it increases the plasma levels of both calcium and phosphate.

Vitamin D deficiency is an example of secondary hyperparathyroidism.

Thyroid Hormones

9

INTRODUCTION

In mammals, thyroid hormones are essential for normal growth and maturation. Therefore, thyroid hormones are major anabolic hormones.

Dietary intake, mainly in the form of iodide (I~) of about 500 |xg per day, is typical. To maintain normal thyroid hormone secretion, 150 µg is the minimal intake necessary. I- is the form absorbed from the small intestine.

What the USMLE Requires You to Know

- All steps in the synthesis and degradation of thyroid hormones
- The effect of dietary iodine on the synthesis of T_4 versus T_3
- Hormone structure versus activity
- Peripheral regulation of hormone activity
- Physiological actions of thyroid hormones
- Regulation of thyroid hormone secretion
- The most common thyroid disorders and the consequences of a dietary deficiency in iodine

THE ORGANIZATION OF THE THYROID AND THE DISTRIBUTION OF BODY IODINE

1. The functional unit is the follicle.
2. The lumen is filled with thyroglobulin, to which are covalently bound large numbers of thyroid hormone molecules.
3. Surrounding the lumen are the follicle cells, which function to both synthesize and release thyroid hormones.
4. These relationships are schematically represented in Figure IX-9-1.

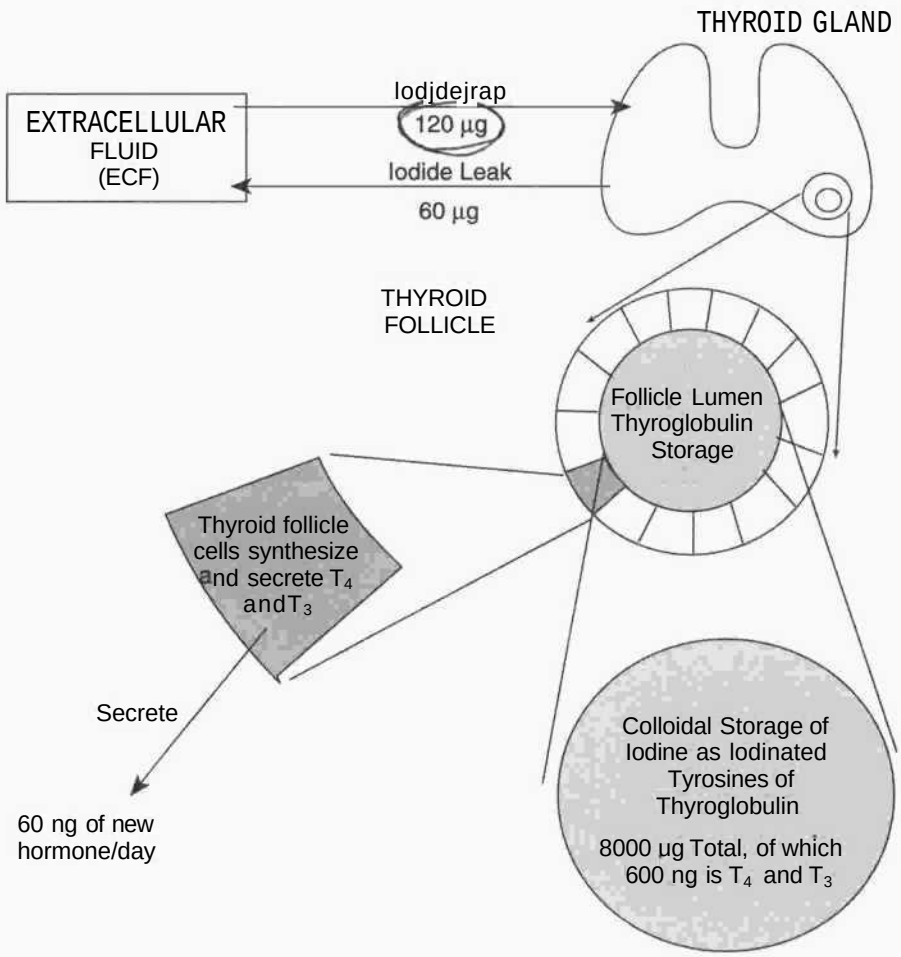


Figure IX-9-1

SYNTHESIS, STRUCTURE, AND SECRETION OF THYROID HORMONES

Synthesis of Thyroid Hormones

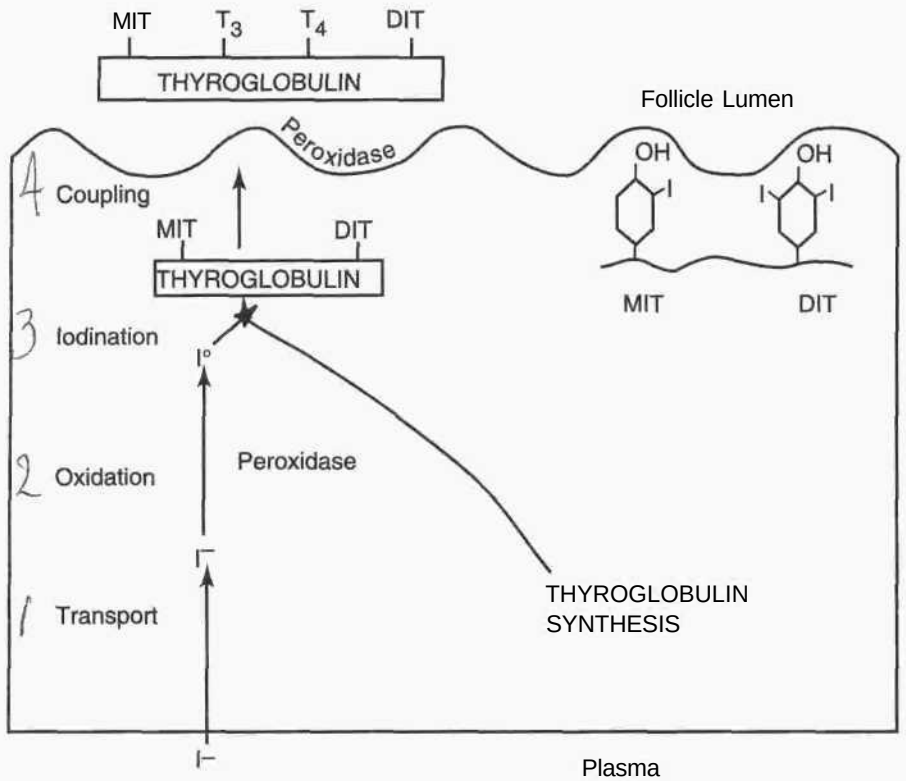


Figure IX-9-2

IodideTransport

An active transport mechanism (pump) on the basal surface of the thyroid follicle cell can raise the concentration of I~ within the cell to as much as 250 times that of plasma. The pump can be blocked by anions like perchlorate and thiocyanate, which compete with \~. Large amounts of iodide will also inhibit the pump and thyroid hormone synthesis (Wolff-Chaikoff effect).

The 24-hour iodide uptake by the thyroid is directly proportional to thyroid function. This is shown in Figure IX-9-3.

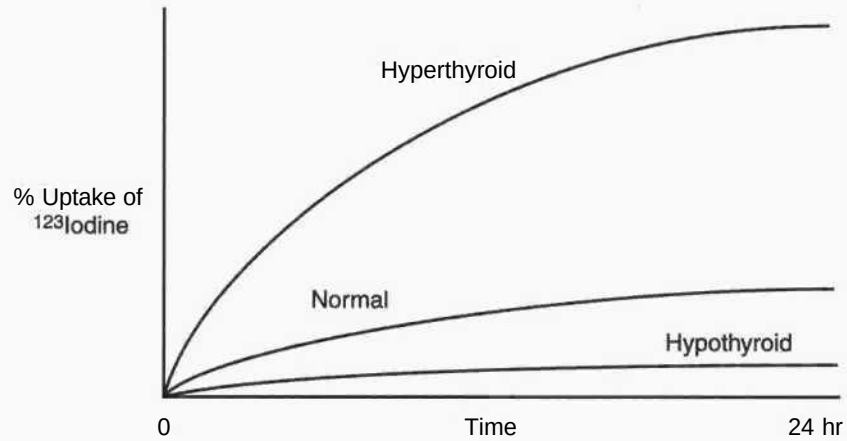


Figure IX-9-3

ThyroglobuUn Synthesis

A high molecular weight protein (>300,000 daltons) is synthesized in ribosomes, glycosylated in the endoplasmic reticulum, and packaged into vesicles in the Golgi apparatus.

Oxidation of I-to I"

The enzyme, peroxidase, which is located at the apical border of the follicle cell, catalyzes oxidation. Peroxidase also catalyzes iodination and coupling.

Iodination

As thyroglobulin is extruded into the follicular lumen, a portion (<20%) of its tyrosine residues are iodinated. The catalyst for this reaction is peroxidase.

The initial products of iodination are mono- and diiodotyrosine (MIT and DIT), respectively, with the latter form predominating, except when iodine is scarce.

Coupling

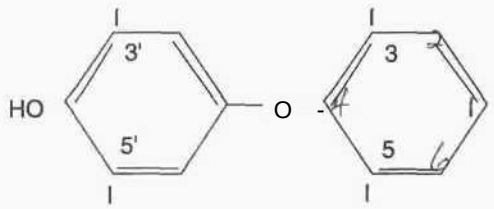
Peroxidase also promotes the coupling of iodinated tyrosine in the thyroglobulin molecule. When two DITs couple, tetraiodothyronine (T4) is formed. When one DIT and one MIT combine, triiodothyronine (T_3) is formed. When iodine is abundant mainly T_4 is formed. But when iodine becomes scarce the production of T_3 increases.

StorageofThyroidHormones

Enough hormone is stored as iodinated thyroglobulin in the follicular colloid to last the body for 2-3 months.

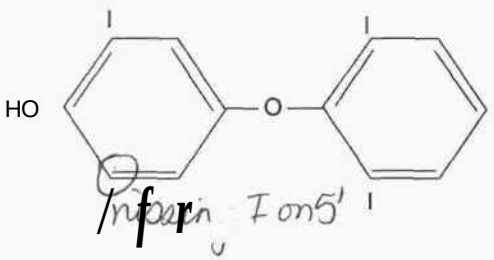
STRUCTURE OF THYROID HORMONES

The chemical structures of T_4, T_3, and reverse T_3 (rT_3) are shown in Figure IX-9-4. Do not memorize structure; rather, note the number and location of iodines attached to the tyrosine residues.



Thyroxine (T4) 3,5,3',5',-tetraiodothyronine

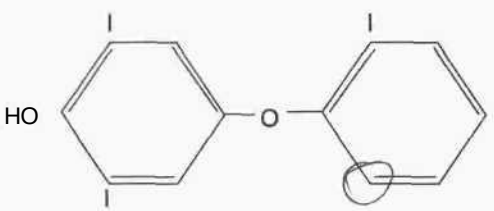
"Jhl Iodines are attached to 3+5



3,5,3'-Triiodothyronine (T_3)' most active Lind n.

-.More-Active Form_gf Hormone

U



3,3',5'-Triiodothyronine (reverse T3)

- No Activity[1]"

Figure IX-9-4

SECRETION OF THYROID HORMONE

Figure IX-9-5 illustrates the main steps in thyroglobulin degradation and the release of thyroid hormones.

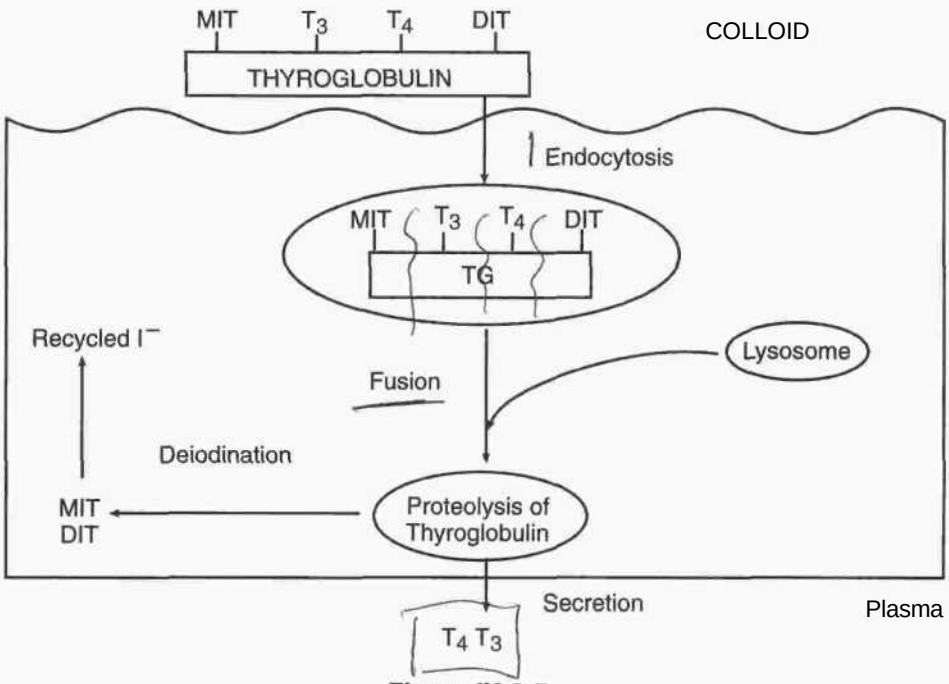


Figure IX-9-5

Endocytosis—Pieces of the follicular colloid are taken back into the follicle by endocytosis.

Fusion—The endocytosed material fuses with lysosomes, which transport it toward the basal surface of the cell.

Proteolysis of thyroglobulin—Within the lysosomes, the thyroglobulin is broken into free amino acids, some of which are T4, T_3, DIT, and MIT.

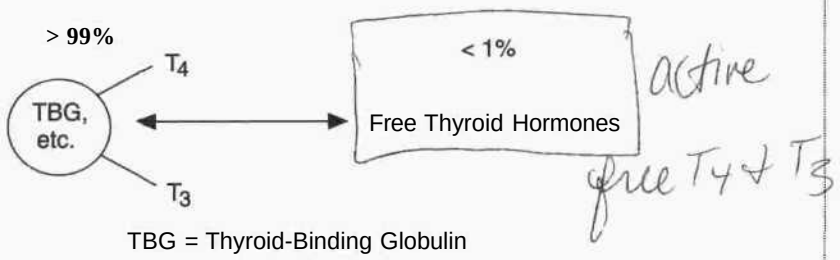
Secretion—T4 and T_3 are secreted into the blood, the ratio usually being about 20 T4 to 1 T_3. This ratio shifts toward T_3 in iodine deficiency.

Deiodination—A microsomal deiodinase removes the iodine from iodinated tyrosines (DIT and MIT) but not from the iodinated thyronines (T_3 and T_4). The iodine is then available for resynthesis of hormone. (Individuals with a deficiency of this enzyme are more likely to develop symptoms of iodine deficiency.)

TRANSPORT OF THYROID HORMONES IN BLOOD

Equilibrium between Bound and Free Circulating Thyroid Hormone

Figure EK-9-6 illustrates the equilibrium between bound and free circulating thyroid hormone.



TBG = Thyroid-Binding Globulin

Figure IX-9-6

T4 has the higher affinity for binding proteins; therefore, it binds more tightly to protein than T_3 does, and consequently the half-life of T4 is greater than that of T_3. Most circulating thyroid hormone is T4. Normally, there is 50 times more T4 than T_3.

T_4 half-life = 6 days

T_3 half-life = 1 day

you have to look at free T_3 to say whether hyper or hypothyroidism (bio. activity)

$T_4 \rightarrow T_3$

The amount of circulating thyroid hormone is about 3 times the amount normally secreted by the thyroid gland each day. Thus, circulating protein-bound thyroid hormones act as a significant reserve.

ACTIVATION AND DEGRADATION OF THYROID HORMONES

T_3 and T4 bind to the same nuclear receptor but T_3 binds more strongly than T4. Thus, because it has greater affinity for the receptor, T_3 is the more active form of thyroid hormone. Some also believe that T4 can be considered simply a prohormone of T_3 and that most of the peripheral activity results from the conversion of T_4 to T_3.

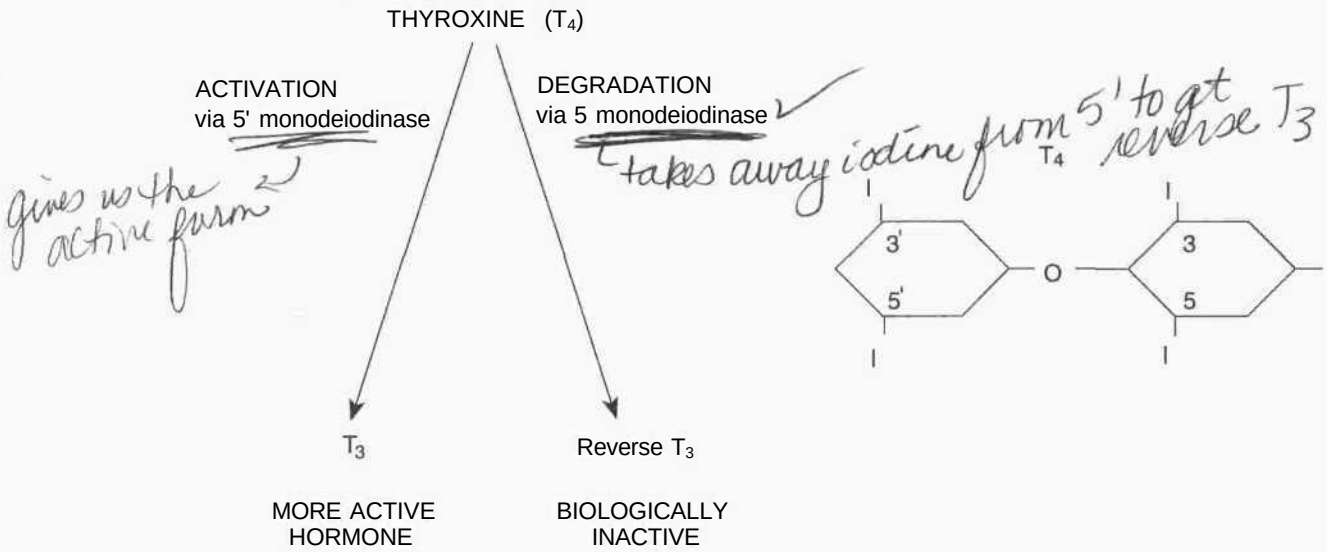


Figure IX-9-7

Many tissues can regulate the conversion of T4 to either T3 or rT^, thereby locally controlling hormone activity. This peripheral conversion of thyroid hormone is represented in Figure IX-9-7.

PHYSIOLOGICAL ACTIONS OF THYROID HORMONES

In many tissues, thyroid hormones are not the prime indicators or the major inhibitors of specific cellular processes. Rather, a multitude of processes function properly only when optimal amounts of thyroid hormones are present. This underscores the permissive nature of thyroid hormones.

Metabolic Rate

Thyroid hormonss-iaefease metabolic rate, as evidenced by increasedO_2 consumption and heat jjrocluclioiL Thyroid hormones increase the activity or the membrane-bound Na/K-ATPase in many tissues, and it can be argued that it is the increased pumping ot Na^ that accounts for most of the increase in metabolic rate. The increase in metabolic rate produced by a single dose of T_4 occurs only after a latency of several hours but may last 6 days or more. Thyroid hormones do not directly affect the metabolic rate of nervous tissue, uterus, or testes. However, thyroid hormones are absolutely necessary for normal brain maturation and essential for normal menstrual cycles.

Growth and Maturation (T_4 and T3 Anabolic Hormones)

Fetalgrowth rates appear normal in the absence of tliyroid hormone production (i.e., if tlie fetus is hypothyroid).

However, without adequate thyroid hormones during the perinatal period, abnormalities rapidly develop in nervous system maturation.

Synapses develop abnormally and there is decreased dendritic branching and myelination. These abnormalities lead to mental retardation.

These neural changes are irreversible unless replacement therapy is started soon after birth.

Prepubertal growth, including bone ossification, is retarded in the absence of thyroid hormones.

Untreated juvenile hypothyroidism (cretinism) results in a form of dwarfism.

A stippled epiphysis is a sign of hypothyroidism in children.

There is no evidence that thyroid hormones act directly on growth or bone formation. Rather, thyroid hormone appears to be permissive or act synergistically with growth hormone or growth factors acting directly on bone.

Thyroid hormone is required for normal synthesis and secretion of growth hormone.

At puberty, increased androgen secretion drives an increased growth hormone secretion.

This will not occur with depressed levels of thyroid hormones.

Lipid Metabolism

Thyroid hormone accelerates cholesterol clearance from the plasma.

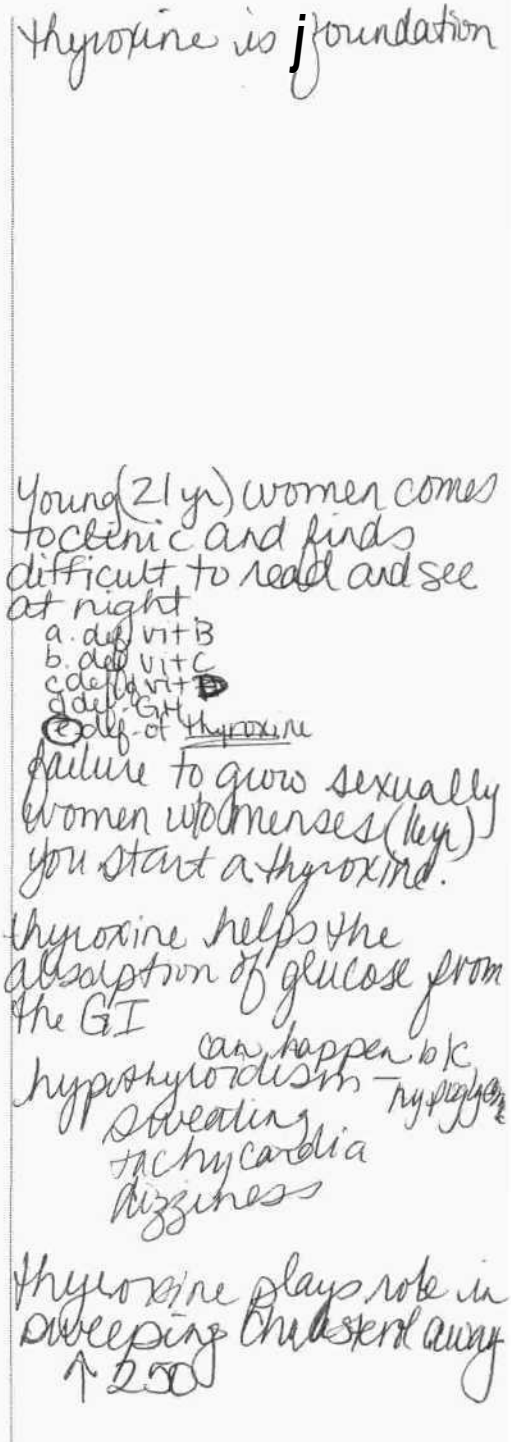
Thyroid hormones are required for conversion of carotene to vitamin A, and, as a consequence, hypothyroid individuals can suffer from night blindness and yellowing of the skin.

CHO Metabolism

Thyroid hormone increases the jgte of glucose absorption from the small intestine.

Autonomic System

Thyroid hormone increases the numbeg-and-afSnity of 3-adrenergic receptors in the heart, thereby increasing the sensitivity to catecholamines.



CONTROL OF THYROID HORMONE SECRETION

Feedback Relationships

Figure IX-9-8 shows the overall control of thyroid function.

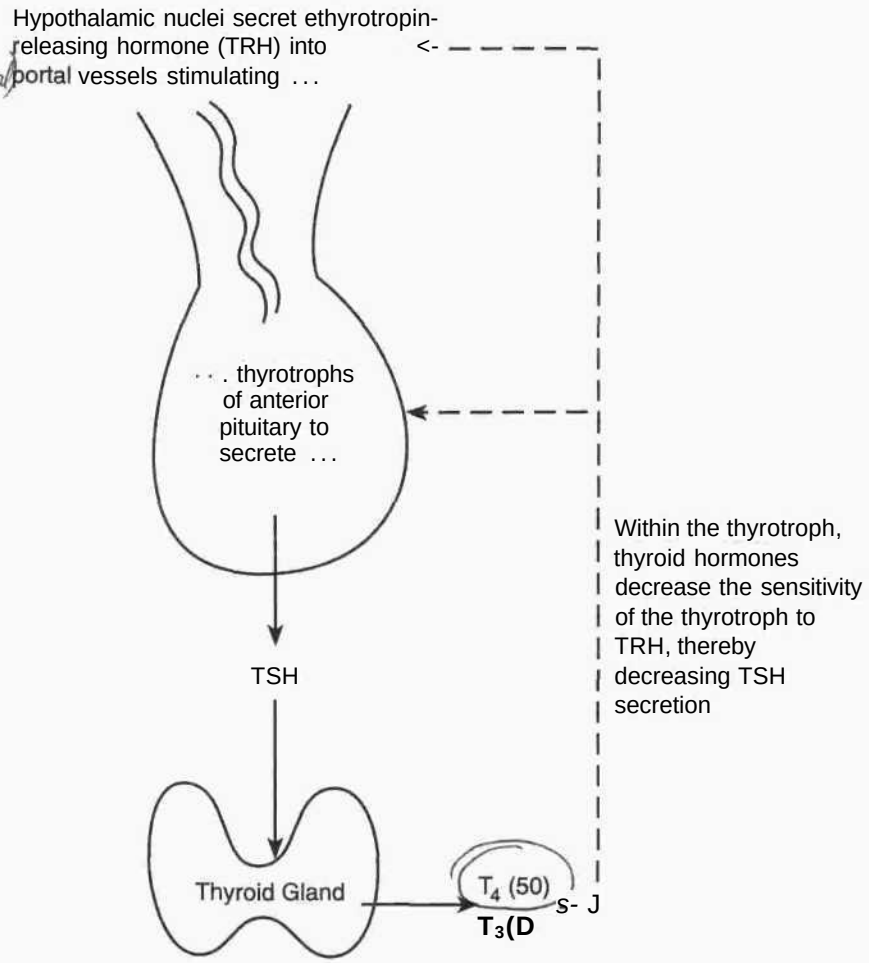


Figure IX-9-8

TRH provides a constant and necessary stimulus for TSH secretion. In the absence of TRH, the secretion of TSH (and T4) decreases to very low levels. The target tissue for TSH is the thyroid, where it increases the secretion mainly of T4.

Negative feedback of thyroid hormones is exerted mainly at the level of the anterior pituitary gland.

Because the main circulating form is T_4, it is T_4 that is responsible for most of the negative feedback.

However, within the thyrotrophs the T_4 is converted to T_3 before it acts to reduce the sensitivity of the thyrotroph to TRH.

As long as circulating free T_4 remains normal, changes in circulating T_3 have minimal effects on TSH secretion. However, TSH secretion increases if there is a significant drop in circulating free T4, even in the presence of an increase in circulating T_3.

Overall Effects of Thyrotropin (TSH) on the Thyroid

Rapidly Induced TSH Effects

TSH tends to rapidly increase (within minutes or an hour) all steps in the synthesis and degradation of thyroid hormones, including:

- Iodide trapping
- Thyroglobulin synthesis and exocytosis into the follicular lumen
- Pinocytotic reuptake of iodinated thyroglobulin back into the thyroid follicular cell
- Secretion of T4 into the blood

Slowly Induced TSH Effects

Changes that occur more slowly (hours or days) in response to TSH include:

- Increased blood flow to the thyroid gland
- Increased hypertrophy of the thyroid cells, which initially leads to increased size of the gland

Goiter

Excessive amounts of TSH eventually produce a goiter. A goiter is simply an enlarged thyroid and does not designate functional status. A goiter can be present in hypo-, hyper-, and euthyroid states. There is no correlation between thyroid size and function.

no correlation of size & function

Clinical Correlate

Low T_3 Syndrome

The activity of 5'-monodeiodinase is inhibited by many forms of metabolic stress, such as starvation, serious illnesses, or after surgery.

Circulating levels of T_3 decrease (metabolic rate decreases), but plasma levels of T_4 and TSH are usually within the normal range.

PATHOLOGICAL CHANGES IN THYROID HORMONE SECRETION

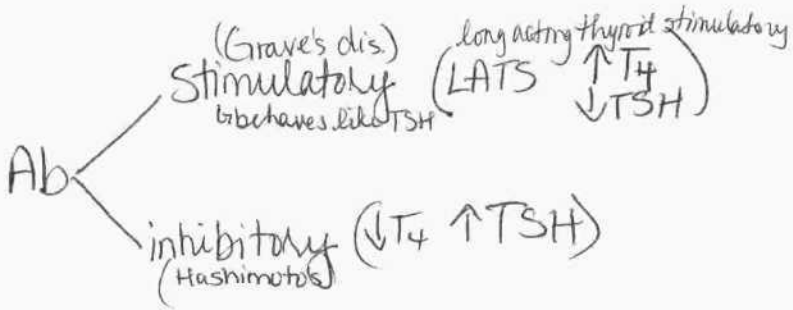
Abnormal feedback relationships are summarized in Table IX-9-1.

Table IX-9-1. The Changes in Feedback Relationships in Several Disorders

	T_4	TSH	TRH
1. Primary hypothyroidism*	⇓	⇑	⇑
2. Pituitary hypothyroidism (secondary)	⇓	⇓	⇑
3. Hypothalamic hypothyroidism (tertiary)	⇓	⇓	⇓
4. Pituitary hyperthyroidism (secondary)	⇑	⇑	⇓
5. Graves' disease (autoimmune)	⇑	⇓	⇓

The more sensitive indicator of primary hypothyroidism is the increased TSH, not the decrease in circulating T_4. Total circulating T4 represents mainly bound T_4, which is not an index of activity. However, the measurement of free T_4 index would be a sensitive indicator of thyroid status. The goal in replacement therapy for primary hypothyroidism is to raise plasma T4 to the point where TSH returns to normal.

A goiter can develop in all of the disorders shown in Table IX-9-1 **except** secondary and tertiary hypothyroidism. This underscores the point that there is no correlation between thyroid size and function.



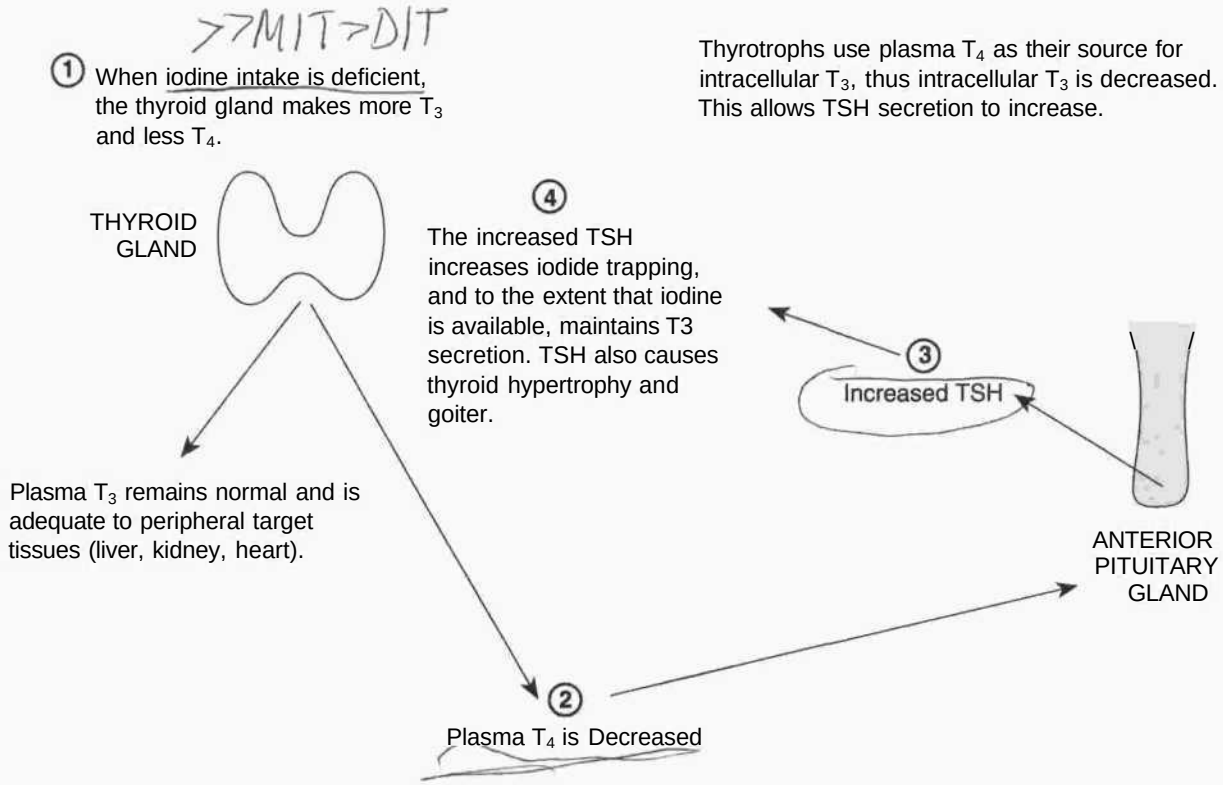


Figure IX-9-9

Thyroidal Response to Low Intake of Iodine

In most cases, if iodine is deficient in the diet but not absent, the individual will remain euthyroid but will develop a goiter. The changes are shown in Figure IX-9-9. The adaptive sequence occurs when dietary intake of iodine is deficient. The sequence of events begins with 1 (decreased secretion of T4) and proceeds through 4, the development of a goiter.

Characteristics of Hypothyroid Adults

Decreased basal metabolic rate and oxygen consumption. An elevated TSH is more diagnostic than the decrease in T4 in primary hypothyroidism. Thyroid-binding globulin, and thus total T_4, will increase in pregnancy and with the use of oral contraceptives. It will decrease in such disorders as nephrotic syndrome and with the use of androgens. Because of these changes, total T4 is often a poor index of thyroid function.

Decreased mental capacity: Thought and speed are slow, and memory is poor.

Plasma cholesterol and other blood lipids tend to be elevated (individuals are slightly overweight).

A complex of protein, hyaluronic acid, and chondroitin sulfate (mucopolysaccharide) accumulates in the extracellular space of the skin. Its oncotic action holds water, giving rise to a nonpitting edema (myxedema).

prolongation of relaxation phase of muscle plantar reflexes

Prolonged relaxation phase of deep tendon reflexes (stretch reflex), physiological jaundice (carotene accumulation), hoarse voice, constipation, anemia

Characteristics of Hyperthyroid Adults *fj-jQ V*

Increased metabolic rate and oxygen consumption

In spite of increased appetite, there is generally weight loss, protein wasting, and muscle weakness (thyrotoxic myopathy).

Excitability, irritability, restlessness

Tachycardia and increased cardiac output (increased B-adrenergic stimulation)

Exophthalmos (Graves' disease)

Chapter Summary

The synthesis of thyroid hormone is almost entirely T_4, but as iodine becomes scarce, the synthesis of T_3 increases.

T_3 is the more active form of the hormone, and peripheral tissues can regulate the conversion of T_4 into either T_3 (more active) or rT_3 (not active).

Thyroid hormones increase the metabolic rate of most tissues. Although it does not affect the metabolic rate of nervous tissue, it is absolutely necessary for postnatal brain maturation.

TSH is regulated mainly by circulating T_4, but the T_4 entering the thyrotrophs must be converted to T_3 before it affects the negative feedback loop.

The most sensitive indicator of primary hypothyroidism is the increase in TSH. The goal of replacement therapy is to suppress TSH back into a normal range.

A goiter is simply an enlarged thyroid and does not indicate functional status.

When iodine is deficient but not absent from the diet, the individual usually remains euthyroid but develops a goiter.

Male Reproductive System

10

OVERALL CONTROL OF ADULT MALE HORMONAL SECRETION

The factors involved in the overall control of adult male hormone secretion are summarized in Figure IX-10-1.

What the USMLE Requires You to Know

- Regulation of male hormone secretion
- Hormonal requirements for spermatogenesis
- Primary and secondary disorders in hormonal secretion
- Hormonal involvement in the development of male and female structures
- Mechanism of erection, emission, and ejaculation

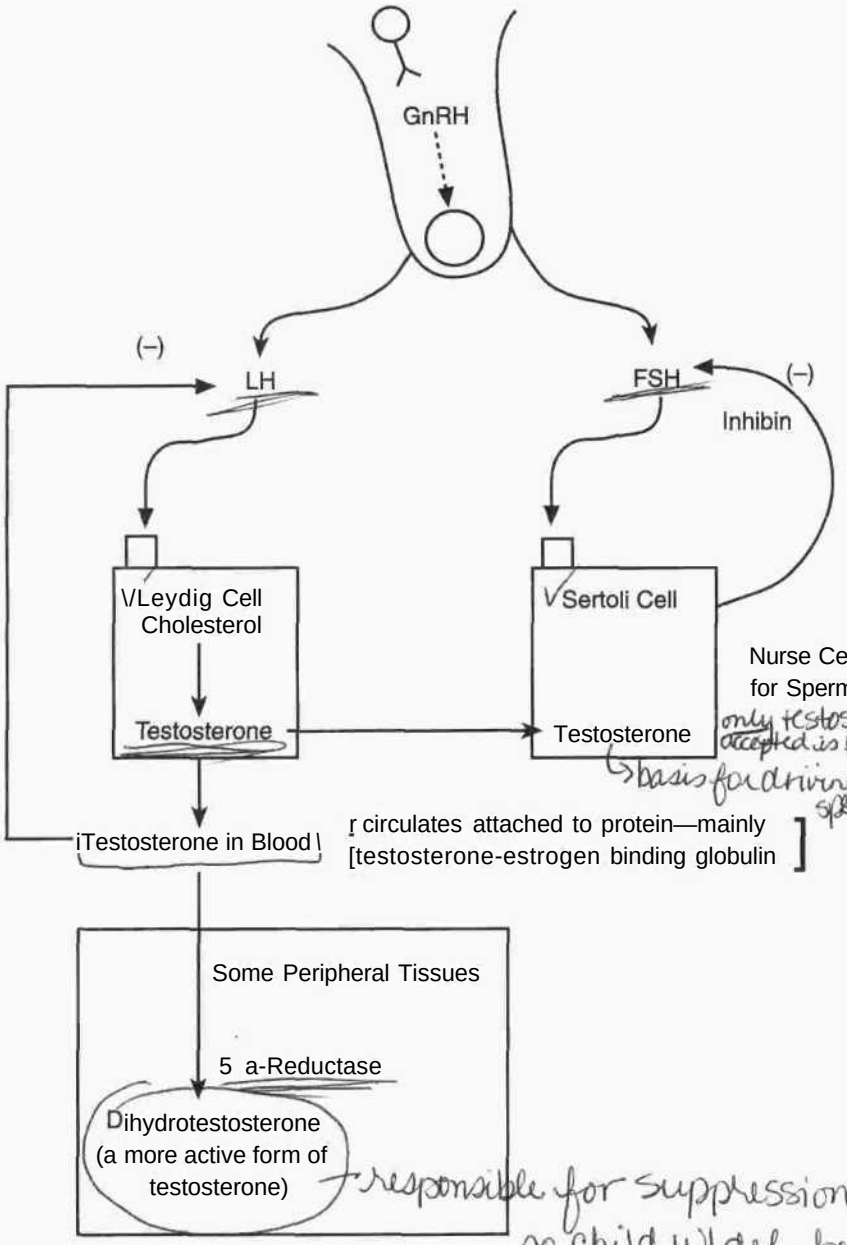


Figure IX-10-1

GnRH — synthesized in preoptic region of hypothalamus and secreted in pulses into hypophyseal portal vessels

- produces pulsatile release of LH and FSH
- pulsatile release of GnRH prevents down-regulation of its receptors in anterior pituitary

LH and FSH — produced and secreted by gonadotrophs of anterior pituitary.

- are glycoproteins
- TSH and hCG (human chorionic gonadotropin, secreted by placenta, has mainly LH activity) also glycoproteins
- all have a and P subunit. It is the p subunit that provides specificity.

Leydig cell testosterone — some diffuses directly to Sertoli cells where it is required for Sertoli cell function.

- produces negative feedback forLH

Sertoli cell inhibin — produces negative feedback for FSH

Hormonal Control of Testicular Function

Figure IX-10-2 illustrates the source and nature of the hormones controlling testicular function.

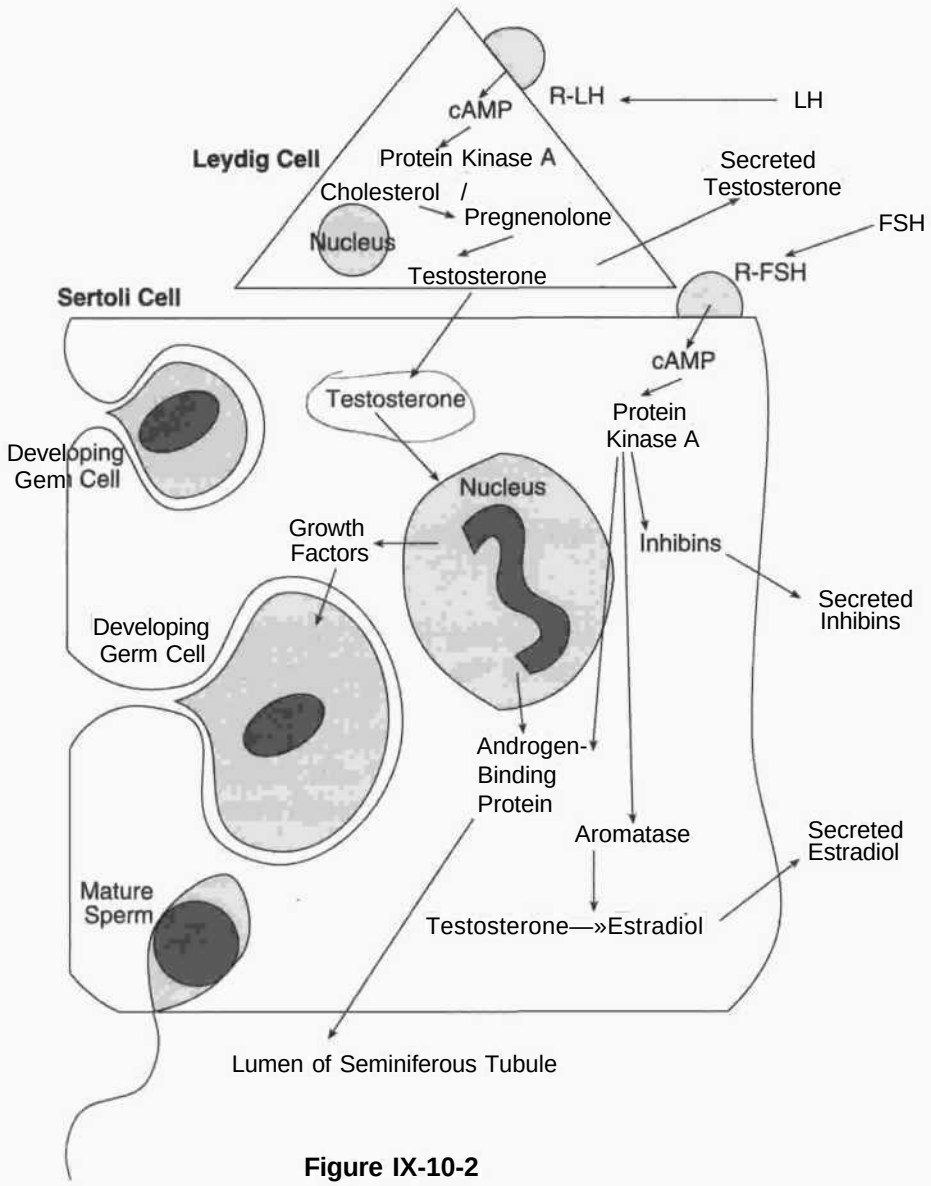


Figure IX-10-2

Sertoli Cells:
1. spermatogenesis
2. androgen binding proteins synthesized
3. you have aromatase which turns testosterone → estrogen

Definitions

Androgen: any steroid that controls the development and maintenance of masculine characteristics.

Testosterone: a natural male androgen of testicular origin, controlled by the luteinizing hormone (LH).

Dihydrotestosterone: a more active form of testosterone.

Methyl testosterone: a synthetic androgen, which is an anabolic steroid sometimes used by athletes.

Adrenal androgens: natural weak androgens (male and female) of adrenal origin, controlled by ACTH.

The Leydig and Sertoli Cells

LH receptors are located on the cell membranes of the interstitial cells of Leydig. When occupied with LH, these receptors, acting through cAMP/protein kinase as second messenger, stimulate increased conversion of cholesterol to pregnenolone. An increased amount of this hormonal precursor results in increased synthesis and secretion of testosterone.

Circulating testosterone provides a necessary negative feedback signal to both the hypothalamus and the anterior pituitary to regulate LH secretion.

Much of the testosterone synthesized by the Leydig cells diffuses into adjacent Sertoli cells.

An androgen-binding protein (ABP) synthesized by the Sertoli cells and secreted into the lumen of the seminiferous tubules helps maintain a high local concentration of testosterone. This protein is reabsorbed and destroyed by the epididymis and is rarely present in blood. The follicle-stimulating hormone (FSH), in conjunction with testosterone, increases the synthesis of this protein.

Normally, the concentration of testosterone in the testes is 50 times that of the blood.

In a normal male, testosterone acting locally facilitates spermatogenesis. Testosterone receptors are located on the nuclear chromatin of the Sertoli cell. Signals arising from these receptors increase the synthesis of proteins. This increases the movement of nutrient substances from the Sertoli cell to the developing germ cell. The membranes of the Sertoli cells surround the germ cells. Nutrients destined for the germ cells must pass through these membranes.

The actions of FSH, though poorly understood, are essential for the initiation of spermatogenesis.

FSH receptors are located on the plasma membrane of Sertoli cells. When occupied with FSH, these receptors acting through a cAMP/protejn-feiftase second messenger increase the production of proteins. **Both FSH anoyLeydig cell jestosteronejtre required for normal spermatogenesisT~** *• — ^21-^*

Note

Inhibins: peptide hormones secreted into the blood. They inhibit the secretion of FSH by pituitary gonadotrophs.

Aromatase: an enzyme that stimulates the aromatization of the A-ring of testosterone, converting it into estradiol. The physiological importance of this conversion is not understood; however, approximately a third of the estradiol in the blood of men arises from Sertoli cells, and the remainder arises from peripheral conversion of testosterone to estradiol by an aromatase present in adipose tissue. One sign of a Sertoii cell tumor is excessive estradiol in the blood of the affected man.

Based on the information presented on the previous pages, you should understand the hormonal changes in the summary in Table IX-10-1.

Table IX-10-1. Hormonal Changes in Specific Altered States

	Sex steroids	LH	FSH
1. Primary hypogonadism	⇓	It	f
2. Pituitary hypogonadism	ll	⇓	I
3. Postmenopausal women	⇓	ir	f
4. Anabolic steroid therapy (male)*	⇑ b/c artificial	⇓	£*)
5. Inhibin infusion (male)'	-	-	I
6. GnRH infusion (constant rate)*	⇓	i	1
7. GnRH infusion (pulsatile)	tr	t	f

*LH suppression causes Leydig cell atrophy in an adult male and therefore reduced testicular androgen production. Because Leydig cell testosterone is required for spermatogenesis, anabolic steroids suppresses spermatogenesis.

Although testosterone is not the normal feedback regulating FSH, high circulating testosterone activity will suppress the release of FSH.

'Because FSH is required for spermatogenesis, giving inhibin suppresses spermatogenesis.

^A constant rate of infusion of the gonadotropin-releasing hormone (GnRH) will cause a transient increase in LH and FSH secretion, followed by a decrease caused by the down-regulation of gonadotroph receptors.

Leydig cell testosterone ↓ so Leydig cell mo^ odhrvp*^.

What happens to libido in 70 yr. old man? stay same or maybe even slight ↑

4 AGE-RELATED CHANGES IN LH AND TESTOSTERONE SECRETION IN THE NORMAL MALE

Figure IX-10-3 depicts the relative plasma LH and testosterone concentrations throughout the life of the normal human male. The numbers refer to the descriptions that follow the figure.

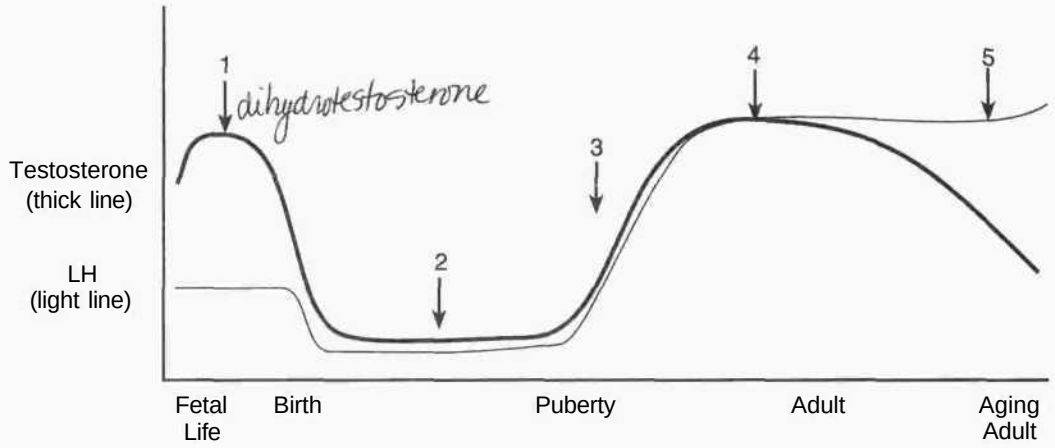


Figure IX-10-3

Clinical Correlate

Pseudohermaphrodite: an individual with the genetic constitution and gonads of one sex and the genitalia of the other.

Female pseudohermaphroditism: female fetus exposed to androgens during the 8th to 13th week of development, e.g., congenital virilizing adrenal hyperplasia.

Male pseudohermaphroditism: lack of androgen activity in male fetus, e.g., defective testes, androgen resistance.

When the loss of receptor function is complete, testicular feminizing syndrome results. Here MIH is present and testosterone is secreted, usually at elevated levels. The external structures are female, but the vagina ends blindly because there are no female internal structures.

Fetal Life

The development of male and female internal and external structures depends on the fetal hormonal environment. The Wolffian and Müllerian ducts are initially present in both male and female fetuses. If there is no hormonal input (the situation in the normal female fetus), female internal and female external structures develop (Müllerian ducts develop, Wolffian ducts regress).

Normal male development requires the presence of three hormones: testosterone, dihydrotestosterone, and the Müllerian inhibiting factor (MIH).

1. (hCG) + LH => Leydig cells => testosterone => Wolffian ducts
   5-a-reductase
2. testosterone => dihydrotestosterone ⇒ urogenital sinus and genital organs
3. Sertoli cells => Müllerian inhibiting factor (MIH) ⇒ absence of female internal structures.

MIH prevents the development of the Müllerian ducts, which otherwise would differentiate into female internal structures. In the absence of MIH, the Müllerian ducts develop. Thus, in addition to normal male structures, a uterus will be present.

Wolffian ducts differentiate into the majority of male internal structures; namely, epididymis, vasa deferentia, and seminal vesicles. In the absence of testosterone, the Wolffian ducts regress.

Dihydrotestosterone induces the urogenital sinus and genital tubercle to differentiate into the external scrotum, penis, and prostate gland. In the absence of dihydrotestosterone, female external structures develop.

Childhood

Within a few months after birth, LH and testosterone drop to low levels and remain low until puberty. The cause of this prolonged quiescence of reproductive hormone secretion during childhood is not known. Interestingly, LH secretion remains low in spite of low testosterone.

Puberty

Near the onset of puberty, the amplitude of the LH pulses becomes greater, driving the mean level of LH higher. Early in puberty, this potentiation of the LH pulses is especially pronounced during sleep. This increased LH stimulates the Leydig cells to again secrete testosterone.

Adult

During adulthood, LH secretion drives testosterone secretion. Thus, it is not surprising that the relative levels of the two hormones parallel one another.

Aging Adult

Testosterone secretion decreases with age. Men in their 70s generally secrete only 60-70% as much testosterone as do men in their 20s. Nevertheless, there is no abrupt decrease in testosterone secretion in men that parallels the relatively abrupt decrease in estrogen secretion that women experience at menopause. The loss of testosterone feedback will cause an increase in LH secretion.

EXTRAGONADAL PROPERTIES: THE ANABOLIC ACTIONS OF ANDROGENS

Effect on Growth during Puberty

During puberty, androgens promote the secretion in the following anabolic sequence:

At puberty, if T_4 is normal,

T androgens drives T growth hormone, which drives T IGF-1.

IGF-I is the major stimulus for cell division of the cartilage-synthesizing cells located in the epiphyseal plates of long bones. Thus, androgens stimulate the growth of long bones. This action of androgens is responsible for the taller average height of men than women.

(14) A boy who takes steroids the epiphyseal plate is closed

Near the end of puberty, androgens promote the mineralization (fusion or closure) of the epiphyseal plates of long bones. After closure has occurred, lengthening of the long bones can no longer occur. Estrogen can also cause plate closure, even in men.

The increased rate of growth of the long bones that also occurs during puberty in women may depend on the increased rate of secretion of adrenal androgens occurring at that time. This increased rate of secretion of adrenal androgens at puberty is sometimes referred to as *adrenarche.*

Effect on Muscle Mass

The capacity of androgens to stimulate protein synthesis, especially in muscle, is responsible for the larger muscle mass in men as compared with women.

Exogenous androgens (anabolic steroids) are sometimes taken by men and women in an attempt to increase muscle mass.

DEPENDENCE OF SPERMATOGENESIS ON LOWER TEMPERATURES OF THE SCROTUM

Effect on Fertility

For unknown reasons, spermatogenesis ceases at temperatures typical of the abdominal cavity. Thus, when the testes fail to descend before or shortly after birth, and the condition (cryptorchidism) is not surgically corrected, infertility results.

testicular and scrotal carcinoma have to have different tests b/c of different supply

CoolingMechanisms

Normally, the scrotum provides an environment that is 4°C cooler than the abdominal cavity. The cooling is accomplished by a countercurrent heat exchanger located in the spermatic cord. Also, the temperature of the scrotum, and the testes, is regulated by relative degree of contraction or relaxation of the cremasteric muscles and scrotal skin rugae that surround and suspend the testes.

Effect on FSH and LH

Sertoli cells, and therefore germ cell maturation, are adversely affected by the elevated temperatures of cryptorchid testes. In adults with bilaterally undescended testes, FSH secretion is elevated, probably as a result of decreased Sertoli cell production of inhibins. Testosterone secretion by the Leydig cells of cryptorchid testes also tends to be low, and as a result, LH secretion of adults with bilateral cryptorchidism is elevated.

ERECTION, EMISSION, AND EJACULATION

Erection

Erection is caused by dilation ofthe blood vessels (a parasympathetic response) - *(X HJT>\-* Of in the erectile tissue ofthe penis (the corpora- and ischiocavernous sinuses). This dilation increases the inflow of blood so much that the penile veins get compressed between the engorged cavernous spaces and the Buck's and dartos fasciae. As a result, for a brief period, inflow of blood to the penis exceeds outflow. Pressure within the penis sometimes equals arterial pressure during a full erection.

Mediators that remove the chronic state of vasoconstriction are probably vasoactive intestinal peptide (VIP) and/or nitric oxide (NO). Acetylcholine may also be involved.

Emission

Emission is the movement of semen from the epididymis, vasa deferentia, seminal vesicles, and prostate to the ejaculatory ducts. The movement is mediated by sympathetic (thoracolumbar) adrenergic transmitters.

Simultaneously with emission, there is also a sympathetic adrenergic-mediated contraction of the internal sphincter of the bladder, which prevents retrograde ejaculation of semen into the bladder. Destruction of this sphincter by prostatectomy often results in retrograde ejaculation.

Emission normally precedes ejaculation but also continues during ejaculation.

Ejaculation

Ejaculation is caused by the rhythmic contraction of the bulbospongiosus and the ischiocavernous muscles, which surround the base of the penis. Contraction of these striated muscles that are innervated by somatic motor nerves causes the semen to exit rapidly in the direction of least resistance, i.e., outwardly through the urethra.

Contrary to commonly held opinion, ejaculation is not parasympathetically mediated; rather, it is mediated by somatic motor efferents.

Chapter Summary

GnRH regulates the secretion of both FSH and LH. A pulsatile input of GnRH to the gonadotrophs is required to prevent down-regulation of its receptors.

LH stimulates Leydig cell testosterone, and testosterone is the negative feedback loop for LH.

Sertoli cells possess FSH receptors, and inhibin is the normal feedback loop for FSH.

Both FSH and Leydig cell testosterone are required for normal spermatogenesis.

The fetal ovary does not secrete hormones. Regardless of genetics (i.e., XX or XY), without input of the male developmental hormones, the fetus will develop female internal and external structures.

Normal male development requires testosterone (internal structures), dihydrotestosterone (external structures), and MIH (suppresses female internal structures).

At puberty, the increase of androgens drives the increase in growth hormone that drives the secretion of IGF-I, which increases bone length.

It is also androgen that causes the closure of the epiphyses and terminates growth. Estrogen will also do this.

Erection is mainly a parasympathetic response, whereas ejaculation requires sympathetic involvement.

Female Reproductive System

11

THE MENSTRUAL CYCLE

The Phases

The menstrual cycle can be divided into the following phases or events. By convention, the first day of bleeding (menses) is called day 1 of the menstrual cycle.

Follicular phase, also called the prohferative or preovulatory phase. This phase is dominated by the peripheral effects of estrogen, which include the replacement of the endometrial cells lost during menses.

Ovulation is characterized by the LH surge, which actually induces ovulation.

Luteal phase is dominated by the elevated plasma levels of progesterone, which, along with the secreted estrogen, prepares the uterus for implantation.

Menses. Withdrawal of the hormonal support of the endometrium at this time causes necrosis and menstruation.

What the USMLE Requires You to Know

- Hormonal regulation of the menstrual cycle
- Hormonal regulation of early versus late pregnancy
- Hormonal changes at parturition
- Hormonal maintenance of lactation

Follicular Phase (Approximately Day 1 to Day 14)

By convention, the first day of bleeding (menses) is called day one of the menstrual cycle.

During the follicular phase, FSH secretion is slightly elevated, causing proliferation of granulosa cells and increased estrogen secretion within a cohort of follicles.

One follicle, possibly the one with the best blood supply, secretes more estradiol than the others. Because estradiol acts locally within the follicle to increase the granulosa cells' sensitivity to FSH, this follicle becomes the dominant follicle, i.e., the one destined to grow and rupture. The remaining follicles, lacking sufficient FSH, synthesize only androgen and become atretic (die).

Figures IX-11-1 through IX-11-4 illustrate the hormonal regulation of the menstrual cycle. The graph represents the plasma hormonal levels throughout the cycle. The length of the menstrual cycle varies, but an average length is 28 days. Each of the plasma hormone concentrations is plotted relative to the day on which its concentration is lowest, i.e., just prior to menses (day 28). The accompanying diagram illustrates specific aspects of the phase under consideration.

foU^cuG^u phase:
mJur'- VA^ estrogen so estrogen level is low

middle: estrogen↑ →(−) LH, (−) FSH (inhibits)
local positive feedback estrogen →(+) estrogen

late: ↑estrogen →(+) LH
this is beginning of LH surge
Granulosa cells develop LH receptors (beginning of luteal phase)

Luteal Phase: early: LH receptors
late: ↑ progesterone →(−) LH

↑ progesterfnJL:
1. keeps ut
2. stops LH surge
↑ basic t
cervical mucus thickens

ovulation is due to: LH surge

14

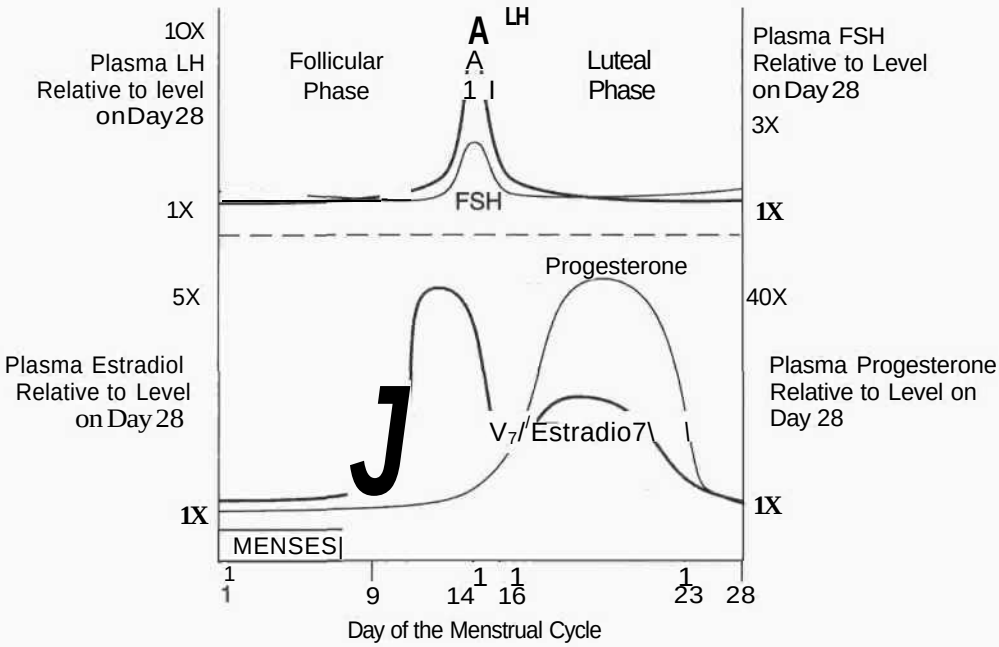


Diagram of Follicular Phase Relationships Approximately Day 1 to 14

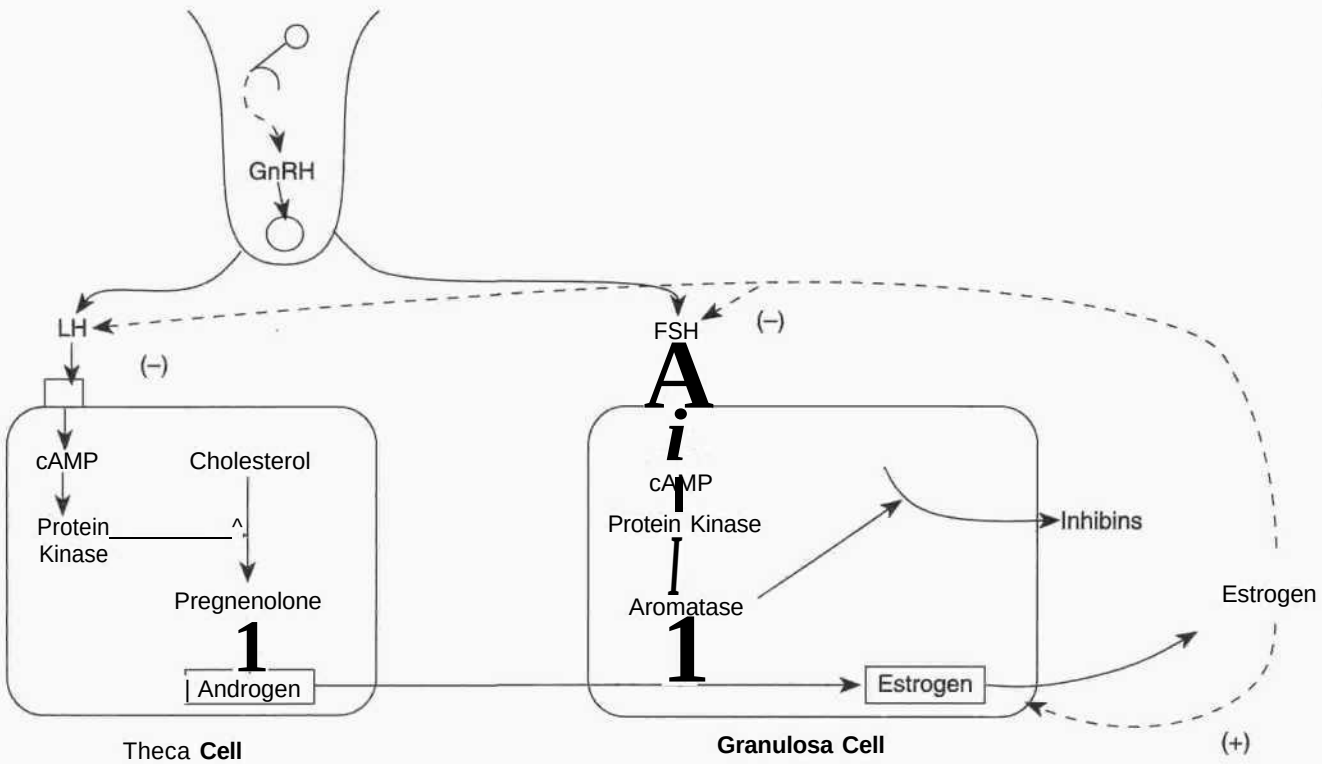


Figure IX-11-1

Theca Cells—Under LH stimulation, which acts intracellularly via cAMP, cholesterol is converted to pregnenolone (i.e., desmolase is activated). The pathway continues through intermediates to androgens. Little androgen is secreted; most of the androgen enters the adjacent granulosa cells.

Granulosa Cells—Possess the follicle's only FSH receptors. When coupled to FSH, these act via cAMP to increase the activity of aromatase; aromatase converts the androgens to estrogens (mainly estradiol).

Estrogen—Some of the estrogen produced by the granulosa cells is released into the blood and inhibits the release of LH and FSH from the anterior pituitary. However, another fraction of the estrogen acts locally on granulosa cells, increasing their proliferation and sensitivity to FSH. This local positive effect of estrogens causes a rising level of circulating estrogens during the follicular phase, but at the same time FSH is decreasing because of the inhibitory effect of estrogen on FSH release. Granulosa cells also release inhibins, but their role in the menstrual cycle is not understood.

Peripheral effects of estrogen produced by the granulosa cells during the follicular phase include:

- Circulating estrogens stimulate the female sex accessory organs and secondary sex characteristics.
- Rising levels of estrogens cause the endometrial cells of the uterine mucosal layers to increase their rate of mitotic division (proliferate).
- Circulating estrogens cause the cervical mucus to be thin and watery, making the cervix easy for sperm to traverse.

Ovulation

Ovulation takes place approximately on day 14.

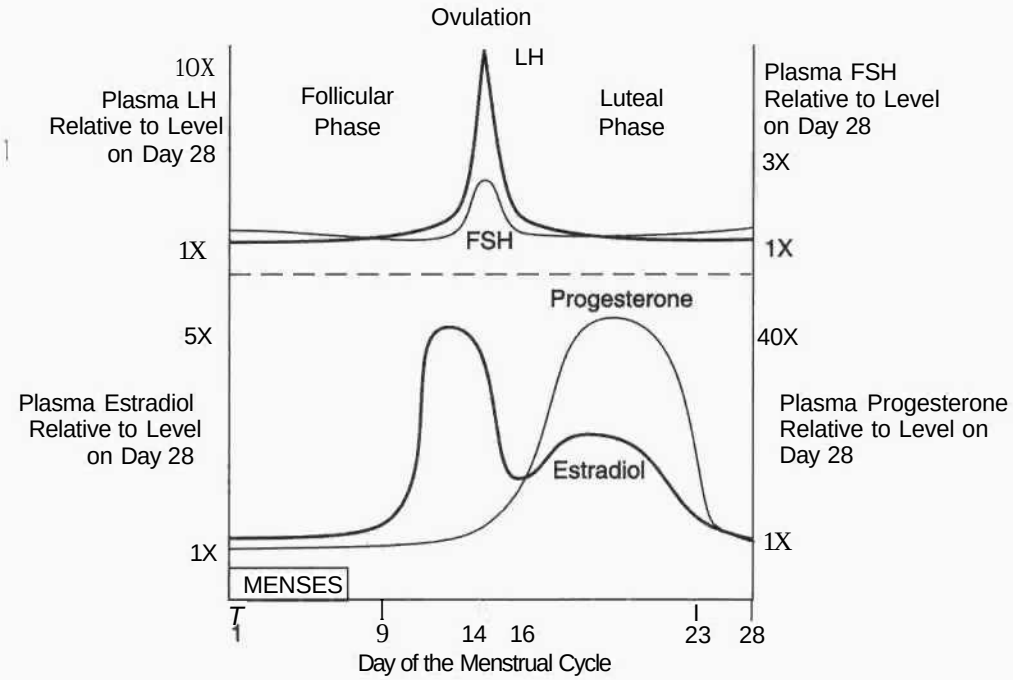
Estrogen Levels

As shown in Figure IX-11-2, near the end of the follicular phase, there is a dramatic rise in circulating estrogen.

When estrogens rise above a certain level, they no longer inhibit the release of LH and FSH. Instead, they stimulate the release of LH and FSH (negative feedback loop to positive feedback loop). This is illustrated in Figure IX-11-2.

This causes a surge in the release of LH and FSH. Only the LH surge is essential for the induction of ovulation and formation of the corpus luteum. Notice from Figure IX-11-2 that the LH surge and ovulation occur after estrogen peaks. Therefore, if estrogens are still rising, ovulation has not occurred.

Follicular rupture occurs 24—36 hours after the onset of the LH surge. During this time interval, LH removes the restraint upon meiosis, which has been arrested in prophase for years. The first meiotic division is completed, and the first polar body is extruded.



Ovulation Occurs Approximately Day 14

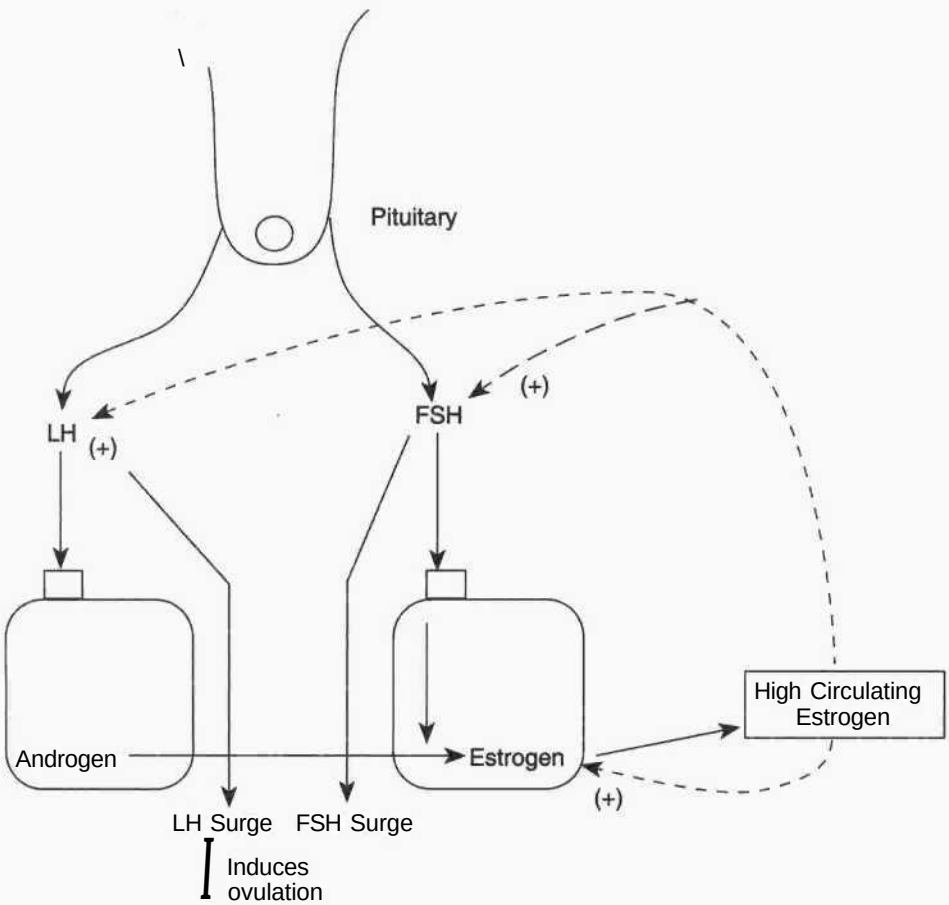
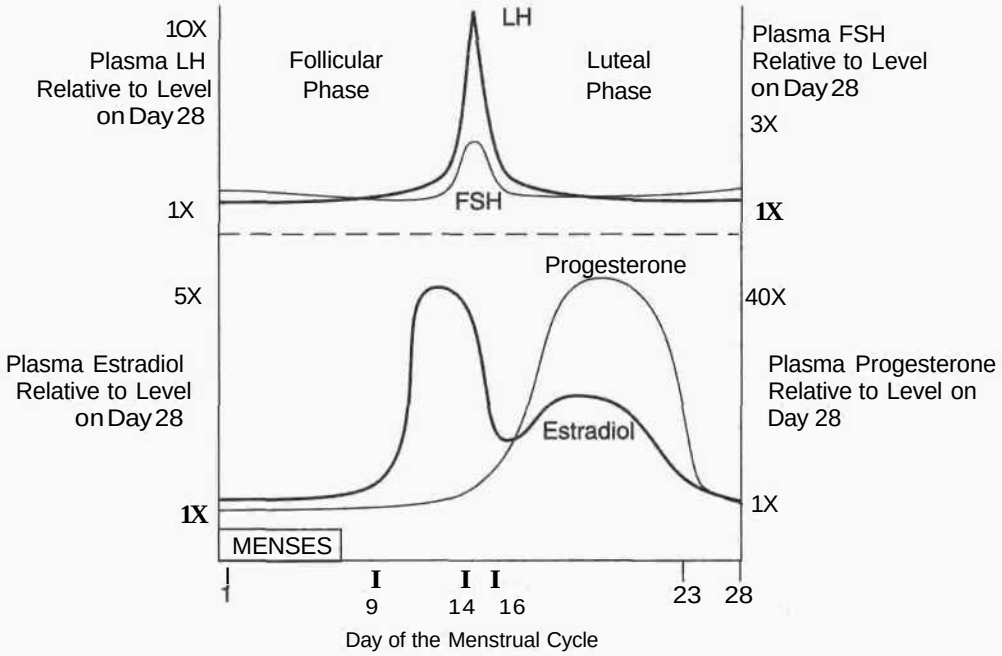


Figure IX-11-2



PREOVULATORY FOLLICLE, DAY 14 OF CYCLE

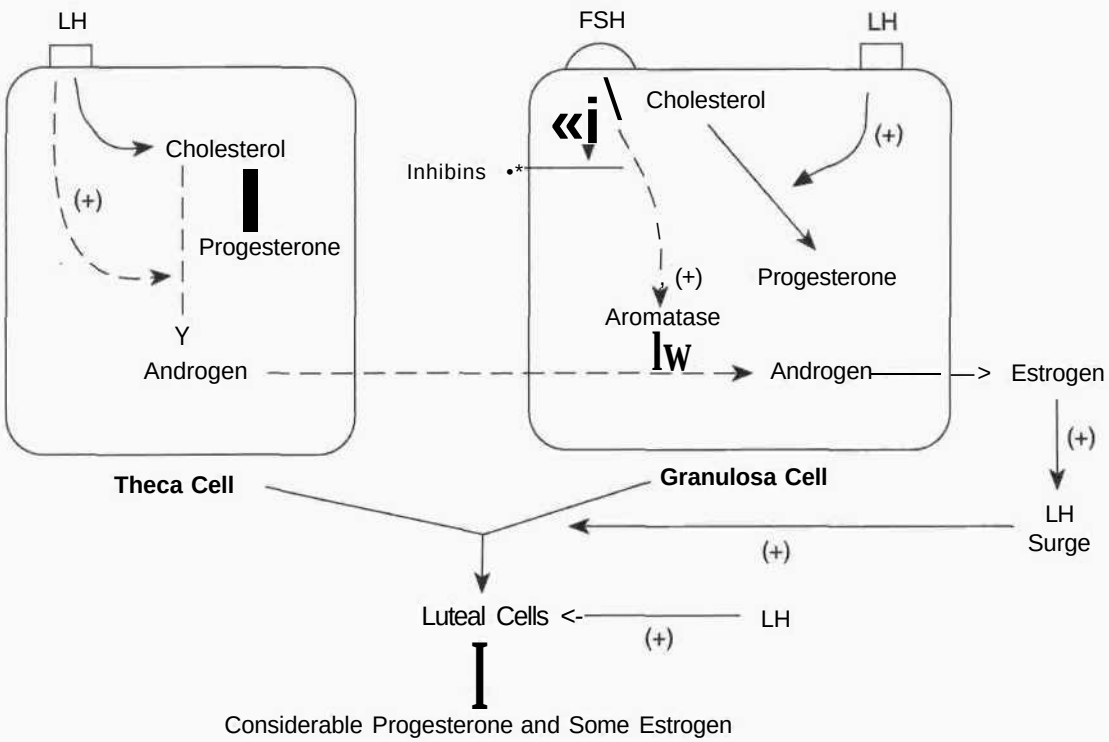


Figure IX-11-3

Luteal Phase (Approximately Day 14 to Day 28)

Preovulatory Follicle

In the latter stages of the follicular phase, intracellular changes within the granulosa and theca cells occur in preparation for their conversion into luteal cells. Estradiol, in conjunction with FSH, causes the granulosa cells to produce LH receptors. The metabolic pathways are then altered to favor the production of progesterone. This would include a decrease in the activity of aromatase and a drop in estrogen production.

This is illustrated in Figure IX-11-3. (Dashed lines represent pathways that are diminishing during the conversion to luteal cells.)

LH Surge

Induced by the elevated estrogens, it causes the granulosa cells and theca cells to be transformed into luteal cells and increase the secretion of progesterone.

Luteal Cells

Once formed, the luteal cells are stimulated by LH to secrete considerable progesterone and some estrogen. Progesterone inhibits LH secretion (negative feedback).

The increased plasma level of progesterone has several actions:

It causes the uterine endometrium to become secretory, providing a source of nutrients for the blastocyst.

It causes the cervical mucus to become thick, sealing off the uterus from further entry of sperm or bacteria.

It has thermogenic properties, causing the basal body temperature to increase by 0.5-1.0°F.

Luteal phase: glands thick (it lasts 14 days)
early: LH receptors → (+) Progesterone
late: ↑ progesterone → (−) LH

↑ progesterone
1. keeps uterine lining intact
2. terminates LH surge
3. causes ↑ in basic body temp (1°)
4. cervical mucus thickens

Luteal phase always 14 days
Follicular phase can change

→ 1st day of menses is 1st day of follicular phase
so the 1st day ends the luteal phase

So women w/ 31 day menses
the optimum time for
conception is 31-14=17

if menses is irregular
do a urinary analysis

Menses

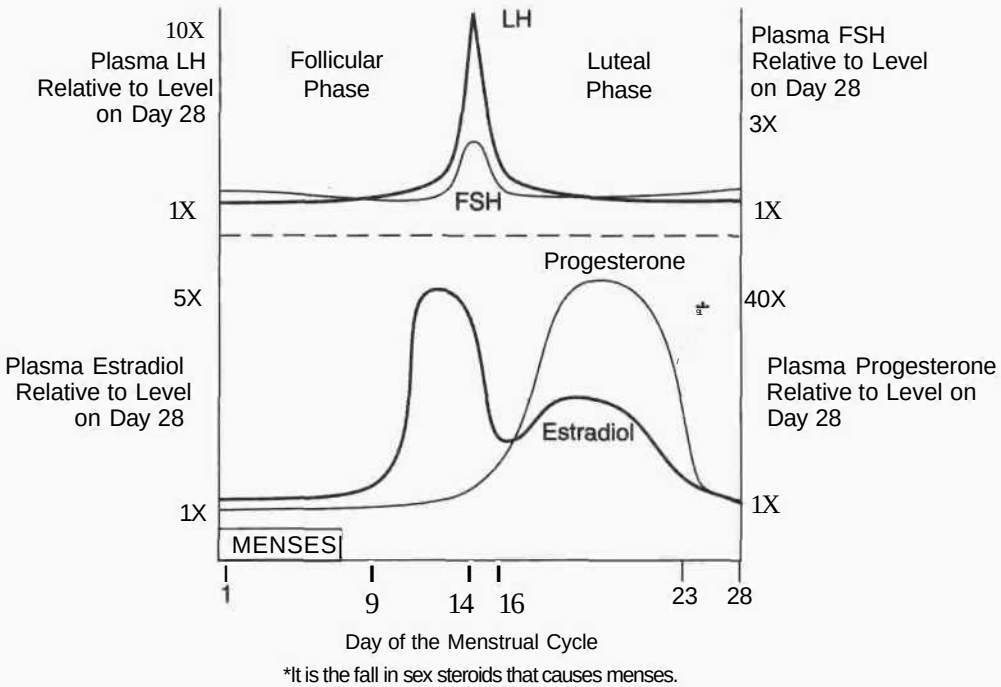
Progesterone inhibits the secretion of LH and contributes to the demise of the corpus luteum, because the corpus luteum depends on LH for its continued stimulation.

Progesterone secretion decreases not only in response to the decreased LH levels, but also the luteal cells become less responsive to LH 1 week after ovulation.

The lower plasma levels of progesterone (and estradiol) no longer support the endometrium, necrosis of the tissue occurs, spiral arterioles break, and menses ensues (loss of the superficial layer of the endometrium, along with some blood).

Menstruation is a passive process due to a lack of gonadal sex steroids.

28 day cycle
"unsafe period"
Day 9-18



*It is the fall in sex steroids that causes menses.

Figure IX-11-4

FEMALE SEX STEROID METABOLISM AND EXCRETION

Solubilization and Excretion

The female sex steroids undergo oxidation or reduction in the liver (and other target tissues), and a glucuronide or sulfate group is attached to the steroidal metabolite. This "conjugation" increases the solubility of the steroids in water, and they thus become excretable in urine.

Estradiol can be excreted as a conjugate of estradiol, but most is first converted to estrone or estriol.

Progesterone is converted in the liver to pregnanediol and is excreted as pregnanediol glucuronide.

Monitoring the Menstrual Cycle

The amount of sex steroids excreted in the urine can be used to monitor the menstrual cycle. For example:

Low progesterone metabolites and low but slowly rising estrogen metabolites characterize the early follicular phase.

Low progestone metabolites and rapidly rising estrogen metabolites characterize the latter part of the follicular phase just before ovulation.

Elevated levels of progesterone metabolites characterize the luteal phase and pregnancy.

New Cycle

During the 3 days prior to and during menses, plasma levels of progesterone and estradiol are at their low point; negative feedback restraint for gonadotropin secretion is removed. FSH secretion rises slightly and initiates the next cycle of follicular growth.

The length of the follicular phase of the menstrual cycle tends to be more variable than the length of the luteal phase. Long cycles are usually due to a prolonged follicular phase and short cycles to a short follicular phase. Once ovulation has occurred, menses generally follows in about 14 days. The length of the menstrual cycle in days minus 14 gives the most likely day of ovulation.

Estrogen Terminology

Estrogen: A generic term for any estrus-producing hormone, natural or synthetic

17β*-Estradiol: Major hormone secreted by the ovarian follicle

Estrone: Major form formed in peripheral tissues from androgens

Estriol: Major estrogen secreted by the placenta

Potency: Estradiol > estrone > estriol

PREGNANCY

Ovum Pickup and Fertilization

In women, the ovum is released from the rupturing follicle into the abdominal cavity, where it is "picked up" by the fimbria of the oviduct. Failure of ovum pick-up may result in ectopic pregnancy, i.e., the implantation of the blastocyst at any site other than the interior of the uterus.

Fertilization occurs in the upper end of the oviduct within 8-25 hours after ovulation. After this, the ovum loses its ability to be fertilized. Sperm retain their capacity to fertilize an ovum for as long as 72 hours after ejaculation.

Sperm are transported from the vagina to the upper ends of the oviduct by contraction of the female reproductive tract. The swimming motions of the sperm are important for penetration of the granulosa cell layer (cumulus oophorus) and membranes surrounding the ovum.

Low sperm counts (<20 million/ml of ejaculate) are associated with reduced fertility because sperm from ejaculates with low counts often contain many sperm with poor motility and an abnormal morphology.

Implantation

At the time of implantation, which occurs about 5 days after fertilization, the trophoblastic cells of the fetus begin to secrete a peptide hormone, human chorionic gonadotropin (hCG).

Fetal hCG possesses a p subunit similar to that of LH, and therefore it has considerable LH activity.

The presence of hCG in the urine can be detected by a variety of test kits for the detection of pregnancy.

Hormonal Maintenance of the Uterine Endometrium

Figure IX-11-5 illustrates the production of estrogen and progesterone during pregnancy. The figure is divided into three phases:

Part of the luteal phase before implantation

Early pregnancy

Late pregnancy

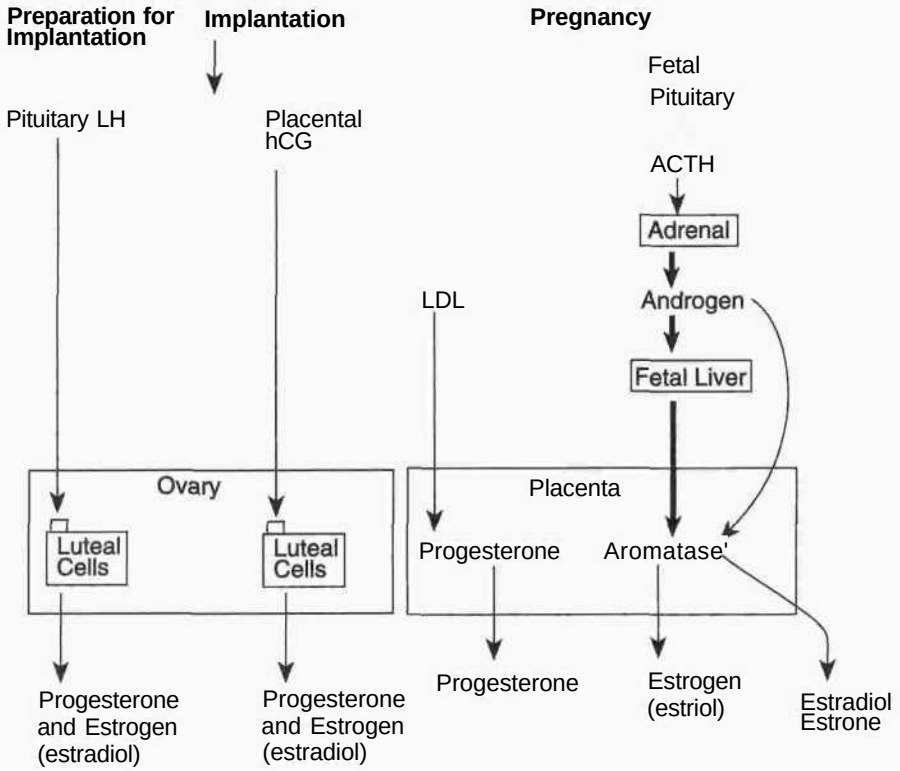


Figure IX-11-5

Preparation for Implantation (Luteal Phase)

Pituitary LH stimulates luteal cells to secrete progesterone and some estrogen. Because the ovaries are the source of the estrogen, it is mainly estradiol.

Implantation to Third Month

At the time of implantation, trophoblastic cells of the fetus begin to secrete hCG. By the 10th day after ovulation, the hCG concentration is sufficiently elevated to stimulate progesterone and estrogen secretion by the corpus luteum, thus rescuing the corpus luteum, which was otherwise destined to regress (i.e., pituitary LH maintains luteal progesterone and estrogen secretion for no more than 10 days after ovulation). hCG peaks in the first 3 months of pregnancy. During this time, it is essential for the continued secretion of progesterone and estrogen by the corpus luteum.

Fourth Month to Term

Placenta secretes enough progesterone and estrogen to maintain the uterus. This is not controlled by hCG. At this time, the ovaries (corpus luteum) can be removed and pregnancy continues.

Blastocyst → hCG
hCG → luteal cells → maintains corpus luteum

Progesterone secretion of the placenta is limited only by the amount of precursor (cholesterol) delivered by low-density lipoproteins (LDL) to the placenta.

Estrogen secretion during pregnancy involves a transfer of steroids from the fetal adrenal cortex and fetal liver to the placenta and then to the maternal circulation.

During midpregnancy, the fetal adrenal, which is as large as the fetal kidney, secretes considerable dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEAS) (weak androgens that do not create problems in a female fetus).

Sequential enzymatic action by the fetal liver and the placenta convert these androgens into estrogens, which enter the maternal circulation. The main estrogen produced is estriol.

Peripheral Effects of Hormonal Changes

The large amount of estrogen and progesterone secreted by the placenta during pregnancy stimulates the following important changes within the mother:

- Massive growth of the uterus, especially the myometrium
- Increased growth of all components (glands, stroma, and fat) of the breasts

Prolactin

AdditionalHormonalChanges

Increased prolactin secretion by the pituitary in response to elevated estrogens.

Secretion of human chorionic somatomammotropin (hCS), also referred to as human placental lactogen (hPL), by the placenta (pronounced during the latter half of the pregnancy).

- hCS (hPL) has considerable amino acid sequence homology with growth hormone but has very little growth-stimulating activity.
- hCS (hPL) has metabolic actions similar to growth hormone; that is, it increases maternal lipolysis and ketogenesis and decreases maternal glucose utilization, thereby making maternal energy stores more available for the fetus.
- However, these anti-insulin actions of hCS(hPL) may also account for the gestational diabetes that develops in some pregnant women.
- hCS is secreted in proportion to the size of the placenta and is an index of placental well-being. Estriol is an index of fetal well-being.

to full blown

diabetes mellitus

insulin receptors Mcmi down regulated

Graphical Representation of Hormonal Levels during Pregnancy

Figure IX-11-6 illustrates the changes in hormone levels during the course of pregnancy.

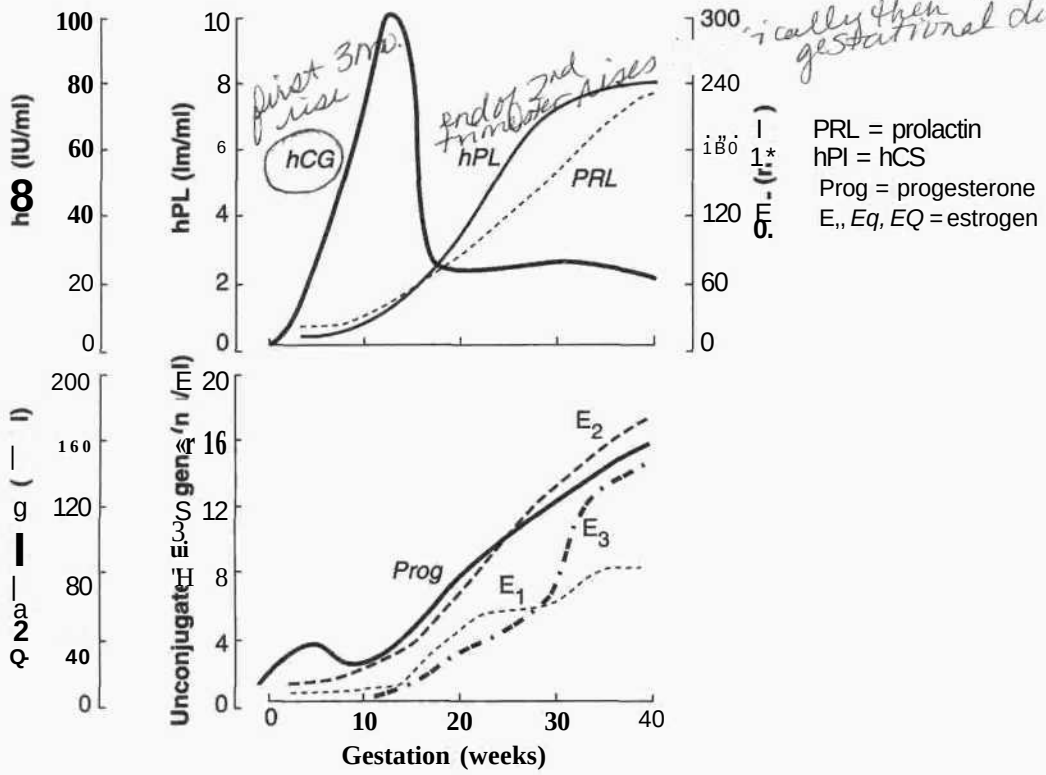


Figure IX-11-6

Changes Induced near the End of Pregnancy

The pubic symphysis, cervix, and vagina become more distensible. These changes make passage of the fetus through the birth canal easier. The peptide hormone relaxin, which is secreted by the ovary, also promotes these changes. Its action is not essential. Parturition in humans is normal in the absence of ovaries.

In response to elevated plasma estrogens, oxytocin receptors increase in the myometrium. Thus, the sensitivity of the uterine myometrium to the excitatory action of oxytocin is increased.

Parturition

The factors that initiate parturition are not well understood, but the following facts are known:

Although oxytocin can be administered to induce uterine contractions, during normal parturition, plasma oxytocin is not elevated until the baby enters the birth canal (a few minutes before birth).

Dead fetus
↓
lysomal attack
↓
↑Toxic fetal proteins
↓
uterus
↓
prostaglandins

Thus, increased oxytocin secretion does not initiate the rhythmic uterine contractions characteristic of the onset of labor.

Oxytocin does, however, cause the uterus to contract immediately after the fetus is expelled, thus limiting blood flow and blood loss.

Acting locally on the myometrium, prostaglandins increase contractions. Oxytocin increases uterine synthesis of prostaglandins.

When a fetus dies, toxic products originating from the fetus increase prostaglandin release in the uterus, thus initiating contractions and a spontaneous abortion (miscarriage). Similarly, administration of prostaglandins induces abortion.

LACTATION

Mammary Gland Growth and Secretion

milk synthesis (when placenta is delivered) b/c ↓ estrogen

Growth of mammary tissue is stimulated by the female sex steroids estrogen and progesterone. However, for these steroids to stimulate maximum growth, prolactin, growth hormone, and cortisol also must be present.

During pregnancy, the high levels of plasma estrogen greatly increase prolactin secretion, but milk synthesis does not occur because the high level of estrogen (and progesterone) blocks milk synthesis.

What hormone responsible for milk ejaculation?
oxytocin

At parturition, plasma estrogen drops, withdrawing the block on milk synthesis. As a result, the number of prolactin receptors in mammary tissue increases several-fold, and milk synthesis begins.

Milk ejection suckling
1. Bonding
2. ↓ PIF
3. ↓ GnRH → ↓ LH/FSH so can't get pregnant again
4. ↑ oxytocin

to str[illegible]ene estrogen

Maintaining Lactation

Suckling is required to maintain lactation.

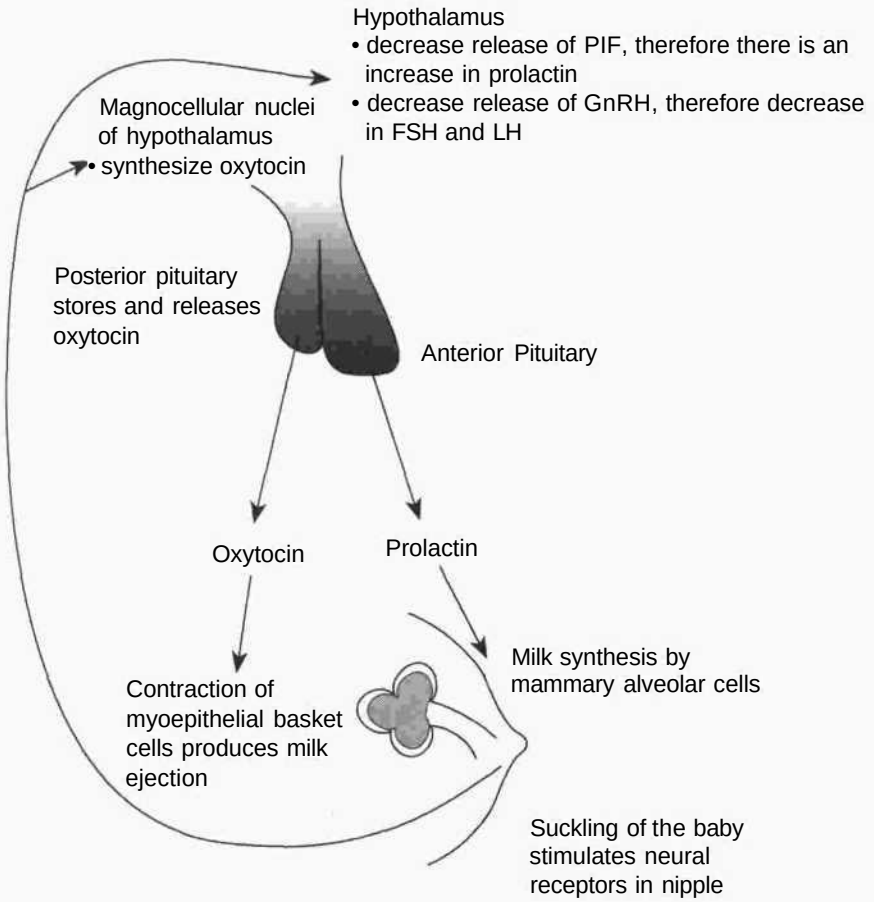


Figure IX-11-7

The suckling of the baby at the mother's breast stimulates receptors in the mother's nipples. Signals from these receptors are transmitted to the hypothalamus and have the following effects:

1. Oxytocin synthesis and secretion are increased. Oxytocin causes the myoepithelial basket cells that surround the alveoli to contract. Preformed milk is ejected into the ducts and out the openings of the nipple; that is, milk ejection is initiated.
2. The release of prolactin-inhibiting factor (PIF = dopamine) by the hypothalamus into the hypophyseal portal vessels is inhibited. This removes a chronic restraint on prolactin secretion. Prolactin secretion increases, and milk secretion is stimulated each time the baby suckles.

3. The secretion of GnRH into the hypophyseal portal vessels is inhibited; secretion of FSH and LH decreases. Thus, follicular growth, estrogen secretion, ovulation, and menses cease. High prolactin levels also contribute to the amenorrhea.

For the suckling stimulus to inhibit GnRH secretion completely, the stimulus must be prolonged and frequent. Supplementation of the mother's milk with other fluids or sources of energy reduces the baby's suckling and allows gonadotropin secretion, follicular growth, and ovulation to occur.

Women who do not wish to breastfeed their children are sometimes administered large doses of estrogen. The estrogen inhibits lactation (by its inhibitory action of milk synthesis), even though estrogen promotes increased prolactin secretion.

Chapter Summary

In the early stages of the follicular phase estrogen is slowly rising. This is followed by a more rapid rise as ovulation approaches. This latter rise occurs because estrogen acts locally to enhance its own production.

Once estrogen rises above a certain level, it no longer suppresses LH and FSH secretion but instead enhances their secretion. This induces a surge in the secretion of both LH and FSH. However, only the LH surge is required for ovulation.

In the luteal phase, LH stimulates the luteal cells to secrete considerable progesterone as well as estrogen. Progesterone always inhibits LH secretion.

It is the drop in progesterone (and estrogen) that withdraws the hormonal support of the endometrium and that causes menstruation.

Variations in the length of the menstrual cycle are due to the follicular phase. Once ovulation has occurred, menstruation begins almost exactly 14 days later.

In the first 2 to 3 months of pregnancy, fetal production of hCG is required for continuation of the secretion of progesterone and estrogen by the ovary.

The ovaries are not required for the last 6 months of pregnancy because the placenta takes over the secretion of both progesterone and estrogen.

Near the end of pregnancy, estrogen induces the appearance of oxytocin receptors in the myometrium. Once this occurs, oxytocin can be administered to induce labor. However, it is unlikely that a rise in oxytocin is the natural signal that begins delivery.

During pregnancy, the rising estrogens are driving an increase in prolactin secretion, but the estrogen also blocks milk synthesis.

At delivery, it is the drop in estrogen that initiates milk synthesis, but suckling is required to maintain lactation.

ENDOCRINOLOGY

Review Questions

Questions 1-9: Select the one best answer.

1. The half-life of a lipid-soluble hormone in blood is:
   A. Directly proportional to its rate of secretion.
   B. Directly proportional to the affinity of the hormone for its plasma protein carrier.
   C. Directly proportional to the number of hormone receptors present in target tissue.
   D. Inversely proportional to the concentration of the hormone's plasma protein carrier.
   E. Inversely proportional to the molecular weight of the hormone.

2. Removal of the anterior pituitary gland from the influence of any of the hypothalamic hormones will result in an increased:
   A. Basal metabolic rate.
   B. Rate of prolactin secretion.
   C. Daily output of urinary 17-keto steroids.
   D. Daily output of urinary 17-hydroxy steroids.
   E Rate of lipolysis.

3. Which one of the following statements correctly compares the effects of removal of the anterior pituitary (hypophysectomy) with the effects of removal of the adrenal glands (adrenalectomy)?
   A. The capacity to withstand a fast will be decreased following hypophysectomy, but not following adrenalectomy.
   B. The daily rate of urinary excretion of 17-hydroxy steroids will be decreased following adrenalectomy, but not following hypophysectomy.
   C. The daily rate of urinary excretion of 17-keto steroids will be decreased following hypophysectomy, but not following adrenalectomy.
   D. The plasma glucose concentration will be elevated following hypophysectomy, but not following adrenalectomy.
   E. A marked loss of Na^+ from the extracellular fluid occurs following adrenalectomy, but not following hypophysectomy.

4. Treatment with a supraphysiologic daily dose of which of the following will elevate total (protein-bound plus free) plasma cortisol, without elevating free plasma cortisol?
   A. A synthetic glucocorticoid.
   B. Cortisol.
   C. Estrogen.
   D. Corticotrophin-releasing hormone (CRH).
   E. None of the above.

Select the one best answer:

5. Cortisol has all of the following actions EXCEPT:
   A. Decreasing the synthesis of gluconeogenic enzymes in the liver.
   B. Decreasing the uptake of amino acids by muscle.
   C. Decreasing the uptake of glucose by muscle.
   D. Increasing liver glycogen synthesis.
   E. Increasing the output of glucose by the liver.

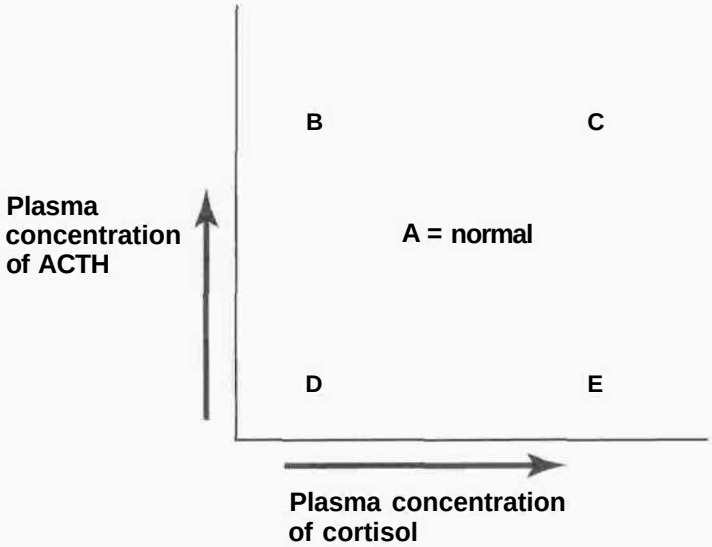
6 In cortisol deficiency, each of the following is deficient EXCEPT:
   A. Catecholamine-induced glycogenolysis.
   B. Catecholamine-induced lipolysis.
   C. Catecholamine-induced vasoconstriction.
   D. Pituitary secretion of ACTH (corticotrophin).
   E. The rate at which a decrease in plasma osmolality is corrected.

7. Administration of supraphysiologic doses of glucocorticoids results in increased:
   A. Eosinophils in plasma.
   B. Breakdown of muscle protein.
   C. Release of histamine from mast cells in response to antigens.
   D. Mineralization of bone.
   E. Fibroblastic activity.

8. Excessive hormonal secretion by the adrenal zona glomerulosa will decrease which of the following:
   A. Renal reabsorption of Na^+.
   B. Plasma concentration of HCO_3~.
   C. Plasma concentration of K^+.
   D. Volume of the extracellular fluid.
   E. Blood pressure.

9. The secretion of renin will be increased by all of the following EXCEPT:
   A. Partially blocking the blood flow in a renal artery.
   B. Weightlessness, as experienced when floating in water.
   C. Heart failure.
   D. Cirrhosis of the liver.
   E. Hemorrhage.

Questions 10-13: Select the letter in the graph below that best represents the hormone concentrations in the situation described.



10. Administration of a blocker of 11 P-hydroxylase.
11. Destruction of the hypothalamo-hypophyseal portal vessels.
12. Two months after removal of one adrenal gland from a normal healthy subject.
13. Acute stress.

Instructions for Questions 14-21: Select the one best answer.

14. The secretion of antidiuretic hormone (ADH) would increase in response to:
   A. Drinking and absorbing one liter of isotonic NaCl.
   B. Weightlessness, as experienced when floating in water.
   C. Failure of the right side of the heart.
   D. Drinking and absorbing 0.5 liters of 600 mOsm/L NaCl solution.
   E. Drinking and absorbing one liter of tap water.

15. A high plasma concentration of insulin will decrease:

A. Uptake of amino acids in muscle.
B. Uptake of glucose by adipose cells.
C. Ketogenesis by the liver.
D. Glycogen synthesis in muscle.
E. Uptake of K^+ by muscle cells.

Select the one best answer:

16. A high ratio of insulin to glucagon in the plasma will promote:

A. Muscle glycogenolysis
B. Liver ketogenesis
C. Lipogenesis
D. Breakdown of muscle protein
E. Liver ureagenesis

17. Which one of the following is likely to be decreased thirty minutes after eating a meal composed primarily of carbohydrate?

A. Plasma glucose.
B. Formation of malonyl CoA in the liver.
C. Glucose oxidation in muscle.
D. Liver gluconeogenesis.
E. Glucose transporters in membranes of muscle cells.

18. Even without insulin, glucose uptake is adequate in all the following tissues EXCEPT:

A. Adipose tissue.
B. Intestinal mucosa.
C. Neurons of the central nervous system.
D. Red blood cells.
E. Renal tubules.

19. Insulin secretion is increased by:

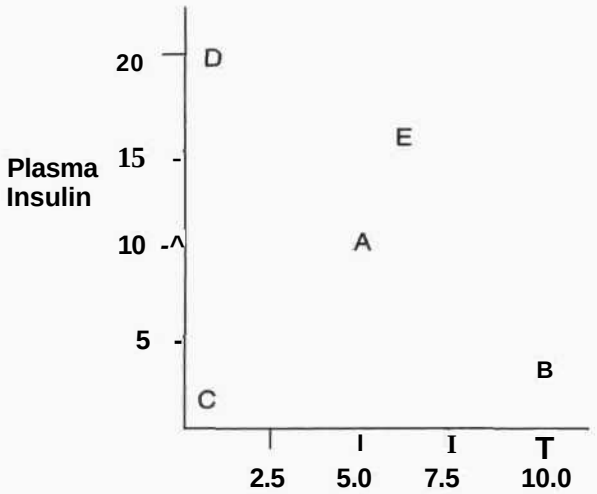
A. Losing weight.
B. Gut hormones.
C. Lowering the plasma glucose concentration.
D. Somatostatin.
E. Stimulation of the adrenergic nerve supply to the pancreas.

20. Glucagon increases all of the following hepatic activities EXCEPT:

A. Gluconeogenesis.
B. Glycogenolysis.
C. Ketogenesis.
D. Lipogenesis.
E. Ureagenesis.

21. Glucagon secretion is:
    A. Decreased by epinephrine.
    B. Decreased by arginine.
    C. Increased by hypoglycemia.
    D. Increased by insulin.
    E. Increased by somatostatin.

Instructions **for** Questions 22-25: Select the letter from the graph below that best represents the hormone concentrations in the situation described.



The units for glucagon and insulin in the above figure represent arbitrary, but equivalent concentrations, in moles x 10^{-9}; i.e., when plasma insulin is 10 and plasma glucagon is 5, the insulin/glucagon molar ratio is 2.0. The letter A represents hormone concentrations after an overnight fast.

22. Eating a large carbohydrate meal.
23. Fasting for one week.
24. An intravenous infusion of arginine.
25. Pancreatectomy.

Questions 26-38: Select the one best answer.

26. A high plasma concentration of epinephrine will increase all of the following EXCEPT:
    A. Free fatty acid output by adipose tissue.
    B. Glucagon secretion.
    C. Glucose output by the liver.
    D. Glucose output by the muscles.
    E. The activity of gluconeogenic enzymes in the liver.

27. Stress, as is experienced in diabetic ketoacidosis, increases the secretion of all of the following hormones EXCEPT:
    A. Corticotropin (ACTH).
    B. Epinephrine.
    C. Glucagon.
    D. Growth hormone.
    E. Insulin.

28. A pituitary tumor that secretes excessive amounts of growth hormone is likely to cause decreased:
    A. Plasma concentration of insulin-like growth factor I (IGF-I).
    B. Uptake of amino acids by muscle.
    C. Plasma concentration of free fatty acids.
    D. Tolerance to a glucose load.
    E. Synthesis of milk.

29. The rate of secretion of growth hormone:
    A. Decreases during deep sleep.
    B. Decreases during exercise.
    C. Increases in response to hypoglycemia.
    D. Decreases steadily from age 6 until full adulthood.
    E. Increases in response to insulin-like growth factor I (IGF-I).

30. The rate of liver gluconeogenesis is:
    A. Decreased by cortisol.
    B. Increased by epinephrine.
    C. Decreased by glucagon.
    D. Increased by insulin.
    E. Less after 3 days of fasting than after 7 days of fasting.

31. Lipogenesis in adipose tissue is:

A. Inhibited by insulin.
B. Promoted by epinephrine.
C. Promoted by glucagon.
D. Promoted by growth hormone.
E. Promoted when glucose enters fat cells.

32. Entry of glucose into muscle is:

A. Increased by cortisol.
B. Increased by exercise.
C. Increased by the entry of free fatty acids into the muscle.
D. Inversely proportional to the plasma glucose concentration.
E. Inversely proportional to the plasma insulin concentration.

33. Free Ca^{2+} ions in the plasma:

A. Decrease when the pH of the plasma increases.
B. Represent 95% of the calcium in plasma.
C. Represent the body's largest pool of calcium.
D. Are decreased by the phosphaturic action of parathyroid hormone.
E. Will decrease markedly if calcium is not included in each day's diet.

34. Parathyroid hormone increases the concentration of plasma Ca^{2+} by all of the following EXCEPT:

A. Counteracting the action that 1,25 di-OH D_3 has on bone.
B. Promoting bone resorption by increasing the activity of osteocytes.
C. Increasing the activity of kidney 1-a-hydroxylase.
D. Decreasing renal reabsorption of HCO_3~.
E. Increasing renal phosphate excretion.

35. If, in a normal person, Ca^{2+} intake is abnormally low for a prolonged period of time, all of the following will increase EXCEPT:

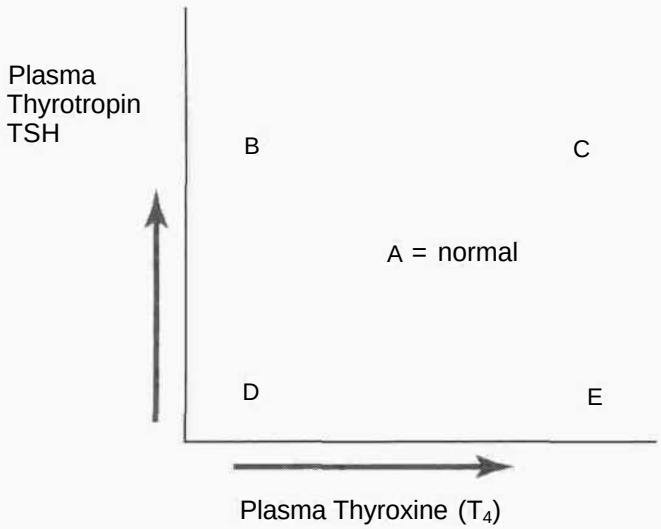
A. Bone resorption by osteocytes.
B. Plasma phosphate.
C. Secretion of parathyroid hormone.
D. Synthesis of Ca^{2+} binding proteins in cells of the intestinal mucosa.
E. Renal synthesis of 1,25 di-OH D_3.

36. Inadequate secretion of parathyroid hormone will produce:
    A. Osteoporosis.
    B. Elevated urinary excretion of hydroxyproline.
    C. Elevated urinary excretion of phosphate.
    D. Elevated plasma Ca^{2+}.
    E. Tetany.

37. In a normal person, most of the body's iodine is stored:
    A. As thyroxine (T_4) and triiodothyronine (T_3).
    B. As T_3 and T_4 in the blood.
    C. As elemental iodine in the endoplasmic reticulum of the follicular cells.
    D. As iodinated tyrosines in the thyroglobulin molecules stored in the luminal colloid of the thyroid follicle.
    E. As I" within the intracellular compartment of muscle and fat.

38. Which of the following treatments is most likely to elicit an early surge of luteinizing hormone (LH) in a normal nonpregnant 21-year-old woman? An injection of:
    A. Estradiol 10 days after the onset of menses.
    B. Progesterone 10 days after the onset of menses.
    C. Estradiol 20 days after the onset of menses.
    D. Progesterone 20 days after the onset of menses.
    E. Progesterone 10 days after the onset of menses followed by an injection of estradiol 10 days later.

Questions 39-44: From the figure below select the letter that best depicts the plasma concentrations of T_4 and TSH in the conditions described.



39. Effect of administration of large doses of triiodothyronine.

40. Effect of blocking the oxygenation of I~ within the thyroid follicle cells.

41. Effect of long-term dietary iodine deficiency.

42. Effect of removal of the anterior pituitary gland.

43. Primary hypothyroidism (myxedema).

44. Primary hyperthyroidism (Graves disease).

Questions 45-48: Match the ITEM listed on the left with the HORMONE (listed on the right) that is most closely associated with the ITEM. Letters may be used once, more than once, or not at all.

ITEM	HORMONE
45. Inhibits milk synthesis during pregnancy.	A. Chorionic gonadotropin (hCG)
46. Promotes synthesis of milk.	B. Estradiol
47. Promotes ejection of milk.	C. Oxytocin
48. Its presence in urine produces a positive pregnancy test.	D. Prolactin
	E. Relaxin

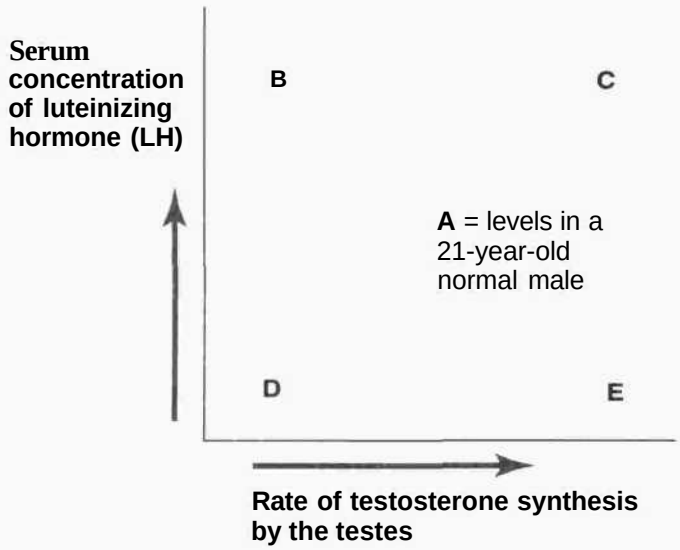
Instructions for Questions 49-51: Select the one best answer.

49. Progesterone asserts which one of the following actions?
    A. Causes the cervical mucus to become thin and watery.
    B. Inhibits the secretion of luteinizing hormone (LH) during the luteal phase of the menstrual cycle.
    C. Causes body temperature to decrease.
    D. Increases the sensitivity of the myometrium to oxytocin.
    E. Stimulates mitosis of endometrial cells.

50. The rate of prolactin secretion is:
    A. Decreased when all hypothalamic hormones are prevented from reaching the anterior pituitary.
    B. Elevated in lactating women even during the intervals between nursing.
    C. Inhibited by dopamine.
    D. Inhibited by estradiol.
    E. Inhibited by thyrotropin-releasing hormone (TRH).

51. The rate of secretion of follicle-stimulating hormone (FSH):
    A. Decreases, if gonadotropin-releasing hormone (GnRH) is injected every two hours.
    B. Is increased by a peptide hormone (inhibin) secreted by Sertoli cells.
    C. Is increased along with LH during the middle of the menstrual cycle.
    D. Is decreased in postmenopausal women.
    E. Is high throughout the follicular phase of the menstrual cycle.

Questions 52-55: Select the letter in the graph below that best fits the relationship between testosterone and LH in the situation described.



52. A normal three-year-old boy.

53. A 21-year-old male taking large doses of an anabolic steroid.

54. A castrated 21-year-old male.

55. A 21 -year-old male with partial deficiency of 21 P-hydroxylase.

Instructions for questions 56-63: Select the one best answer.

56. All the following statements regarding testosterone are correct EXCEPT:
    A. For its optimal action in the prostate and in the penis, testosterone must be converted to dihydrotestosterone.
    B. Near the end of puberty, testosterone promotes the calcification of the epiphyseal plates of long bones.
    C. Near the onset of puberty, testosterone inhibits the production of insulin-like growth factor I (IGF-I).
    D. Sertoli cells convert testosterone into estradiol.
    E. Testosterone stimulates the synthesis of protein in muscle.

57. In response to a mild hemorrhage, (500 ml from an otherwise healthy 70-kg male), which one of the following items will DECREASE?

A. Secretion of ACTH.
B. Secretion of aldosterone.
C. Sympathetic adrenergic input to the intestine.
D. Total peripheral resistance to blood flow.
E. Free water clearance.

58. Being weightless in a space capsule for several days produces all the following effects EXCEPT:

A. Decreased secretion of antidiuretic hormone.
B. Decreased volume of blood in the leg veins.
C. Increased volume of extracellular fluid.
D. Negative Ca^{2+} balance.
E. Negative Na^{+} balance.

59. An intravenous infusion of a large dose of insulin elicits an increase in the serum concentration of all of the following hormones EXCEPT:

A. Corticotropin (ACTH).
B. Epinephrine.
C. Pancreatic C peptide.
D. Growth hormone.
E. Norepinephrine.

60. In diabetic ketoacidosis:

A. Greater than normal amounts of Na^{+} and K^{+} are lost in the urine.
B. K^{+} entry into muscle and fat cells is increased.
C. The minute volume of alveolar ventilation is below normal.
D. The plasma concentration of HCO_3~ is above normal.
E. The urine is alkaline.

61. All of the following hormones promote a positive calcium balance EXCEPT:

A. Adrenal androgens.
B. Calcitonin.
C. Estradiol.
D. Parathyroid hormone.
E. Testosterone.

62. A prolonged fast (one week) produces:

A. A negative nitrogen balance.
B. An increased basal metabolic rate.
C. Decreased growth hormone secretion.
D. Decreased hepatic production of p-OH butyrate.
E. Hypoglycemic shock.

63. A 5-year-old girl weighing 18 kg is brought into the emergency room. Her urine osmolality is 310 mOsm/L, and her parents say that she has a daily urine output of about 4 liters. The most likely diagnosis is:

A. Excessive urination caused by drinking too many sweetened soft drinks.
B. Nephrogenic drinking syndrome.
C. Syndrome of inappropriate ADH secretion (SIADH).
D. Diabetes insipidus.
E. Diabetes mellitus.

Questions 64-66: Select your answers from the following table, in which the plasma concentrations of insulin and connecting (C) peptide are compared with the concentrations present in a normal person after an overnight fast. In each of the four choices, the patient was severely hypoglycemic.

Choice	Plasma insulin compared to normal fasting level	Plasma C peptide compared to normal fasting level
A	Less than normal	Less than normal
B.	Less than normal	Greater than normal
C.	Greater than normal	Greater than normal
D.	Greater than normal	Less than normal

64. Insulinoma.

65. Patient is secretly injecting himself/herself with excessive amounts of insulin.

66. Lack of food intake in a patient suffering from a chronic deficiency of cortisol secretion.

Questions 67-68: Select the one best answer.

67. As compared with the concentration of Na^+ in the plasma and urine of a normal person, the Na^+ in the plasma and urine of a patient with inappropriate ADH secretion (SIADH) will be:

Choice	**Plasma concentration of Na+**	**Urine concentration** of Na+
A.	Below normal	Below normal
B.	Above normal	Above normal
C.	Above normal	Below normal
D.	Below normal	Above normal
E.	Normal	Normal

68. Giving the standard "low dose" of the synthetic glucocorticoid, dexamethasone, will suppress urinary excretion of 17-hydroxysteroids in patients with:

A. Hypercortisolism due to hypersecretion of pituitary ACTH, i.e., Cushings disease.
B. Hypercortisolism due to ACTH secretion from an ectopic source.
C. Primary hypocortisolism, Addison's disease.
D. Hypercortisolism due to a tumor of the adrenal cortex that secretes cortisol independently of ACTH secretion.
E. A patient with normal pituitary and normal adrenal function.

Answers

1. Ans B — The time for the concentration of a hormone in plasma to decrease by 50% (assuming no further hormone is secreted) is the plasma half-life. For lipid-soluble hormones, the half-life is primarily determined by the affinity of the hormone for its plasma protein carrier, i.e., the higher the affinity, the longer the half-life. Half-life is not related to hormone-secretion rate, the number of hormone receptors, or the molecular weight of the lipid-soluble hormone.

2. Ans B — The hypothalamus secretes a hormone (prolactin-inhibiting factor = PIF) into the hypophyseal portal vessels that chronically inhibits prolactin secretion; thus removal from the influence of PIF increases prolactin secretion. Most of the other hypothalamic hormones promote the secretion of their respective pituitary hormones. The hypothalamus secretes a promoter (GHRH) and an inhibitor (somatostatin) of GH secretion; nevertheless removal of all hypothalamic hormones diminishes GH secretion. With regard to the other choices, loss of hypothalamic TSH would diminish T_4 secretion and thus lower metabolic rate; loss of CRH would diminish ACTH secretion and thus decrease urinary excretion of 17-keto-and 17-hydroxysteroids; decreased GH secretion would decrease lipolysis.

3. Ans E — Following adrenalectomy, but not following hypophysectomy, secretion of the mineralocorticoid, aldosterone, is absent. Loss of aldosterone results in excessive Na^+ excretion accompam'ed by loss of ECF volume, the net effect often being fatal hypotension. Regarding choices A-D, both adrenalectomy and hypophysectomy will abolish (or greatly lower) the plasma glucocorticoid (cortisol) and adrenal sex steroid concentration, resulting in decreased 17-hydroxy-and 17-ketosteroid excretion. Loss of glucocorticoid will decrease the capacity of the individual to mobilize energy stores during a fast, and the diminished rate of liver gluconeogenesis will lower blood glucose.

4. Ans C — High plasma concentrations of estrogen, such as are present in pregnancy and in women taking estrogen-containing contraceptive pills, stimulate increased production of cortisol-binding globulin (CBG) by the liver. The increased CBG binds cortisol, thus increasing the total plasma cortisol, but only a temporary decrease in free cortisol occurs. This is because any decrease in free cortisol, however brief, elicits increased ACTH secretion which, in turn, increases cortisol secretion sufficiently to return free cortisol to normal. Treatment with a synthetic glucocorticoid would decrease ACTH and free cortisol. The treatments described in B, D, and E would all increase free plasma cortisol.

5. **Ans** A Cortisol increases (not decreases) the synthesis of gluconeogenic enzymes. The actions described in B, C, D, and E are all actions of cortisol.

6. **Ans** D ACTH secretion (choice D) is elevated in cortisol deficiency due to the lack of the negative feedback action of cortisol. Glycogenolysis, lipolysis, and catecholamine-induced vasoconstriction (choices A-C) are all deficient in the absence of cortisol. For reasons that are not well understood, when cortisol is deficient, a decrease in plasma osmolality (such as is elicited by drinking a liter of water) fails to suppress ADH secretion. Thus in people with cortisol deficiency, a water load may require 24 or more hours to be excreted. (Normally, it is excreted in 2-3 hours).

7. **Ans** B In the presence of high levels of glucocorticoids, muscle proteins are broken down. Regarding choices A, C, D, and E, respectively: High doses of glucocorticoids decrease the plasma eosinophil count; decrease the antigen-induced release of histamine by mast cells; cause bone demineralization (osteoporosis) by decreasing the synthesis of bone-matrix proteins; and decrease fibroblastic activity.

8. **Ans** C Aldosterone, the hormone secreted by the zona glomerulosa, promotes Na^+ reabsorption and K^+ excretion in the collecting ducts of the kidney; thus excess aldosterone will cause plasma K^+ to decrease. Increased renal H^+ excretion also occurs with simultaneous HCO_3~ movement into the ECF and plasma making them more alkaline. As increased amounts of Na^+ are retained, so also is water, causing the volume of the ECF and blood pressure to increase.

9. **Ans** B In a weightless state, blood normally in the extremities shifts to the trunk, thus stimulating baroreceptors in the large veins and atria. The resulting baroreceptor reflex decreases sympathetic tone to the renal juxtaglomerular cells which, in response, decrease renin secretion. All of the other choices would decrease blood pressure in the renal artery and thus increase renin secretion.

10. **Ans** B A blocker of 11 p-hydroxylase will prevent the adrenal cortex from synthesizing cortisol, and when cortisol decreases, ACTH secretion increases.

11. **Ans** D Destruction of the hypothalamo-hypophyseal portal vessels will prevent the hypothalamic hormone, CRH, from reaching the anterior pituitary. As a result ACTH secretion will decrease, and with less ACTH, cortisol secretion will also decrease.

12. **Ans** A Initially following removal of one adrenal gland, cortisol secretion would decrease. However, with less cortisol reaching the hypothalamus and anterior pituitary, ACTH secretion would increase. This causes the adrenal cortex of the remaining adrenal gland to hypertrophy and increase its output of cortisol. Within two months, cortisol secretion and thus ACTH secretion would return to normal levels.

13. **Ans** C Stress increases CRH secretion. As a result ACTH and cortisol secretion increase.

14. **Ans** D Drinking and absorbing 0.5 liters of 600 mOsm/L NaCl (twice the osmolality of plasma) would increase the osmolality of the ECF and thereby increase ADH secretion. Drinking one liter of tap water (choice E) would have the opposite effect on ECF osmolality and ADH secretion. One liter of isotonic saline (choice A) would not alter osmolality, but would expand the plasma volume, causing atrial and venous baroreceptors to send increased signals to the hypothalamus and inhibit ADH secretion. Weightlessness (choice B) shifts blood from the legs to the trunk causing atrial baroreceptors to be stimulated, again decreasing ADH secretion. In right heart failure (choice C), the backed-up blood distends the atria and large veins; therefore increasing baroreceptor stimulation and inhibiting ADH secretion.

15. **Ans** C Insulin increases the formation of malonyl CoA in the liver, hence increasing fatty acid synthesis (lipogenesis) and decreasing fatty acid oxidation. As a result ketogenesis decreases. All other choices describe processes that are increased by insulin.

16. **Ans** C Insulin increases the formation of malonyl CoA in the liver, hence increasing fatty acid synthesis (lipogenesis). Insulin also increases the activity of lipoprotein lipase in capillary endothelial cells, thereby increasing triglyceride uptake by fat cells. Also, because insulin increases glucose uptake by fat cells, an adequate supply of ot-glycerol phosphate, an essential intermediate for triglyceride synthesis, is assured, and triglyceride synthesis is promoted.

17. **Ans** D Thirty minutes after eating, the plasma ratio of insulin to glucagon will be high. Because insulin promotes amino acid uptake and inhibits protein breakdown throughout most body tissues, the supply of amino acids reaching the liver is decreased; thus liver gluconeogenesis is decreased. Regarding choices C and E, insulin increases glucose uptake in muscle cells by increasing the number of glucose transporters, and although this action increases glycogen synthesis, it also increases glucose oxidation. The muscular

weakness of diabetics is due in part to the inability to utilize glucose as an energy source in spite of high levels of glucose in the blood.

18. Ans A Glucose uptake is greatly increased by insulin in adipose tissue.

19. Ans B Hormones secreted by the gut, especially gastric inhibitory peptide (GIP), but also secretin and cholecystokinin, are strong promoters of insulin secretion. Regarding choice A: Generally, body weight is proportional to food intake as is insulin secretion. High rates of insulin secretion may lead to insulin resistance, by down-regulating insulin receptors in target tissues. Losing weight is accomplished by decreasing food intake, and/or increasing exercise, both of which decrease insulin secretion. Lowering insulin secretion allows the number of insulin receptors to increase, and insulin sensitivity returns to normal. Regarding choice E, P-adrenergic receptors promote, and a-adrenergic receptors inhibit, insulin secretion. Nevertheless, when the adrenergic nerve supply to the pancreas is stimulated (as during prolonged strenuous exercise), the effect of the a-receptors predominates, and insulin secretion is inhibited. Simultaneously, the secretion of glucagon is increased.

20. Ans D Glucagon, a stress hormone, would if anything break down fat (lipolysis).

21. Ans C Hypoglycemia is a potent stimulus for glucagon secretion.

22. Ans D The elevated plasma glucose following a meal will promote insulin secretion and inhibit glucagon secretion.

23. Ans B The slight decrease in plasma glucose during fasting will promote glucagon secretion. Without food intake, the normal stimuli for insulin secretion (gut hormones and increased plasma glucose) will be absent, thus allowing insulin secretion to decrease.

24. Ans E Elevated plasma levels of amino acids, especially arginine, evoke the secretion of insulin and glucagon.

25. Ans C Because the islet cells of the pancreas are the source of insulin and glucagon, the plasma levels of both will drop following pancreatectomy.

26. Ans D Because muscles lack glucose-6-phosphatase, the end product of epinephrine-induced glycogenolysis in muscles is lactate rather than glucose.

27. Ans E Stress does not increase insulin secretion, but does increase the

secretion of the remaining hormones listed. This fact complicates the status of the patient in diabetic ketoacidosis as the stress associated with this serious condition increases the secretion of all of the counter-regulatory hormones to insulin, but not insulin itself.

28. **Ans** D Growth hormone counteracts the action of insulin, thereby decreasing the uptake of glucose by muscle and fat. For this reason, it is common for acromegalic patients to have abnormal glucose tolerance tests. Regarding choice E, growth hormone has homologous regions in amino acid structure to prolactin. In fact, synthetic bovine growth hormone is used to increase milk secretion in dairy cattle.

29. **Ans** C Hypoglycemia is a strong stimulus for growth hormone secretion.

30. **Ans** B During exercise and during emergency situations, epinephrine secretion increases. This epinephrine not only promotes liver and muscle glycogenolysis and adipose tissue lipolysis, it also promotes liver gluconeogenesis. Regarding choice E, the rate of gluconeogenesis is rapid during the first three days of a fast; this source provides essential glucose for the central nervous system (CNS) during these days. As the fast continues, lipolysis increases, as does ketone body production by the liver. These ketone bodies provide about 2/3 of the energy for the CNS. This spares body protein, allowing the body's only source of glucose during a prolonged fast to last for a longer period of time.

31. **Ans** E The entry of glucose into fat cells increases the available supply of oc-glycerol phosphate, thereby promoting the esterification of fatty acids into triglycerides.

32. **Ans** B Exercise increases the uptake of glucose by muscle through a mechanism that does not require insulin, thus accounting for the decreased requirement for insulin in diabetics who undertake a vigorous daily exercise program. The entry of FFA (choice C) into muscle results in an accumulation of citrate, which inhibits phosphofructokinase. When the activity of this important glycolytic enzyme is inhibited, glucose oxidation is decreased and glucose is diverted into glycogen. Once the glycogen stores are filled, glucose-6-phosphate accumulates and inhibits phosphorylation of glucose. This causes intracellular glucose concentration to increase, slowing the further entry of glucose. This mechanism allows glucose to be spared for CNS metabolism whenever plasma glucose is low, because in such conditions, lipolysis (and thus FFA) is elevated. Cortisol (choice A) decreases the uptake of glucose into muscle. Regarding choice D, as long as insulin is present, uptake of glucose

is directly proportional to the plasma glucose, and as long as adequate glucose is available, glucose uptake is directly proportional to plasma insulin.

33. **Ans** A About half the calcium in plasma is free and half is bound to protein anions, or to citrate or phosphate. When the blood pH increases, (or in other words H^+ concentration decreases), more anions become available to bind Ca^{2+}, causing the free Ca^{2+} concentration to decrease. As evidence, hyperventilation lowers H^+ concentration and can initiate tetany in patients with borderline low plasma Ca^{2+}. The largest pool of body Ca^{2+} (choice C) is bone, not the plasma Ca^{2+}. Many days of dietary Ca^{2+} deficiency are necessary before plasma Ca^{2+} concentration decreases significantly (choice E).

34. **Ans** A PTH increases plasma Ca^{2+} by the actions listed in B-E. It does not, however, act in opposition to 1,25 di-OH D_3 in bone. Both of these hormones act together on bone cells to promote bone resorption and to increase plasma Ca^{2+}.

35. **Ans** B A prolonged deficiency in Ca^{2+} intake will cause a slight decrease in plasma Ca^{2+}. This elicits a compensatory increase in PTH secretion, which increases renal phosphate excretion (lowering plasma phosphate). The PTH also increases osteocytic activity, thus increasing Ca^{2+} resorption from bone, and increases renal synthesis of 1,25 di-OH D_3. These actions of PTH prevent Ca^{2+} levels in blood from decreasing greatly. In other words, plasma Ca^{2+} concentration is preserved at the expense of bone integrity.

36. **Ans** E Without adequate PTH, plasma Ca^{2+} decreases and tetany develops.

37. **Ans** D Most of the body's iodine is stored extracellularly in the lumen of the follicle as iodinated tyrosines (MIT and DIT) on thyroglobulin. In individuals with an ample dietary intake of iodide, enough iodine for at least one month of thyroid hormone synthesis and secretion is stored in the thyroid follicle.

38. **Ans** A The stimulus for the ovulation-inducing surge of LH secretion is the rising level of plasma estradiol during the follicular stage of the cycle. Ten days after the onset of menses (day 10 of the cycle) is the midfollicular stage and an injection of estradiol would elicit an early surge. Estradiol given 20 days after the onset of menses (midluteal stage) does not elicit an LH surge, because the high plasma concentrations of progesterone block the facilitative effect of estradiol on LH secretion.

39. Ans D High plasma levels of T_3 would increase intracellular concentration of T_3 in the pituitary thyrotrophs, and thereby decrease their sensitivity to thyrotropin-releasing hormone (TRH). This would result in decreased TSH secretion and, subsequently, decreased T_4 secretion.

40. Ans B If I~ cannot be oxygenated to 1°, then T_4 and T_3 cannot be synthesized. The low plasma concentration of these hormones will sensitize the pituitary thyrotrophs to TRH, causing them to secrete more TSH.

41. **Ans** B In long-term iodide deficiency, the T_4/T_3 secretion ratio, which is normally 20/1, decreases, and as a result, plasma levels of T_4 decrease. Since the pituitary thyrotrophs are dependent upon plasma T_4 for their intracellular supply of T_3, the thyrotrophs become hypersensitive to TRH and increase their secretion of TSH.

42. **Ans** D Removal of the anterior pituitary gland removes the source of TSH, and without TSH, T_4 secretion decreases greatly.

43. **Ans** B In primary hypothyroidism, the thyroid gland fails to secrete adequate amounts of T_4. As a result, the intrapituitary concentration of T_3 diminishes, and the thyrotrophs become hypersensitive to TRH. This causes TSH synthesis and plasma TSH to greatly increase.

44. **Ans** E In primary hyperthyroidism, the thyroid gland hypersecretes T_4 in response to thyroid-stimulating immunoglobulins (TSI) present in the blood. The elevated T_4 increases the intrapituitary concentration of T_3 which then decreases the sensitivity of the thyrotrophs to TRH. This causes TSH secretion and plasma TSH to greatly diminish.

45. **Ans** B Estradiol promotes the growth of mammary tissue. Progesterone (not a choice) also stimulates mammary growth. For these steroids to exert their maximum growth-promoting effect, prolactin, GH, and cortisol must also be present.

46. **Ans** D Prolactin is the major stimulator of milk synthesis.

47. **Ans** C Oxytocin causes the myoepithelial cells that surround the mammary alveoli to contract, thus ejecting preformed milk into ducts.

48. Ans A hCG, a glycoprotein hormone with LH activity, is secreted by the blastocyst immediately upon implantation. This hormone is small enough to be filtered through the glomerulus and appears in the urine by the time of the first missed menses. Its presence in urine is indicative of pregnancy.

49. Ans B Progesterone inhibits the secretion of LH during the luteal phase of the menstrual cycle; regarding choice A, progesterone causes the cervical mucus to become thick, forming a plug preventing entry of foreign material into the uterus; regarding choice C, progesterone is thermogenic and increases the body temperature about 0.5°F during the luteal phase of the cycle; regarding choice D, estrogen (not progesterone) increases the sensitivity of the myometrium to oxytocin, i.e. progesterone "quiets " the uterus, regarding choice E, estradiol (not progesterone) stimulates mitosis of endometrial cells. Progesterone causes the estrogen-primed uterus to synthesize glycogen, which will be a source of energy for the embryo shortly after implantation.

50. Ans C Dopamine, a biogenic amine present in the hypothalamus, is a potent inhibitor of prolactin and may be PIE Regarding choice A, its secretion being chronically inhibited by prolactin-inhibiting factor (PIF), prolactin increases when all hypothalamic hormones are prevented from reaching the anterior pituitary gland. Regarding choice B, the rate of prolactin secretion in lactating women is only elevated while nursing the baby. Because estradiol secretion is low in lactating women, the basal rate of prolactin secretion is also low. Prolactin secretion increases only during nursing. Regarding choice D, estradiol promotes the secretion of prolactin but inhibits the action of prolactin on mammary tissue. Estradiol is not required for prolactin secretion as the neural stimulus of suckling inhibits PIF secretion, thereby promoting prolactin secretion. Regarding choice E, TRH increases prolactin secretion.

51. Ans C Because GnRH is secreted into the portal vessels during the midcycle LH surge, and because GnRH stimulates FSH secretion as well as LH secretion, the rate of FSH secretion is increased at midcycle. Regarding choice A, if GnRH is injected every two hours (i.e., in a manner similar to normal GnRH secretion), FSH secretion (as well as LH secretion) will increase. Regarding choice B, inhibin inhibits FSH secretion, and the relative absence of inhibin (as well as the absence of gonadal steroids) accounts for the elevated FSH secretion in postmenopausal women (choice D). Regarding choice E, FSH secretion is slightly elevated during menses and during the early follicular phase, but then decreases until the midcycle LH surge.

52. Ans D In a normal three-year-old boy the testes are not secreting testosterone because the pituitary is not secreting LH; thus the levels of both hormones are low.

53. **Ans** D The young adult male who takes large doses of an anabolic steroid (usually a potent, orally active derivative of testosterone) will suppress his secretion of pituitary LH; therefore secretion of testosterone by his testes will also decline.

54. **Ans** B Without testes, the adult male will secrete no testosterone. Since testosterone normally suppresses the secretion of pituitary LH, the secretion of LH will be greatly elevated.

55. Ans D The 21-year-old male with untreated 21 p-hydroxylase deficiency (one form of adrenogenital syndrome) will secrete excessive amounts of adrenal sex steroids. These steroids (dehydroepiandrosterone and androstenedione) are weak androgens; however, in adrenogenital syndrome, their plasma concentration is high enough to suppress pituitary LH secretion. As a result, testosterone secretion by the testes is low.

56. **Ans** C Near the onset of puberty, testosterone, acting in concert with-a slight increase in GH secretion, increases the production of IGF-I. This synergism is responsible for the increased rate of growth (the growth spurt) seen during puberty.

57. **Ans** E A hemorrhage would lower pressure in the atria and large veins where the venous baroreceptors are located. Stimuli from these receptors chronically inhibit ADH secretion. In a hemorrhage, these receptors will be stretched less, and will send fewer stimuli to the CNS, allowing more ADH to be synthesized and secreted. The increased ADH will increase reabsorption of water in the renal collecting ducts, causing free water clearance to decrease, i.e., to become negative. Regarding choice A, hemorrhage is a stress and causes AGTH secretion to increase. Regarding choice B, during a hemorrhage, sympathetic input to the kidney increases. This stimulates renin secretion. Renin catalyzes the conversion of angiotensinogen to angiotensin I. After conversion in the lung to angiotensin II, this hormone stimulates increased secretion of aldosterone by the cells of the adrenal zona glomerulosa. Regarding choices C and D, hemorrhage will increase sympathetic tone in the splanchnic and skin vasculature, increasing total peripheral resistance.

58. **Ans** C Being weightless allows blood that is normally pooled in the large leg veins to redistribute throughout all of the body's veins. As a result, a significant portion of this blood shifts to the large veins of the abdomen and chest. This stretches the baroreceptors in the atria and large veins causing them to send more signals to the CNS. These signals inhibit the secretion of ADH. With decreased

ADH (choice A), water excretion increases and the volume of the ECF decreases (choice C). Ca^{2+} is lost (choice D) because the bones are no longer under the stress of gravity. The stress of gravity, acting through poorly understood local factors within bone, normally inhibits bone decalcification. Na^+ is lost because the redistribution of blood results in decreased sympathetic tone to the renal vasculature; thus decreasing renin, angiotensin, and aldosterone production. The loss of Na^+ also contributes to the diminished ECF volume.

59. **Ans** C

Since the intravenous insulin will decrease plasma glucose, it will also decrease insulin secretion, and therefore, C peptide secretion. Hypoglycemia is stressful and causes increased ACTH and epinephrine secretion and increased release of norepinephrine from postganglionic sympathetic neurons (choices A, B, and E). Epinephrine and norepinephrine promote liver and muscle glycogenolysis, thus increasing glucose availability. ACTH, by increasing cortisol, blocks the uptake of glucose by muscle and fat, thus sparing glucose. GH secretion is also increased (choice D). It promotes lipolysis, providing an alternate energy supply for tissues other than the CNS, and also blocks the uptake of glucose by muscle.

60. **Ans** A

In diabetic ketoacidosis large amounts of keto anions are filtered through the glomerulus. The kidney balances these anions with H^+ to the extent that it can, but the kidney's maximum capacity to secrete H^+ can only produce a urine with a H^+ concentration corresponding to a pH of about 4.5. Since the pK of keto anions is about 4.0, urine of maximum acidity still contains approximately 3 keto anions for each ketoacid.

$$pH = pK + \log \frac{\text{keto anions}}{\text{ketoacid}}$$

$$pH = pK + 0.5$$

$4.5 = 4.0 + 0.5$; the antilog of 0.5 is 3

Because urine must remain electrically neutral, the keto anions that are not matched with ketoacid must be matched with another cation. Na^+ and K^+ are the only ones available; thus they are lost in the urine in ketoacidosis. Regarding choice B, insulin increases the activity of Na/K-ATPase. At the plasma membrane this enzyme pumps Na^+ out and brings K^+ in. When this enzyme is deficient, as in insulin deficiency, muscle and fat cells lose considerable amounts of K^+. The K^+ that enters the plasma is subject to being lost in the urine through the mechanism described above. Regarding choice C, since the blood is acidic in diabetic ketoacidosis, the H^+ drives respiration and hyperventilation (evidenced by a decreased alveolar PCO_2) develops. In spite of this respirato-

ry compensation, the blood remains acidic. Regarding choice D, in the process of secreting large amounts of H^+, the cells of the kidney tubule move HCO_3~ into the blood. Even this does not neutralize the large amount of ketoacid. Regarding choice E, for reasons given above, the urine in ketoacidosis is acidic.

61. Ans D Parathyroid hormone promotes bone demineralization, thereby elevating plasma Ca^{2+}. The elevated Ca^{2+} increases the filtered load of Ca^{2+}, and even though PTH promotes renal reabsorption of Ca^{2+}, the increased filtered load is not balanced, and net Ca^{2+} loss occurs (especially in primary hyperparathyroidism). Calcitonin (choice B) inhibits the osteodastic resorption of bone, thereby producing a positive Ca^{2+} balance. The sex steroids (choices A, C, and E) promote bone calcification. The androgens are especially important in promoting calcification at puberty. The deficiency of estradiol in postmenopausal women favors net demineralization of bone and osteoporosis develops.

62. **Ans** A A prolonged fast produces negative nitrogen balance. Although in a long fast, ketone bodies provide much of the brain's energy, some glucose is still necessary, and the only source of this glucose is body protein. In a long fast, cortisol secretion, though low, continues. It, along with the high levels of glucagon (and low levels of insulin), allows sufficient gluconeogenesis to occur to maintain brain function. In summary, since some protein breakdown is occurring to fuel essential gluconeogenesis, and no protein is being consumed, nitrogen balance is negative during a long fast. Regarding choice B, during fasting the ratio of T_3/rT_3 in plasma decreases, and the relative deficiency of active thyroid hormone decreases the metabolic rate. Regarding choice C, GH secretion is normal or slightly increased during a long fast, possibly because of the slightly lowered mean blood glucose. Regarding choice D, because lipolysis is stimulated during a long fast, a substantial amount of FFA reach the liver where they are oxidized to ketone bodies, such as p OH butyrate. Regarding choice E, mean blood glucose does decrease in a long fast, but almost never reaches the levels necessary to produce hypoglycemic shock. Furthermore, the decrease is gradual and occurs while the brain is shifting over to ketone bodies for an energy source; thus hypoglycemic shock does not occur.

63. **Ans** E Choices A, B, and D would result in a large daily output of urine, but it would be hypotonic (about 150 mOsm/L). Choice C would result in a low daily output of a hypertonic urine. This girl has an osmotic diuresis caused by loss of glucose, and electrolytes in her urine. Her urine is isotonic with her plasma, but her plasma has an unusually high osmolality (310 whereas normal is 292). Each 100

mg of glucose/100 ml of plasma increases plasma osmolality by 5 mOsm/L. The high filtered load of glucose has exceeded the transport maximum of her renal tubules.

64. **Ans** C The insulinoma will secrete increased amounts of C peptide as well as insulin.

65. **Ans** D The plasma insulin will be elevated because the radioimmunoassay of insulin does not distinguish between injected and secreted insulin. The elevated insulin lowers blood glucose, thereby decreasing the secretion of endogenous insulin, and along with it, C peptide.

66. **Ans** A When cortisol secretion is deficient, the patient is unable to mobilize stored glycogen, fat, or protein. As a result, they often suffer from hypoglycemia, especially if they do not eat regularly. The low plasma glucose lowers plasma insulin and, along with it, C peptide.

67. **Ans** D The excessive plasma ADH will stimulate reabsorption of water in the renal collecting duct. This will expand the ECF and the blood volume, and slightly elevate blood pressure. As a result, the secretion of renin, angiotensin II, and aldosterone will decrease. The decrease in aldosterone decreases renal Na^+ reabsorption. Urine Na^+ concentration increases, while plasma Na^+ concentration decreases.

68. **Ans** E A low dose of dexamethasone suppresses pituitary ACTH secretion (and therefore 17-hydroxysteroid production and excretion) in people with a normal pituitary response to the negative feedback action of glucocorticoids. Regarding choice A, people with hypersecretion of cortisol due to excessive ACTH secretion by a pituitary microadenoma (Cushing's disease) continue to hypersecrete ACTH (and thus cortisol) when administered a low dose of dexamethasone; however a high dose of dexamethasone will usually suppress their ACTH (and cortisol and 17-hydroxysteroid) secretion. Regarding choice B, ectopic hypersecretion of ACTH is not inhibited by either low or high doses of dexamethasone. Regarding choice D, the excess hypercortisolism is not due to ACTH, but rather to an autonomously secreting cortical tumor; hence suppressing ACTH, which is already low because of cortisol suppression, will not suppress 17-hydroxysteroid secretion. Regarding choice C, cortisol (17-hydroxysteroid) secretion is already low, because the cortex is not capable of responding to ACTH (present in the blood in high concentration); thus suppressing ACTH with dexamethasone will not lower 17-hydroxysteroid production further.

SECTION X

Gastrointestinal Physiology

Gastrointestinal Physiology

1

GENERAL FEATURES OF NERVOUS AND ENDOCRINE CONTROL

Nervous Control

Sympathetic

The diagram below illustrates how the synaptic junction at the end of a nerve fiber secretes norepinephrine (NE), which then induces responses in the gastrointestinal (GI) system.

< NE → ↓ motility, ↓ secretions, ↑ constriction of sphincters

An increase in sympathetic activity slows processes.

Parasympathetic

< ACh → ↑ motility, ↑ secretions

< VIP → ↓ constriction of sphincters

< GRP (bombesin) → Gcell → ↑ gastrin

An increase in parasympathetic activity promotes digestive and absorptive processes.

What the USMLE Requires You to Know

- Intrinsic properties of smooth muscle
- Swallowing reflex and regional motility
- Salivary and gastric secretions
- The dual hormonal regulation of pancreatic secretions
- Composition of bile
- Recycling of the bile salts
- Digestion and absorption of carbohydrate, protein, and lipid
- Regional reabsorption of water and electrolytes

Note

VIP = vasoactive intestinal peptide, an inhibitory parasympathetic transmitter

GRP = gastrin releasing peptide; stimulates the release of gastrin from G cells

Endocrine Control

Table X-l-1. The Endocrine Control of the GI System

Hormone**	**Source**	Stimulus	**Stomach** Motility **and Secretion**	**Pancreas**	**Gall Bladder**
1. Secretin	S cells lining duodenum	Acid entering duodenum	Inhibits	Stimulates fluid secretion (HCO_3~)	
2.CCK	Cells lining duodenum	Fat and amino acids entering duodenum	Inhibits emptying	Stimulates enzyme secretion	1. Contraction 2. Relaxation sphincter (Oddi)
3. Gastrin	G cells of stomach Antrum Duodenum	Stomach distension Parasym (GRP) Peptides Stomach acid inhibits*	Stimulates		
4.GIP	Duodenum	Fat, CHO, amino acids	Inhibits		

CCK = cholecystokinin; GIP = gastric inhibitory peptide (glucose insuUnotropic peptide)

*Note: In a non-acid-producing stomach (e.g., chronic gastritis), the reduced negative feedback increases circulating gastrin.

**A11 four hormones stimulate insulin release.

MOTILITY

Control of Smooth Muscle

Intrinsic Properties of Smooth Muscle

Stretch produces a contractile response.

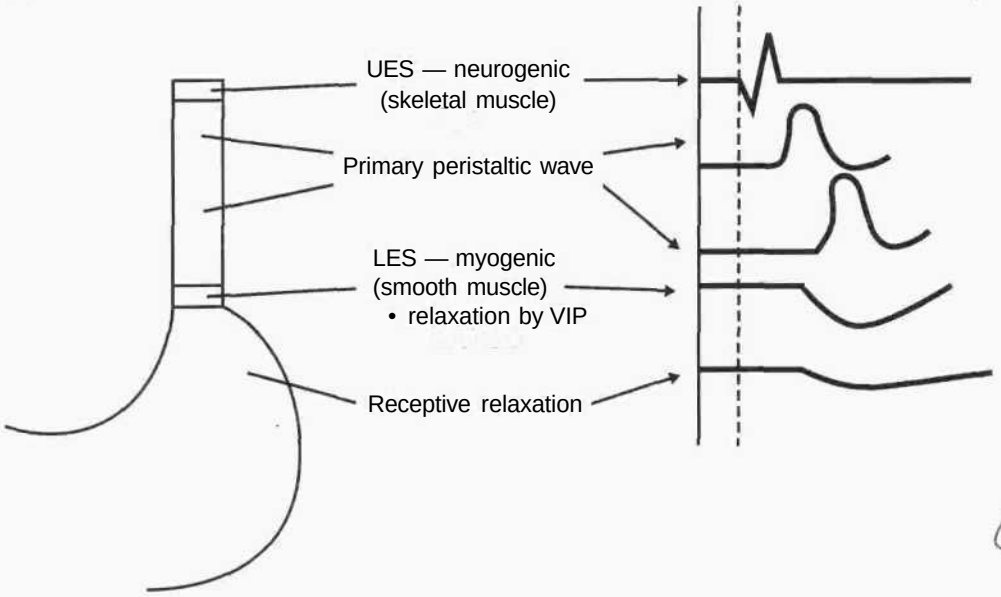
Electrical syncytium (gap junctions) electrically connects fibers.

Pacemaker activity (basic electric rhythm) is responsible for the intrinsic motor activity.

Swallowing

Swallowing is a reflex controlled from the brain stem.

Efferent input is via the vagus for all events, and these are summarized in Figure X-1.



GERD

Figure X-1

An increase in sympathetic activity slows processes.

Events during swallowing:

Relaxation of upper esophageal skeletal muscle sphincter (UES)

Primary peristaltic wave

Relaxation of lower esophageal smooth muscle sphincter (LES) via VIP acting as an inhibitory transmitter

Relaxation of proximal stomach (receptive relaxation)

If the primary peristaltic wave is not successful, a secondary peristaltic wave will be initiated by a local distension of the esophagus.

In achalasiai'the LES fails to relax during a swallow, due to abnormalities of the enteric nerves. Primary peristalsis in the esophageal body is poor. Swallowed food is retained in the esophagus.

Gastric Motility

The primary factors and additional aspects are illustrated in Figure X-2.

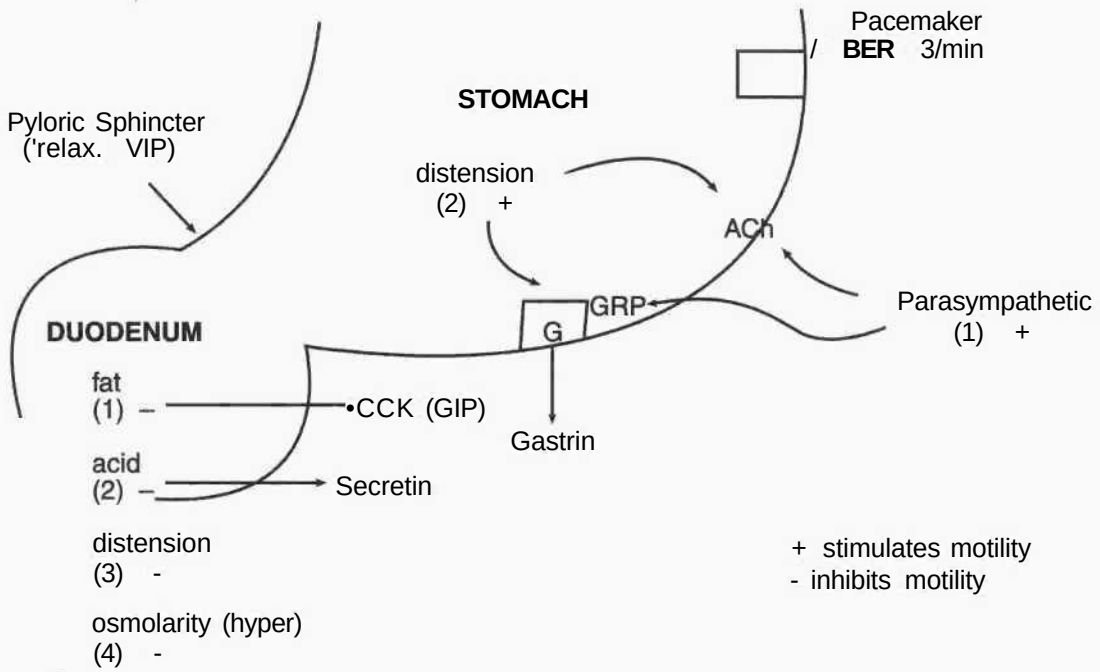


Figure X-2

ACh = Acetylcholine
BER= Basic electrical rhythm
GIP = Gastric inhibitory polypeptide
GRP = Gastrin-releasing peptide
VIP = Vasoactive intestinal polypeptide
+ stimulates motility
- inhibits motility

Stimulation
Increased parasympathetic activity via acetylcholine and gastrin release.

Local distension.

Inhibition
Low pH of stomach contents inhibits the release of gastrin. acid indigestion

Feedback from duodenal overload (neural and hormonal).

Stomach Emptying
Liquids > CHO > protein > fat (> = faster than)

Small Intestinal Motility

Segmentation contractions (mixing) and peristaltic movements (propulsive)

Ileocecal sphincter

Distension of ileum—relaxation of sphincter

Distension of colon—contraction of sphincter

Colon Motility

Segmentation contractions (haustrations), peristalsis, and mass movements.

Migrating Myoelectric Complex (MMC)

A propulsive movemgnLinitiated during fasting, which begins in the stomach and moves undigested material from the stomach" and small intestine into the colon.

Repeats every 90-120 minutes during fasting.

Correlated with high circulating levels of motilin, a hormone of the small intestine.

SECRETIONS

Salivary Secretions

Almost entirely under the control of the parasympathetic system, which promotes secretions.

The initial fluid formation in the acinus is via a chloride pump, and the electrolyte composition is similar to interstitial fluid.

NaCl is reabsorbed in the ducts, making the secretions hypotonic.

These and additional aspects are illustrated in Figure X-3.

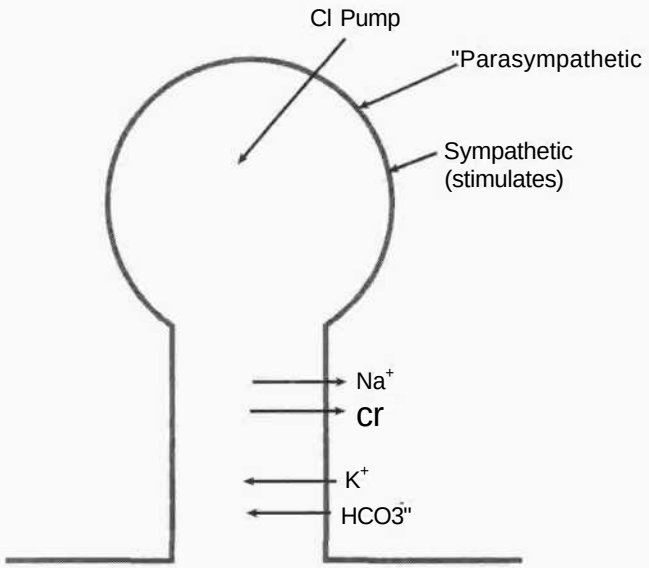


Figure X-3

CompositionofSalivarySecretions

Low in Na^+, Cl~ because of reabsorption.

High in K+, HCC>3~ because of secretion.

a-Amylase (ptyalin): secreted in the active form and begins the digestion of carbohydrates.

Mucus, glycoprotein.

Low tonicity: Salivary fluid is hypotonic because of reabsorption of NaCl and impermeability of ducts to water.

Gastric Secretions

Secretions of the Main Cells Composing the Gastric Glands

Parietal Cells

HCl.

Intrinsic factor (required for life) combines with vitamin B_{12} and is reabsorbed in the distal ileum.

Chief Cells

Pepsinogen is converted to pepsin by H+, as illustrated in the diagram below.

pepsmogen $\xrightarrow{H^+}$ pepsin (proteins to peptides)

Pepsinogen is initially converted to active pepsin by acid.

Active pepsin continues the process.

Pepsin is active only in the acid pH medium of the stomach.

Pepsin begins the digestion of protein.

Mucous Cells

Mucous, *WCOfr-f QAjTbO mA^xe* around stomach gastric ulcer is more often associated w/ normal acid

The viscous solution produced by the mucous cells protects the stomach lining from the caustic actions of the HCl. Secretion is stimulated by prostaglandins.

Ionic Composition

Compared to extracellular fluid, gastric secretions are high in H^+, K^+, Cl~; but low in Na+.

Vomiting stomach contents produces a metabolic^ alkalosis and a loss of body potassium.

Control ***of Acid Secretion***

There are 3 natural substances that stimulate parietal cells:

Acetylcholine, acting as a transmitter.

Locally released histamine.

The hormone gastrin.

The overall regulation of parietal cell secretion is illustrated in Figure X-4.

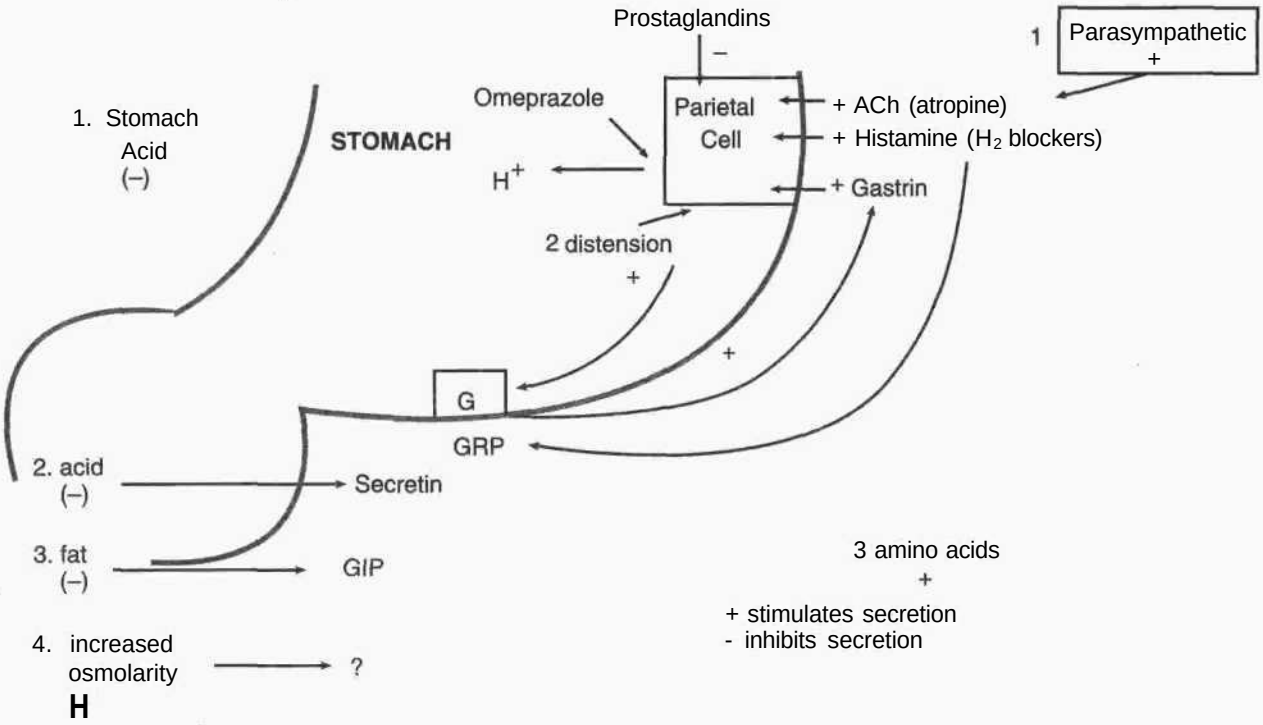


Figure X-4

Cellular Mechanisms of Acid Secretion

Hydrogen ions are secreted by a H/K-ATPase pump.

The source of the H^+ is CO2. The demand for CO2 is so great following a meal that CO2 can actually be extracted from the arterial blood.

Because of this extraction and the secretion of HCO_3~, the venous blood draining the stomach after a meal can be very alkaline. This is illustrated in Figure X-5.

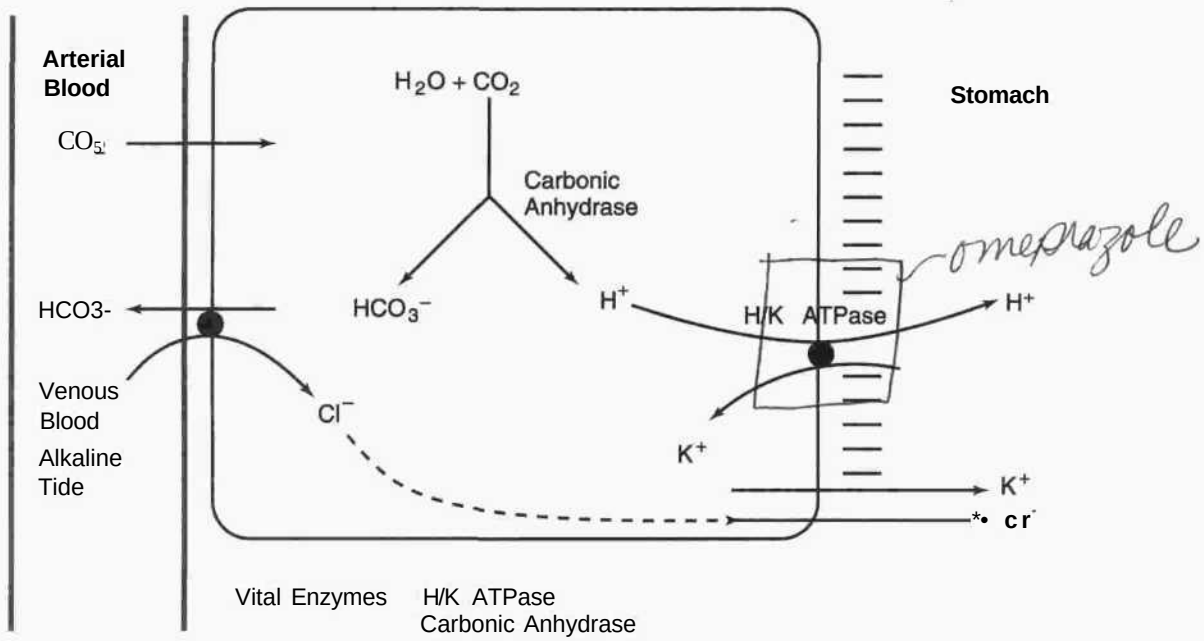


Figure X-5

Pancreatic Secretions

Enzymes Secreted in the Active Form

Pancreatic Amylases

Hydrolyzes oc-l,4-glucoside linkages of complex carbohydrates, forming three smaller compounds:

- a-Limit dextrins: still a branched polysaccharide
- Maltotriose, a trisaccharide
- Maltose, a disaccharide

Cannot hydrolyze P linkages of cellulose.

Which of fall. secreted in an inactive form
a. cholesterol esterase
b- phospholipase A_2
c. α amylase
d. procarboxypeptidase

Pancreatic Lipases

Glycerol ester lipase (pancreatic lipase): needs colipase to be effective. Colipase displaces bile salt from the surface of micelles. This allows pancreatic lipase to attach to the droplet and digest it, leading to formation of two free fatty acids and one monoglyceride (a 2-monoglyceride, i.e., an ester on carbon 2).

Cholesterol Esterase (Sterol Lipase)

Hydrolyzes cholesterol esters to yield cholesterol and fatty acids.

Phospholipase A_2

Acts on phospholipids, namely lecithin, to form lysolecithin.

Enzymes Secreted in an Inactive Form

Proteases

Include trypsinogen, chymotrypsinogen, procarboxypeptidase.

Activation Sequence

The activation sequences are summarized below.

trypsinogen —(enterokinase*)→ trypsin (endopeptidase)

chymotrypsinogen —(trypsin)→ chymotrypsin (endopeptidase)

procarboxypeptidase —(trypsin)→ carboxypeptidase (exopeptidase)

*Enterokinase (also known as enteropeptidase) is an enzyme secreted by the lining of the small intestine. It is not a brush border enzyme. It functions to activate some trypsinogen, and the active trypsin generated activates the remaining proteases.

Ionic Composition

Pancreatic secretions are high in HCO_3^- and low in Cl^-.

As the secretion rate increases, HCO_3^- concentration increases.

Secretions are isotonic due to high water permeability of ducts.

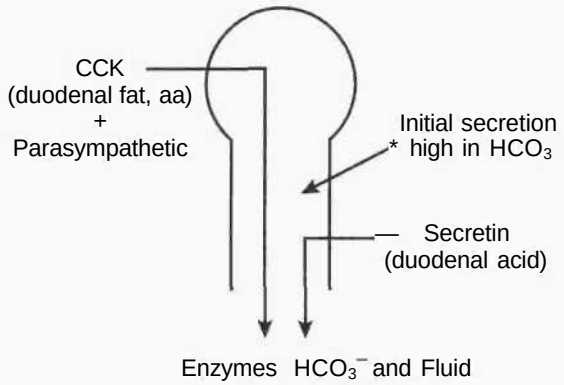


Figure X-6

Control of Pancreatic Secretions

There is a minor parasympathetic effect on pancreatic secretions.

Almost all the regulation is via two hormones: secretin and cholecystokinin.

Secretin
Released from the duodenum in response to acid entering from the stomach.

Action on the pancreas is the release of fluid high in HCC>3~.

This released HCO3- rich fluid is the main mechanism which neutralizes stomach acid entering the duodenum.

Cholecystokinin (CCK)
Released from the duodenum in response to partially digested materials (e.g., fat, peptides, and amino acids).

Action on the pancreas is the release of enzymes (amylases, Upases, proteases).

Composition and Formation of Bile

Overview

Figure X-7 summarizes the major components of bile. A complete description follows.

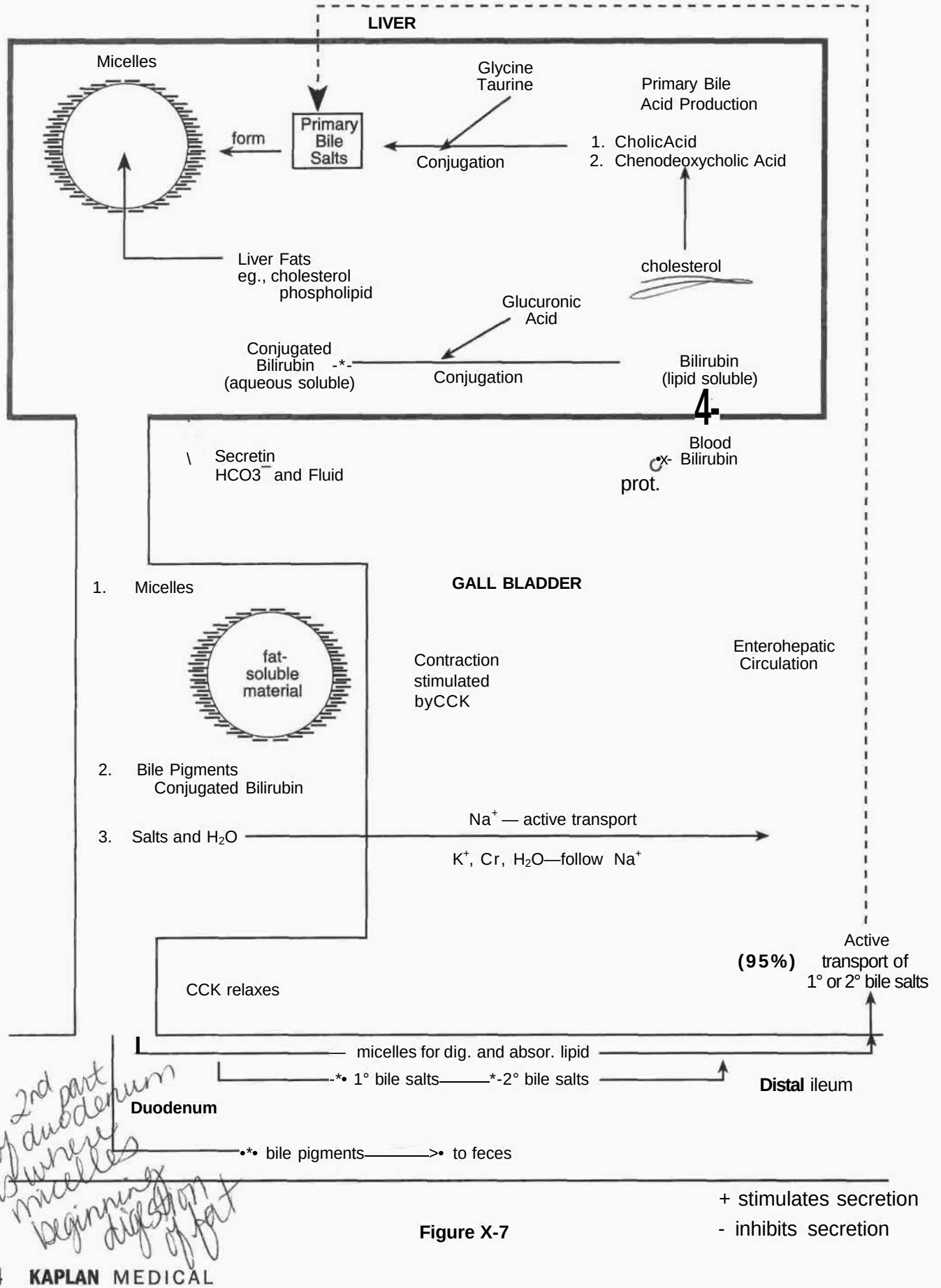

LIVER
Micelles
form
Primary Bile Salts
Glycine
Taurine
Conjugation
Primary Bile Acid Production
1. CholicAcid
2. Chenodeoxycholic Acid
cholesterol
Liver Fats
eg., cholesterol
phospholipid
Glucuronic Acid
Conjugated Bilirubin (aqueous soluble)
Conjugation
Bilirubin (lipid soluble)
Blood
Bilirubin
prot.
Secretin
HCO3⁻ and Fluid
1. Micelles
GALL BLADDER
fat-soluble material
Contraction stimulated byCCK
Enterohepatic Circulation
2. Bile Pigments
Conjugated Bilirubin
3. Salts and H2O
Na+ — active transport
K+, Cr, H2O—follow Na+
CCK relaxes
(95%)
Active transport of 1° or 2° bile salts
micelles for dig. and absor. lipid
1° bile salts
2° bile salts
Distal ileum
Duodenum
bile pigments
to feces
+ stimulates secretion
- inhibits secretion

Figure X-7

Bile Salts and Micelles

Primary bile acids known as cholic acid and chenodeoxycholic acid are synthesized by the liver from cholesterol. The lipid-soluble bile acids are then conjugated primarily with glycine. The conjugated forms are water-soluble but contain a lipid-soluble segment. Because they are ionized at neutral pH, conjugated bile acids exist as salts of cations (Na^+) and are, therefore, called bile salts.

Which of following not transported in micelle?
a. lecithin
b. vit D
c. cholesterol
d. glycerol
e. vit A

Bile salts are actively secreted by the liver.

Secondary bile acids are formed by deconjugation and dehydroxylation of the primary bile salts by intestinal bacteria, forming deoxycholic acid (from cholic acid) and lithocholic acid (from chenodeoxycholic acid). Lithocholic acid has hepatotoxic activity and is excreted.

Micelle Formation

When bile salts become concentrated, they form micelles. These are water-soluble spheres with a lipid-soluble interior. As such, they provide a vehicle to transport lipid-soluble materials in the aqueous medium of the bile fluid and the small intestine.

Micelle Function

Micelles are vital in the digestion, transport, and absorption of lipid-soluble substances from the duodenum to the distal ileum. In the distal ileum, and only in the distal ileum, can the bile salts be actively reabsorbed and recycled (enterohepatic circulation). Lack of active reabsorbing mechanisms (or a distal ileum) causes loss in the stool and a general deficiency in bile salts, as the liver has a limited capacity to manufacture them. This deficiency can lead to fat malabsorption and cholesterol gallstones.

BilePigments

Bilirubin

A major bile pigment, bilirubin is a lipid-soluble metabolite of hemoglobin. Transported to the liver attached to protein, it is then conjugated and excreted as water-soluble glucuronides. These give a golden yellow color to bile.

Stercobilin

Produced from metabolism of bilirubin by intestinal bacteria. It gives a brown color to the stool.

A young child has diarrhea for past 5 days. He has been treated and sent home. What do you advise his mother? Do not give him milk, sugar

C

SaltsandWater

The HCC>3~ component is increased by the action of secretin on the liver.

The active pumping of sodium in the gall bladder causes electrolyte and water reabsorption, which concentrates the bile.

Bile pigments and bile salts are not reabsorbed from the gall bladder.

Phospholipids(MainlyLecithin)

Insoluble in water but are solubilized by bile salt micelles.

Cholesterol

Present in small amounts. It is insoluble in water and must be solubilized by bile salt micelles before it can be secreted in the bile.

5) The digestion of carb. + prot. completed by pancreatic enzymes.
No. they make them to disaccharides + dipeptides

ControlofBileSecretionandGallBladderContraction

Secretin causes secretion of HCO_3~ and fluid into bile canalicular ducts.

Secretion of bile salts by hepatocytes is directly proportional to hepatic portal vein concentration of bile salts.

It terminates in brush border of small intestine

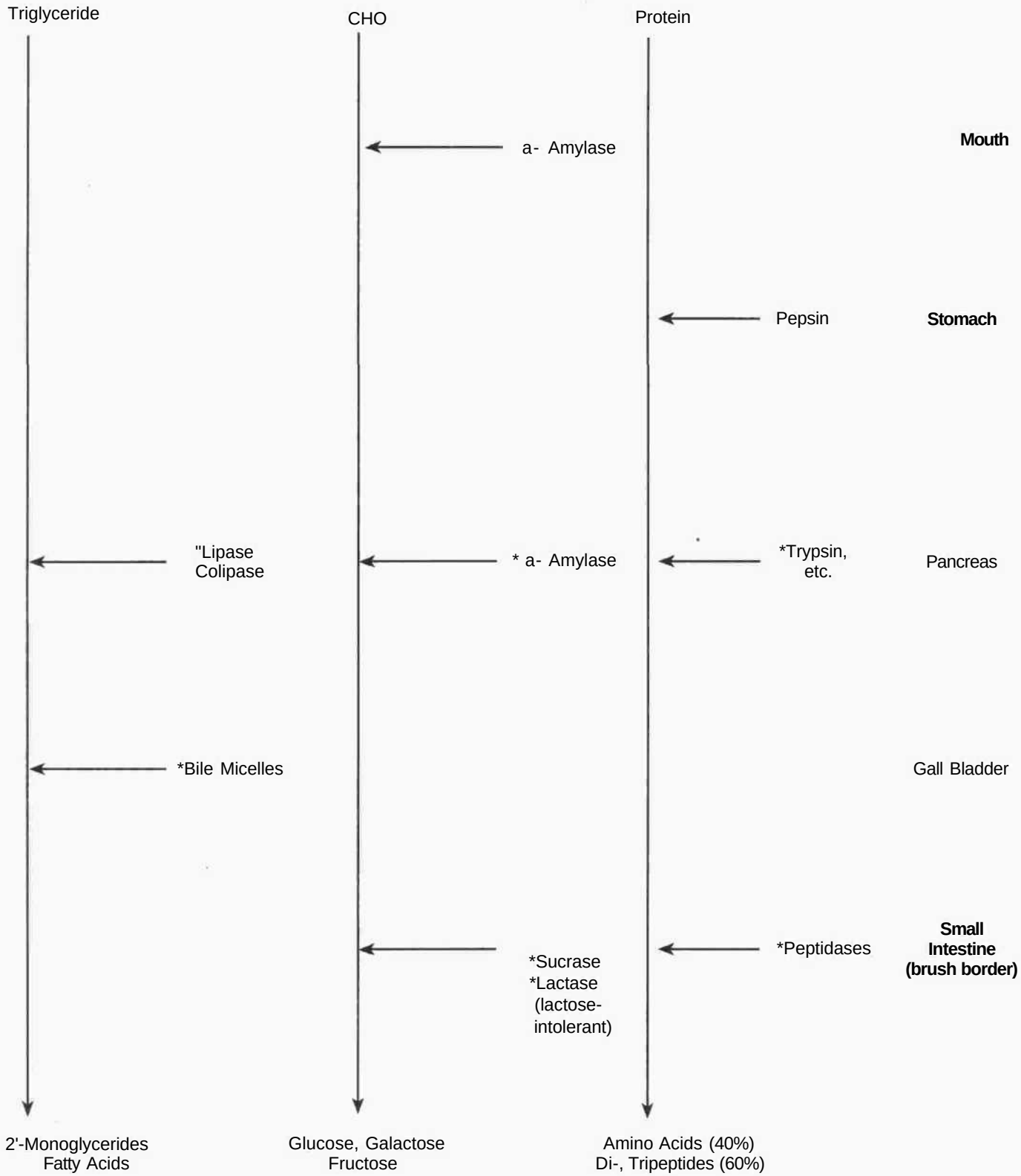
W W-J **u**CK causes gall bladder contraction and sphincter of Oddi relaxation.

DIGESTION

General Features

Figure X-8 summarizes the regional entry of the major digestive enzymes proceeding from the mouth, stomach, and through the small intestine. A text summary follows.

Gluten-sensitive enteropathy (celiac disease) produces generalized malabsorption.



•Required for digestion

Figure X-8

Summary of Digestive Enzymes and End Products

Triglycerides

Stomach: Fatty materials are pulverized to decrease particle size and increase surface area.

Small intestine: Bile micelles emulsify the fat, and pancreatic Upases digest it. Micelles and pancreatic lipase are required for triglyceride digestion. The major end products are 2-monoglycerides and fatty acids.

Carbohydrates

Mouth: Salivary a-amylase begins the digestion, and its activity continues in the stomach until acid penetrates the bolus; however, it is not a required enzyme.

Small intestine: Pancreatic a-amylase, a required enzyme for CHO digestion, continues the process. Hydrolysis of starch by a-amylase goes on in solution in the lumen of the small intestine, mostly in the duodenum. Further processing or splitting of these trisaccharides, disaccharides, and oligosaccharides is necessary but does not take place in solution; rather, it occurs on the brush border. The enzymes—a-dextrinase (or a-glucoamylase), isomaltase, and maltase—are all bound to the brush border (apical membrane of enterocytes). Brush border enzymes have their highest activity in the jejunum (upper). These brush border enzymes are required for digestion mainly because disaccharides—e.g., sucrose, lactose—are not absorbed from the gut.

The a-dextrinase cleaves terminal a-1,4 bonds, producing free glucose.

Lactase hydrolyzes lactose into glucose and galactose. Lactase deficiency (lactose intolerance) leads to osmotic diarrhea.

Sucrase splits sucrose into glucose and fructose.

Maltase (also a brush border enzyme) breaks down the maltose and maltotriose to to form 2 and 3 glucose units, respectively.

The monosaccharide end products—glucose, galactose, and fructose—are readily absorbed from the small intestine, also mainly in the jejunum.

Note

Pancreatic enzymes are required for triglyceride, CHO, and protein digestion. Circulating CCK is almost totally responsible for their secretion following a meal.

Proteins

Stomach: Pepsin begins the digestion of protein in the acid medium of the stomach; however, it is not an essential enzyme.

Small intestine: Digestion continues with the pancreatic proteases (trypsin, chymotrypsin, elastase, and carboxypeptidases A and B), which are essential enzymes.

All these pancreatic enzymes are secreted as inactive proenzymes (zymogens).

Protein digestion is completed by the small intestinal brush border enzymes, dipeptidases, and an aminopeptidase. The main end products are amino acids (40%) and dipeptides and tripeptides (60%).

ABSORPTION

Carbohydrate and Protein

Figure X-9 illustrates the major transport processes carrying sugars and amino acids across the luminal and basal membranes of cells lining the small intestine.

Clinical Correlate

Sprue

Sprue is a generic term for several malabsorptive disorders.

These include:
Gluten-sensitive enteropathy (celiac disease), which results in flattening of villi and generalized malabsorption. Some individuals are sensitive to gluten, a component of some grains. Normal function returns if gluten is avoided by removal of wheat or rye flour from the diet.

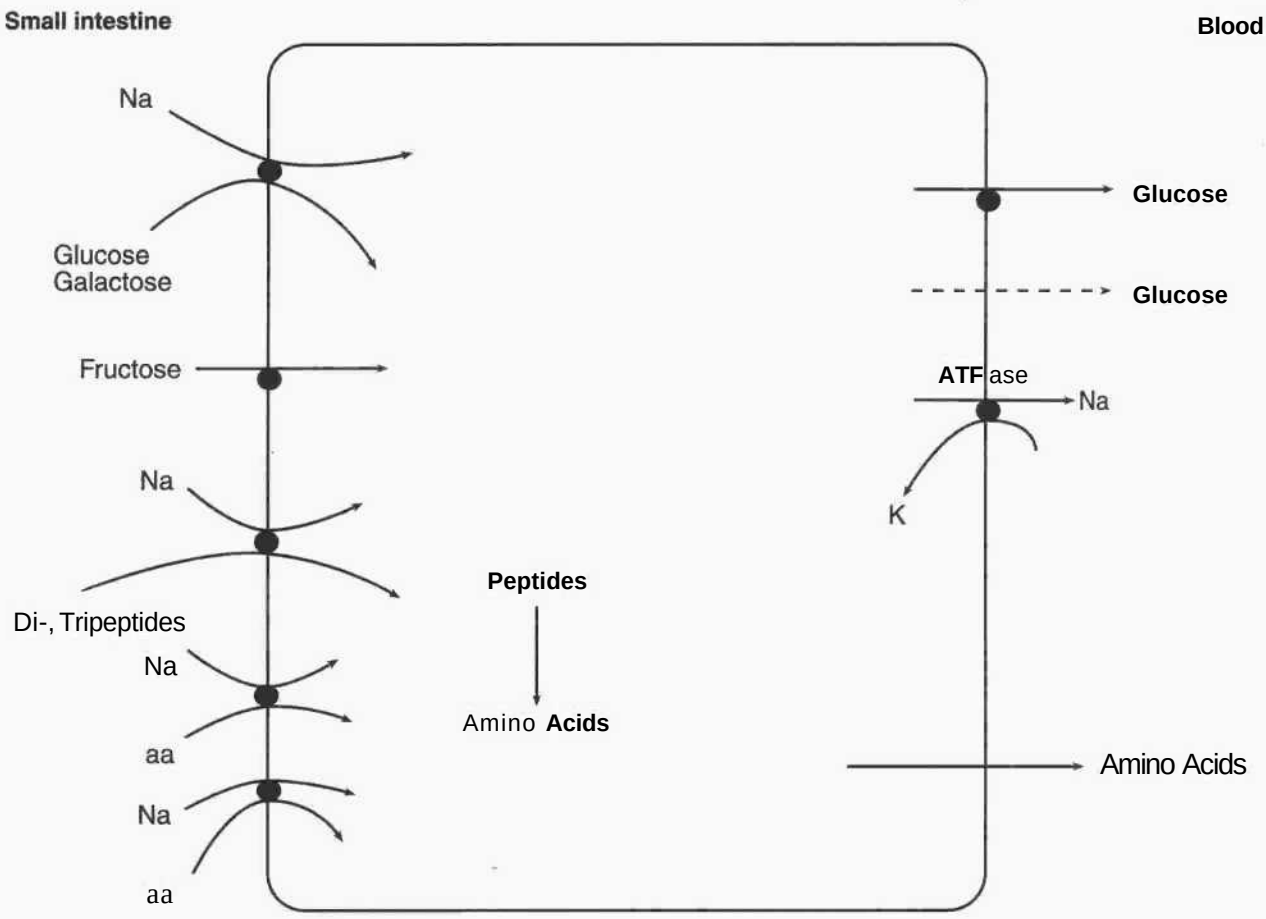


Figure X-9

Carbohydrate

Luminal membrane: Glucose and galactose are actively absorbed (secondary active linked to sodium) via the same carrier. Fructose is absorbed independently.

Basal membrane: Glucose is absorbed passively mainly via facilitated diffusion, although some simple diffusion may also contribute.

Protein

Luminal membrane: secondary active transport linked to sodium and receptor-mediated endocytosis.

Basal membrane: simple diffusion of amino acids, although it is now known some protein-mediated transport also occurs.

Lipids

Figure X-10 summarizes the digestion and absorption of lipid substances. The end products of triglyceride digestion, 2-monoglycerides and fatty acids, remain as lipid-soluble substances that are then taken up by the micelles.

Digestive products of fats found in the micelles and absorbed into the intestinal lumen may include:

Fatty acids (long chain)
2-Monoglyceride
Cholesterol
Lysolecithin
Vitamins A, D, E, K
Bile salts, which stabilize the micelles

Micelles diffuse to the brush border of the intestine. The diffusion through the unstirred layer is the rate-limiting step of fat absorption.

The digested lipids then diffuse across the brush border in the lipid matrix. In the mucosal cell, triglyceride is resynthesized and forms lipid droplets (chylomicrons). These leave the intestine via the lymphatic circulation (lacteals).

They then enter the blood stream via the thoracic duct.

The more water-soluble short-chain fatty acids can be absorbed by simple diffusion directly into the blood stream.

The bile salts are actively reabsorbed in the distal ileum.

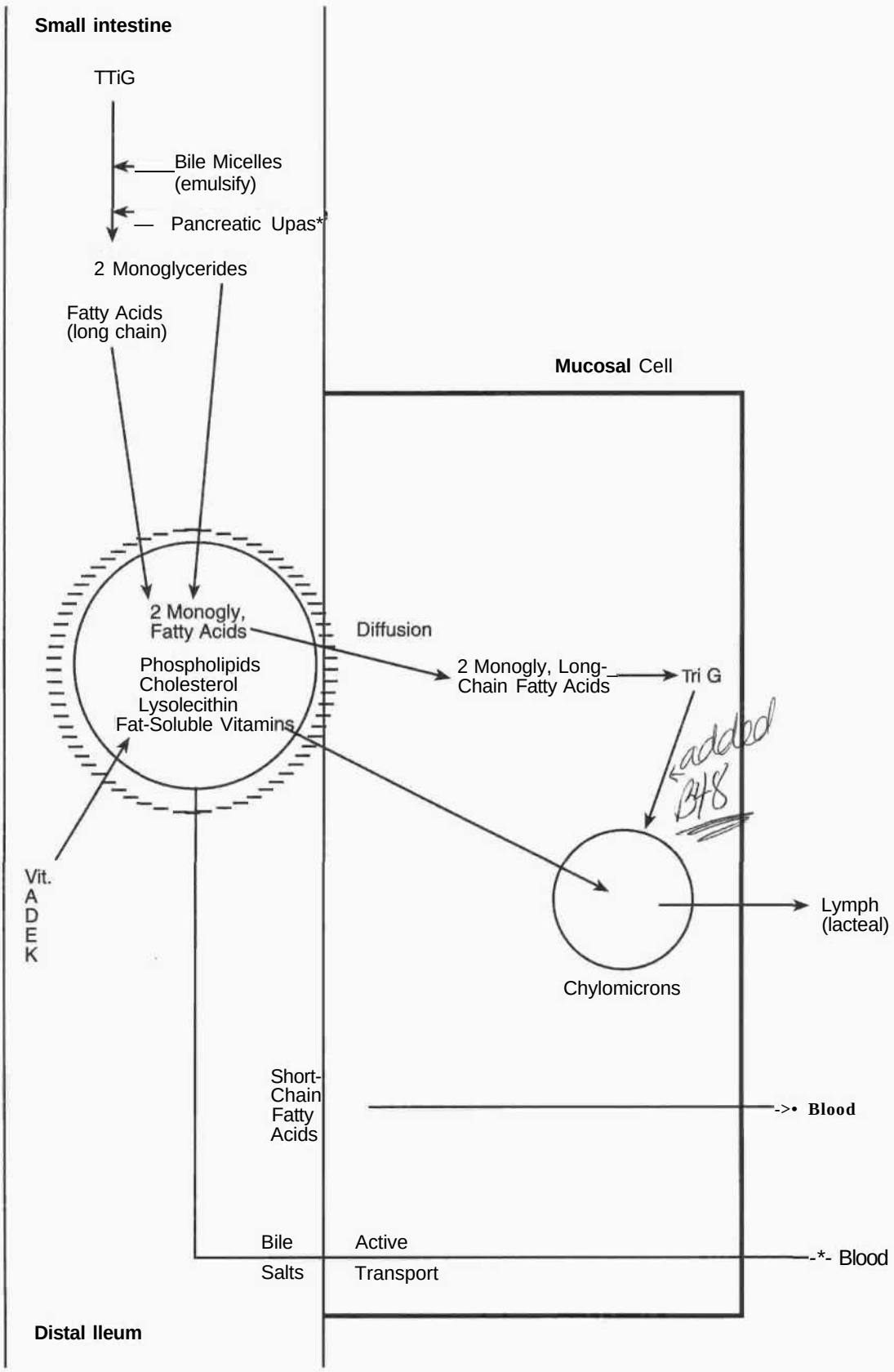

Small intestine
TTiG
Bile Micelles
(emulsify)
Pancreatic Upas*
2 Monoglycerides
Fatty Acids
(long chain)
Mucosal Cell
2 Monogly,
Fatty Acids
Diffusion
Phospholipids
Cholesterol
Lysolecithin
Fat-Soluble Vitamins
2 Monogly, Long-
Chain Fatty Acids
Tri G
added
B48
Vit.
A
D
E
K
Lymph
(lacteal)
Chylomicrons
Short-
Chain
Fatty
Acids
Blood
Bile
Salts
Active
Transport
Blood
Distal Ileum

Figure X-10

Clinical Correlate

Cholera

Cholera epidemics have killed countless individuals. Death is due to dehydration and electrolyte imbalance. Electrolyte secretion is via a cAMP-dependent chloride pump in the small and large intestine.

Cholera toxin irreversibly activates cAMP in these cells and produces a chloride-rich watery diarrhea.

Treatment is theoretically simple, namely, hydration and appropriate electrolyte replacement.

vit. B_{12} absorbed in ileum b/c need IF

Electrolytes

The net transport of electrolytes along the length of the small and large intestine is summarized in Figure X-l 1 and discussed in more detail below.

Electrolyte secretion occurs via a cAMP-dependent chloride pump in the small and large intestine. This is the site of action of the cholera toxin.

Duodenum

Hypertonic fluid enters this region, and following the movement of some water into the lumen, the fluid becomes and remains isotonic.

The absorption of divalent ions and water-soluble vitamins is mainly in the upper small intestine.

Iron is absorbed mainly from the duodenum.

Jejunum

Overall, there is a net reabsorption of water and electrolytes. The cellular processes involved are almost identical to those described in the renal physiology section for the cells lining the nephron proximal tubule.

Ileum

Net reabsorption of water, sodium, chloride, and potassium continues, but there is a net secretion of bicarbonate.

It is in the distal ileum, and only in the distal ileum, where the reabsorption of bile salts and intrinsic factor with vitamin B_{12} take place.

Colon

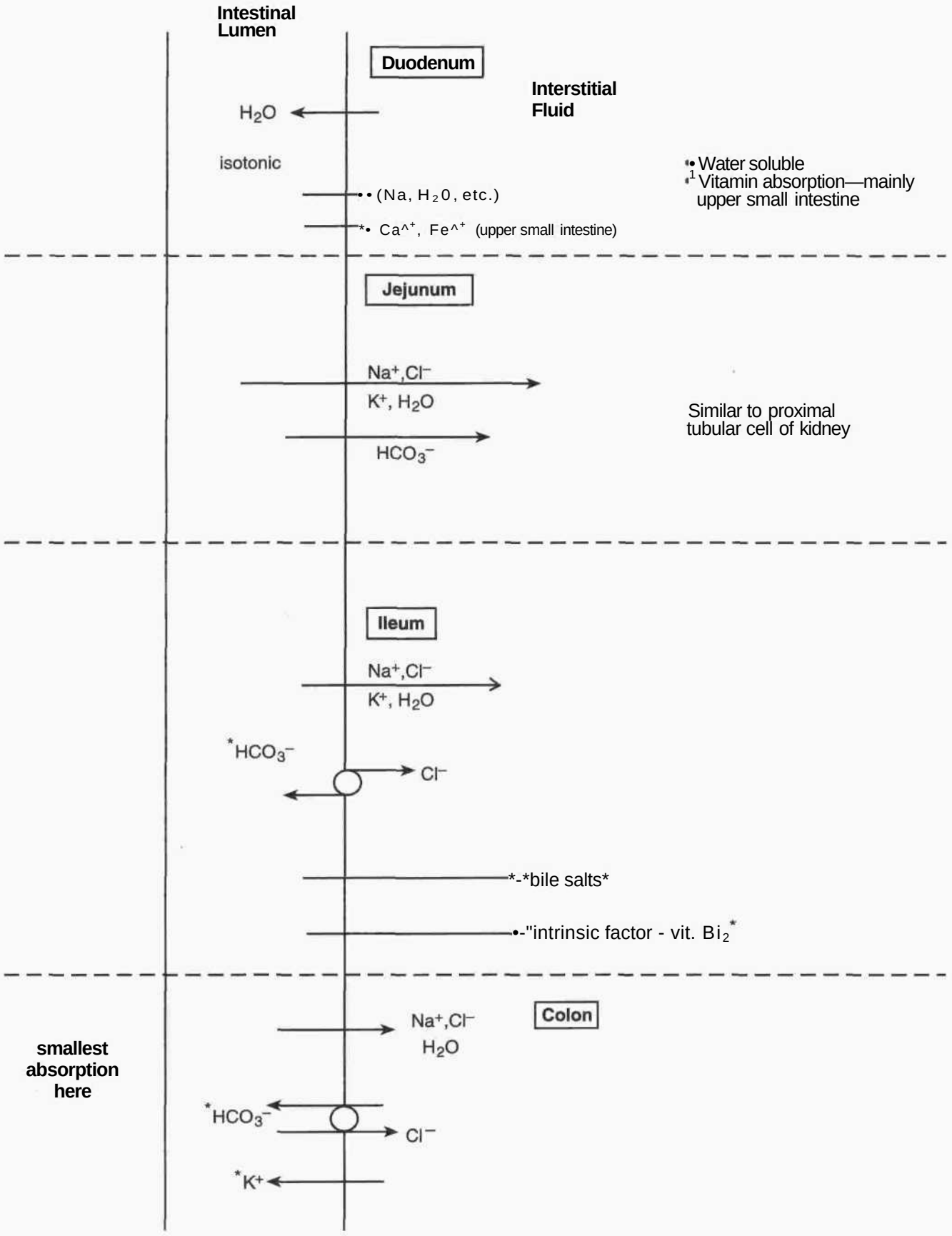
The colon does not have digestive enzymes or the protein transporters to absorb the products of carbohydrate and protein digestion.

Also, because bile salts are reabsorbed in the distal ileum, very few lipid-soluble substances are absorbed in the colon.

There is a net reabsorption of water and sodium chloride, but there are limitations.

- Most of the water and electrolytes must be reabsorbed in the small intestine, or the colon becomes overwhelmed.
- Most of the water and electrolytes are absorbed in the ascending and transverse colon; thereafter, the colon mainly has a storage function.

There is a net secretion of bicarbonate and potassium. Therefore, diarrhea usually produces a metabolic acidosis and hypokalemia.


Intestinal Lumen
Duodenum
Interstitial Fluid
H2O
isotonic
•• (Na, H20, etc.)
*• Ca^+, Fe^+ (upper small intestine)
•• Water soluble
1 Vitamin absorption—mainly upper small intestine
Jejunum
Na+,Cl−
K+, H2O
HCO3−
Similar to proximal tubular cell of kidney
Ileum
Na+,Cl−
K+, H2O
*HCO3−
Cl−
*-*bile salts*
•-"intrinsic factor - vit. Bi2*
Colon
Na+,Cl−
H2O
smallest absorption here
*HCO3−
Cl−
*K+

FigureX-11

Chapter Summary

Stretching smooth muscle causes a contractile response.

Because of regional pacemaker activity, there is always some basal motor activity in the GI tract.

Swallowing is a reflex controlled from the brain stem.

Following a meal, local distension and parasympathetic activity increase stomach motility. An overload of the duodenum decreases stomach motility.

There are mixing and propulsive movements in the small intestine and colon.

Salivary secretions are regulated via parasympathetic input. The reabsorption of sodium chloride produces a fluid that is hypotonic.

Gastric acid secretion via a hydrogen/potassium-ATPase pump is stimulated by acetylcholine, histamine, and gastrin. A low stomach pH and a duodenal overload inhibit acid secretion.

The release of pancreatic enzymes depends on cholecystokinin. These enzymes are required for the digestion of carbohydrate, protein, and lipids.

The release of bicarbonate-rich pancreatic fluid depends upon secretin. This fluid entering the duodenum is required for the neutralization of acid entering from the stomach. Pancreatic juice is isotonic.

Bile salts form micelles that are required for the digestion and absorption of lipids. Only in the distal ileum can they be actively reabsorbed. They must be recycled because the liver has a limited ability for their synthesis.

Bile pigments are water-soluble compounds excreted via the bile and intestine.

Electrolytes and water, but not bile pigments or bile salts, can be absorbed from the gall bladder lumen.

Digestion of lipid requires bile micelles and pancreatic lipases. End products absorbed include 2-monoglycerides and fatty acids.

Digestion of carbohydrate requires pancreatic amylases and the small intestinal brush border enzymes. End products absorbed will be the monosaccharides. Disaccharides cannot be absorbed from the small intestine.

Digestion of protein requires the pancreatic proteases, which must be initially activated by enterokinase. Also required are the small intestinal brush border enzymes. End products absorbed include amino acids and very small peptides.

Absorption of carbohydrate, amino acids, and small peptides is mainly by secondary active transport at the luminal membrane in the small intestine.

Lipids are absorbed by diffusion via micelles; the chylomicrons formed in mucosal cells enter the lymphatics.

Most of the water and electrolytes are reabsorbed in the small intestine. The distal ileum reabsorbs the bile salts and intrinsic factor-vitamin B_{12} complex.

The colon has a net secretion of bicarbonate and potassium.

GASTROINTESTINAL PHYSIOLOGY

Review Questions

GastrointestinalMotility

Questions 1-3: Select the best answer.

1. The basic electrical rhythm or slow waves recorded from intestinal smooth muscle:
   A. Is thought to result from ACh release from parasympathetic nerves in both longitudinal and circular muscle.
   B. Is synonymous with generator potentials.
   C. Varies in rate in different regions of the gastrointestinal system.
   D. All of the above.
   E. Only A and C.

2. All of the following would generally depolarize intestinal smooth muscle EXCEPT:
   A. Distension.
   B. Adrenergic transmitters.
   C. Cholinergic agents.
   D. Myenteric plexus activation.
   E. Vagal discharge.

3. The lower esophageal sphincter normally:
   A. Reduces its tone under the influence of gastrin.
   B. Increases its tone from the parasympathetic release of vasoactive intestinal peptide
   C. Is composed of both skeletal and smooth muscle.
   D. Has a yield pressure greater than intragastric pressure.

Questions 4-6: Select all correct answers.

4. Functions that do not need extrinsic innervation include:
   A. Initiation of swallowing
   B. Stomach emptying
   C. Defecation
   D. Mixing and propulsion in small intestine

5. The strength of peristaltic waves passing over the stomach is influenced by:
   A. Presence of 2-monoglycerides in the duodenum.
   B. Distension of duodenum.
   C. Osmotic pressure of chyme leaving the stomach.
   D. Rate of release of adrenergic substances in the intrinsic plexus.

6. Efferent impulses from vagal fibers to stomach may mediate:
   A. Increase strength of gastric peristalsis
   B. Relaxation of the gastric fundus during swallowing
   C. Increased secretion from parietal cells
   D. Vasoconstriction in gastric mucosa

Gastrointestinal Secretions

Questions 1-4: Select all the correct answers.

1. During storage in gall bladder, bile undergoes an increase in:
   A. Osmotic pressure.
   B. H^+ concentration
   C. Water content.
   D. Bile salt concentration.

2. Bile contains:
   A. Lecithin.
   B. Cholesterol.
   C. Micelles.
   D. Chymotrypsinogen.

3. Unconjugated bilirubin is:
   A. Necessary for intestinal absorption of fatty acids.
   B. Highly soluble in plasma.
   C. The form of bilirubin normally found in the bile canaliculus.
   D. Elevated in the serum in case of hemolytic jaundice.

4. Obstruction of bile duct would result in:
   A. increased content of lipids in feces
   B. increased excretion of dietary cholesterol in feces
   C. increased conjugated bile pigments in the serum
   D. decreased excretion of bilirubin glucuronides in urine

Question 5: Select the best answer.

5. After secretion into the duodenum, the enzyme trypsinogen is converted into its active form, trypsin, by:
   A. Enterokinase.
   B. Procarboxypeptidase.
   C. Lysolecithin.
   D. An alkaline pH.
   E. An acid pH.

Question 6: Select the best answer.

6. A patient deficient in trypsin inhibitor has a primary abnormality that involves the:
   A. Oxyntic (parietal) cells of the stomach.
   B. Pancreas.
   C. Small intestine epithelium.
   D. Salivary glands.
   E. Liver.

Questions 7-10: Select all the correct answers.

7. Neutralization of acidic stomach contents entering duodenum is due to:
   A. Pancreatic juice.
   B. Bile.
   C. Secretions of intestinal glands.
   D. Saliva.

8. Trypsin and chymotrypsin are similar in that they:
   A. Are activated in the intestine.
   B. Occur in precursor form in the pancreas.
   C. Are active in an alkaline or neutral medium.
   D. Require vitamin K for their synthesis.

9. Free H^+ in the gastric juice of a mammal is:
   A. Associated with increased alkalinity of the plasma leaving the stomach.
   B. Well-correlated with gastric peptic activity under physiological conditions.
   C. Controlled by both hormonal and autonomic nervous mechanisms.
   D. Produced by same stomach epithelial cells secreting pepsinogen.

10. Low gastric pH:
   A. Inhibits release of gastrin
   B. Inhibits release of histamine
   C. Is necessary for pepsin activity
   D. Reduces irritation caused by aspirin

Questions 11-16: For each group of questions, use corresponding A-D scheme for answers.

Questions 11-14.

A. Gastrin.
B. Secretin.
C. Cholecystokinin.
D. Gastric inhibitory peptide.

11. Major stimulant of HCO_3~ secretion in bile duct.

12. Causes contraction of the gall bladder.

13. Increases stomach acid secretion.

14. Polypeptide that primarily stimulates release of pancreatic amylase.

Questions 15-16.

A. HC1.
B. HCO3-.
C. Mucin.
D. NaCl.

15. Serves as lubricant in gastrointestinal tract

16. Regulates gastrin output in stomach.

Question 17: Select the best answer.

17. Which of the following competes for many of the same receptor sites as gastrin because of a chemical structure similar to gastrin?
A. secretin.
B. glucagon.
C. histamine.
D. cholecystokinin.
E. gastric inhibitory peptide.

Question 18: Select all the correct answers.

18. Carbonic anhydrase is active in high concentration in the:
    A. chief cells of the stomach
    B. parietal cells of the stomach
    C. duodenal mucosa
    D. pancreatic duct cells

GastrointestinalDigestionandAbsorption

DIRECTIONS: For each group, chose one answer from A-D multiple choice.

Questions 1-5.

A. Glucose.
B. Amino acids.
C. Glucose and amino acids.
D. Triglycerides.
E. Glucose, amino acids, and triglycerides.

1. Absorption by small intestine utilizes Na^+ carrier.
2. Moved from intestinal epithelial cell to intracellular space by diffusion.
3. Mainly transported to blood vessel by lacteal.
4. Absorption used same carrier as galactose.
5. Absorbed by secondary active transport.

Questions 6-9.

A. Carbohydrates.
B. Proteins.
C. Carbohydrate and protein.
D. Triglycerides.
E. Carbohydrates, proteins, and triglycerides.

6. Absorption only after formation of soluble complexes with bile salts.
7. Enzymatic digestion in alkaline or neutral environment.
8. Absorption of digestive products involves carrier-mediated transport hi small intestine.
9. Digestion is partially completed before entering duodenum.

Question 10: Select the best answer.

10. Major site of vitamin B_{12} absorption is:
    A. stomach
    B. duodenum
    C. jejunum
    D. ileum
    E. descending colon

Questions 11-13: Select all the correct answers.

11. Substances that enter the circulation as chylomicrons via lymphatic ducts are:
    A. cholesterol
    B. short-chain fatty acids
    C. vitamin K
    D. glycerol

12. Cholecystokinin is important in fat absorption because it:
    A. stimulates the gall bladder to contract.
    B. potentiates effect of secretin on the secretion of bicarbonate by the pancreas.
    C. stimulates the secretion of pancreatic lipase.
    D. increases the strength of gastric peristalsis.

13. In a normal individual, the enterogastric reflex will be elicited by:
    A. increased duodenal wall tension
    B. irritation of small intestine mucosa
    C. protein metabolites in the duodenum
    D. acid chyme in the duodenum

Question 14-20: Select the best answer.

14. Which of the following statements most accurately describes amino acid uptake from the intestinal lumen? Amino acid:

A. crosses the mucosal membrane by a process of passive diffusion
B. crosses the mucosal membrane by a carrier-mediated transport process requiring the concomitant transfer of Na^+ in the same direction
C. crosses the serosal membrane by a carrier-mediated transport process requiring the concomitant transfer of Na^+ in the opposite direction
D. is actively transported across the serosal membrane against a concentration gradient
E. uptake is independent of high-energy phosphate bonds in the cell.

15. Calcium absorption in the small intestine is increased by:

A. vitamin D
B. parathyroid hormone
C. hypocalcemia
D. none of the above
E. only A and B

16. Long-chain fatty acids absorbed by the intestinal mucosa cells reach the blood in the form of:

A. monoglycerides
B. diglycerides
C. micelles
D. chylomicrons
E. free fatty acids

17. Rate of absorption of glucose from the small intestine can be reduced by presence in the small intestine of:

A. mannose
B. fructose
C. xylose
D. galactose
E. arabinose

18. The major lipolytic digestive enzymes in man:
    A. are found in gastric juices
    B. are activated by enterokinase
    C. are potentiated by bile salts
    D. produce 2-monoglycerides, free fatty acids, and glycerol
    E. require a pH of greater than 10 for optimal activity

19. Potassium is normally:
    A. passively absorbed in the small intestine and actively secreted in the proximal colon
    B. passively absorbed in the small intestine and actively absorbed in the proximal colon
    C. actively absorbed throughout small and large intestine
    D. passively absorbed throughout small and large intestine
    E. actively secreted in the small intestine and actively absorbed in the proximal colon

20. A patient deficient in sucrase has a primary abnormality that involves the:
    A. parietal cells of the stomach
    B. pancreas
    C. small intestinal epithelium
    D. salivary glands
    E. liver

Questions 21-23: Select all the correct answers.

21. Materials whose intestinal absorption is greatly aided by the presence of bile salts and phospholipids:
    A. cholesterol
    B. vitamin B_{12}
    C. long-chain fatty acids (14 C atoms or greater)
    D. short-chain fatty acids (10 C atoms or less)

22. After removal of the ileum, one observes a decrease:
    A. in size of bile acid pool
    B. in fat content of feces
    C. in absorption of vitamin B_{12}
    D. in fecal volume

23. Micelle formation is necessary for absorption and transport to intestinal epithelium oft
    A. cholesterol
    B. short-chain fatty acids
    C. vitamin D
    D. glycerol

Question 24: Select the best answer.

24. The basic mechanism for fluid movement out of lumen of the intestine is thought to depend on active:
    A. water transport and passive ion movements
    B. Cl~ transport, with Na^+ and water following passively
    C. Na^+ transport by intestinal epithelium with water following passively
    D. HCO_3~ transport with water following passively
    E. none of the above.

Question 25: Select all the correct answers.

25. The colon:
    A. Actively absorbs H_2O.
    B. Actively absorbs Na^+ and Cl~.
    C. Has mass movements for mixing of contents.
    D. Secretes HCO3-and K+.

GI Answers

Motility

1. **Ans C.** The basic electrical rhythm is the result of the regional pacemaker activity. It is an intrinsic characteristic of these cells and each region will have a different rate or rhythm.

2. **Ans** B. Depolarization of a smooth muscle cell is an excitatory stimulus. From the list provided this would include distension. An inherent property of smooth muscle cells is that a stretch causes depolarization and a contraction. Parasympathetics releasing ACh, and other cholinergic drugs also depolarize and increase activity, much of this working through the myenteric plexus. On the other hand, adrenergic activity to the gut inhibits smooth muscle and decreases activity.

3. **Ans** D. The lower esophageal sphincter should always maintain a yield pressure greater than intragastric pressure to prevent reflux of stomach contents into the esophagus. After a meal gastrin is released and there is an increase in stomach motility and intragastric pressure. To prevent esophageal reflux gastrin also increases the tone in the lower esophageal sphincter. VIP is an inhibitory parasympathetic transmitter released during swallowing to relax the lower sphincter. The lower sphincter is smooth muscle, the upper esophageal sphincter is skeletal muscle.

4. **Ans** B, D. The reflexes at the ends of the GI tract, swallowing and defecation, involve the central nervous system. But most other activity does not require central nervous system involvement. This would include stomach emptying and the mixing and propulsive movements of the small intestine.

5. **Ans** A, B, C, D. There are a number of stimuli originating from stomach chyme entering the duodenum that inhibit stomach activity. This would include fat via gastric inhibitory peptide, distension initiating a nervous reflex, the high osmotic pressure of the chyme, and, although not included in this question, the presence of acid causing the release of secretin. Sympathetic adrenergic substances will also inhibit motor activity.

6. **Ans** A, B, C. Vagal activity to the stomach increases after a meal and promotes both motor and secretory activity. Another action of the vagus is that it causes relaxation of the proximal stomach as part of the swallowing reflex (called receptive relaxation). Vagal or parasympathetic activity is not involved in vasoconstriction; if anything, vasodilation would be promoted.

Secretions

l.AnsD. The main change in the gall bladder is the absorption of water and electrolytes. Bile salts and bile pigments are not absorbed, but the removal of water causes these substances to become more concentrated.

2. **Ans** A, B, C. Micelles, which are composed of bile salts, are also a vehicle for lipid transport and contain lipids such as lecithin and cholesterol. Chymotrypsinogen is the precursor to a protease secreted by the pancreas.

3. **AnsD.** Unconjugated bilirubin is a lipid-soluble compound produced from the degradation of hemoglobin. It is transported to the liver attached to protein because it is lipid rather than water soluble. In the liver it is made **water soluble** and excreted in the bile.

4. **Ans** A, B, C. Obstruction of the bile duct means bile cannot enter the duodenum. Bile micelles are important in the digestion and absorption of lipid, and their absence causes increased lipids in the stool. Also, conjugated (water-soluble) bile pigments will appear in the plasma, and because they are water-soluble they will be filtered by the kidney and appear in the urine.

5. **Ans** A. A big point made in class was the fact that enterokinase must be present in the duodenum specifically to activate trypsinogen to trypsin. Trypsin then activates the remaining pancreatic proteases. Without enterokinase pancreatic proteases will not be adequately activated and protein digestion cannot proceed normally.

6. Ans B. Trypsin inhibitor is a substance secreted by the pancreas along with the protein proenzymes.

7. **Ans** A, B, C. The main mechanism that neutralizes stomach acid entering the duodenum is the release of secretin that causes the release of pancreatic bicarbonate. "A" would be the best answer to this question. There is, however, some contribution from bile and intestinal secretions. There is no contribution from salivary secretions whose bicarbonate will be neutralized by stomach acid.

8. **Ans** A, B, C. These are proteases that are converted to their active forms in the duodenum (initiated by enterokinase acting on trypsinogen). The inactive precursors are secreted by the pancreas. These enzymes are active in the neutral or slightly alkaline environment of the small intestine.

9. **Ans** A, B, C. The secretion of one H^+ into the stomach is associated with the secretion of one HCO_3~ into the venous system. This causes stomach venous blood to become more alkaline. Also, after a meal the demand for CO_2 by the parietal cells as a source of H^+ is so high that it extracts CO_2 from capillary blood. Thus, venous blood draining the stomach after a meal is low in CO_2 and high in HCO_3~~ which makes for a very alkaline state. There is generally a good correlation between secretion of the parietal cells (secreting H^+)and chief cells (secreting pepsin) in the gastric glands. Hormonal control is via gastrin (stimulates) and secretin (inhibits). Nervous control is via the release of acetylcholine (stimulates) from parasympathetic nerve endings.

10. Ans A, B, C. A low gastric pH acts as a negative feedback loop to inhibit the release of gastrin. If the stomach becomes alkaline, the acid suppression of gastrin release is eliminated and the result is high circulating gastrin. The local release of histamine, which stimulates the parietal cells, is also suppressed by stomach acid. The protease pepsin has an acid pH optimum and thus can only function in the stomach. When chyme enters the duodenum, pepsin is no longer active.

11. **Ans** B. Secretin as a stimulant for bicarbonate secretion is mainly via the pancreas, but it does have a slight effect in increasing the bicarbonate level of bile.

12. **Ans** C. Contraction of the gall bladder is caused by cholecystokinin.

13. **Ans** A. A major target tissue for gastrin is the stomach where it stimulates both secretion and motility. Secretin inhibits stomach secretion and motility.

14. **Ans** C. The peptide hormone that stimulate the secretion of pancreatic enzymes is cholecystokinin.

15. **Ans** C. Mucin is produced throughout the GI tract, and one function is as a lubricant.

16. **Ans** A. Stomach acid acts a negative feedback loop on the release of gastrin. Lack of stomach acid production produces high circulating gastrin.

17. **Ans** D. Gastrin and cholecystokinin are both peptides with similar structures.

18 **Ans** B, D. Carbonic anhydrase is required for the conversion of CO_2 into H^+ and HCO_3~, thus this enzyme will be present in the parietal cells in the stomach and the pancreatic cells.

Digestion and Absorption

1. **Ans** C. Both glucose and amino acids are absorbed from the small intestine via secondary active transport linked to sodium. An increase in intraluminal sodium will accelerate the uptake of glucose and amino acids. The reverse is also true, low intraluminal sodium would slow the absorption of glucose and amino acids.

2. **Ans** B. This question is a little tricky in this format. A major mechanism in the final absorption of amino acids involves simple diffusion across the basal membrane. The main mechanism of glucose absorption here is facilitative diffusion but a small amount of simple diffusion does occur; it is not usually considered significant.

3. AnsD. A major point was that the chylomicrons containing the end products of lipid absorption are absorbed into the lymphatic and not the general circulation. The products of carbohydrate and protein digestion are absorbed directly into the systemic capillaries.

4. AnsA. There are not separate carriers for glucose and galactose. They must compete for the same carrier. Adding galactose will slow the transport of glucose and vice versa.

5. **Ans** C. Both glucose and amino acids are absorbed across the luminal membrane via secondary active transport linked to sodium.

6. **Ans** D. Bile salts are important for the digestion and the absorption of lipid-soluble substances, not the water-soluble products of carbohydrate and protein digestion.

7. **Ans** E. Digestion in the small intestine takes place at a pH which is close to neutral. Protein is also digested in the acid medium of the stomach.

8. **Ans** C. The end products of carbohydrate and protein digestion are absorbed across the luminal membrane via secondary active transport. CHO absorption also involves facilitative transport.

9. **Ans** C. The digestion of CHO starts in the mouth by salivary oc-amylase. Protein digestion begins in the stomach by pepsin secreted from gastric glands.

10. **Ans** D. Vitamin B_{12} attached to intrinsic factor is absorbed in the distal ileum. A nonfunctional distal ileum will lead to a vitamin B_{17} deficiency and anemia.

11. **AnsA,** C. These would include lipid-soluble but not water-soluble compounds. Cholesterol and vitamin K are lipid-soluble compounds. Short-chain fatty acids are fairly water soluble and can diffuse directly into the systemic circulation. Long-chain fatty acids, on the other hand, being lipid soluble, must enter as part of the chylomicrons via the lymphatics. Glycerol is a water-soluble compound.

12. **Ans** A, B, C. Cholecystokinin has 2 important roles in the absorption of fat. It causes contraction of the gall bladder and relaxation of the sphincter of Oddi permitting bile to enter the duodenum. It is also responsible for the secretion of pancreatic enzymes which would include pancreatic Upases. Cholecystokinin and secretin potentiate each other's effect on the pancreas (synergistic action). Cholecystokinin has a small effect on stomach motility, but it is debatable whether this is significant.

13. **Ans** A, B, C, D. The enterogastric reflex which slows activity in the stomach will be initiated by anything that increases activity in the small intestine. The general statement is that anything that tends to overload the small intestine will act to slow the stomach. Everything listed will increase the load on the small intestine; therefore, all will contribute to the enterogastric reflex.

14. **Ans** B. Amino acids are generally initially absorbed across the luminal membrane via secondary active transport linked to sodium and across the serosal membrane by simple diffusion, although other processes are probably involved as well.

15. **Ans** A. A major action of vitamin D is the absorption of calcium and phosphate from the small intestine. The small intestine is not a target tissue for parathyroid hormone. In hypocalcemia there can be increased absorption of calcium from the small intestine, but this will occur only if the activity of vitamin D increases.

16. **Ans** D. Absorbed long-chain fatty acids are resynthesized to triglycerides which then form a major part of the chylomicron.

17. **Ans** D. Since glucose and galactose compete for the same carrier, the presence of galactose will decrease the absorption rate of glucose. Fructose is absorbed by a mechanism completely independent from glucose and galactose.

18. Ans D. Most lipases are secreted by the pancreas as active enzymes. The major end products are 2-monoglycerides and free fatty acids. However, some triglycerides are completely digested to fatty acids and glycerol. Enterokinase is responsible for the activation of trypsinogen to trypsin. All of this takes place in the fairly neutral pH of the small intestine.

19. **Ans** A. Throughout the small intestine there is a net reabsorption of potassium. However, in the colon there is net secretion, and because of this, diarrhea can lead to hypokalemia.

20. **Ans** C. Sucrase is one of the required small intestinal brush border enzymes.

21. **Ans** A, C. Correct answers here would include any lipid substances. Vitamin B_{12} is absorbed via intrinsic factor, and short-chain fatty acids are water soluble.

22. Ans A, C. To be more specific, if the distal ileum is removed, intrinsic factor with attached vitamin B_{12} cannot be absorbed and bile salts cannot be reabsorbed and recycled. Since the liver has a limited capacity to synthesize replacements, there will usually be a bile salt deficiency. This will disrupt the digestion and absorption of most lipid substances and increase the fat content of the stool.

23. Ans A, C. The correct answers would include any fat-soluble substances.

24. Ans C. The absorption of water and most electrolytes from the intestine is driven by the active reabsorption of sodium.

25. Ans B, D. The colon actively absorbs sodium and chloride and passively absorbs water. No cell actively absorbs water. The colon also demonstrates a net secretion of potassium and bicarbonate. This is important because with diarrhea, the loss of potassium can cause hypokalemia and the loss of bicarbonate can cause a metabolic acidosis. Mass movements are propulsive movements.