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ABC PHYSIOLOGY

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By

Dr. M. Awais Hassan Awaan

Editor

Prof. Zahid Bulandshahri

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An Easy Approach TO Physiology

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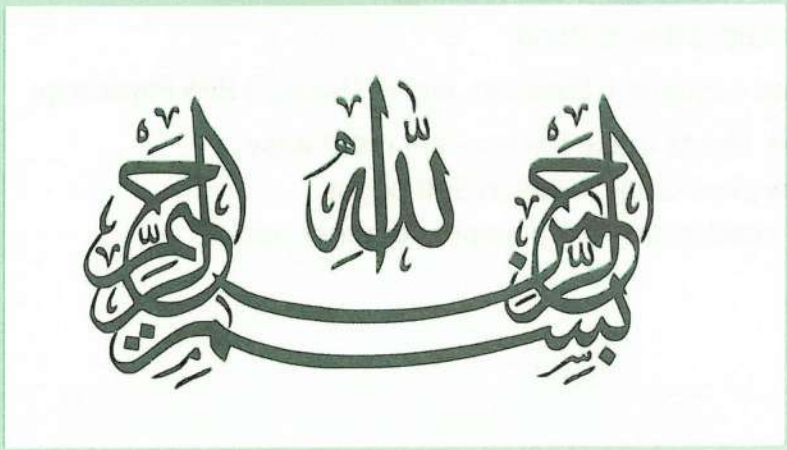
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MEDICAL PHYSIOLOGY

Features

- According to syllabus
- To the point
- Time saving
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- Contain tables
- Clear Headings & subheadings
- Concept base material
- Based on guyton, L.Sherwood, Jaypee, Ganong & BRS Physicology
- Flow charts make the concept more easy
- Now physiology is just in 300 pages
- No need of any extra helping or other book

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Preface

Aslam-u-Alikum !

I am feeling proud and honor to present this book "Physiology by AVI Series". This book will prove to be a helpful key for medical students. I am thankful to Allah Almighty who make me able to write this book. I would like to thank all colleagues whose contributions and advice have been a great help and who were so generous with illustration material. I am also thankful to all the students who are appreciating my recent work and their appreciation intend me to write further books. I am also thankful to my publisher, Al- Khair Publishers (ABC)

This book has several features that are designed to help students link personal experience to Physiology concepts and that illustrate the application of physiology principles, There are also features that make it easy for students to follow the material and study for examinations This book makes the vast and complex field of Medical Physiology more accessible by the use of graphics and numerous illustrations with detailed explanatory legends. The many tables present knowledge in a cogent and useful form. Most chapters begin with a concise summary, and in-depth and supplementary knowledge are provided in boxes separating them from the main body of text. This book is a concise review of the medically important aspects of physiology. It covers both the basic and clinical aspects of the function of human body. It also discusses important infectious diseases using an organ system approach. Its two major aims are (1) to assist those who are preparing for the USMLE (National Boards) and (2) to provide students who are currently taking medical physiology courses with a brief and up-to-date source of information. The goal is to provide the reader with an accurate source of clinically relevant information at a level appropriate for those beginning their medical education.

As it is well said that "Nothing is perfect in this world so far that pencils have eraser." Constructive critics, comments, objections and suggestion from users and students will be highly appreciated. Thanks

Malik Muhammad Awais Hassan Awaan

Dedication

Dedicated with love to my Grand parents

Mr. & Mrs. Gulaab Deen

To my parents

Mr. & Mrs. Inayat Ali

And also to

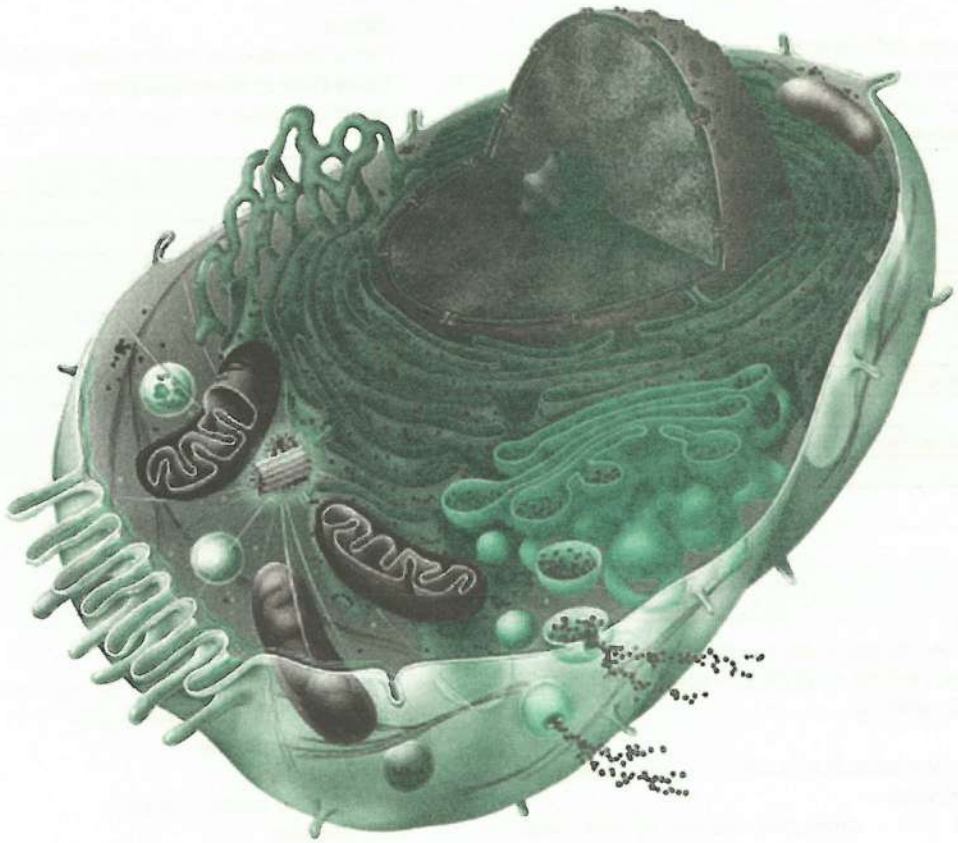
Mr. & Mrs. Bilal Azeem

Contents in Detail

Chapter # 1

Cell Physiology

Contents



INTRODUCTION

Physiology

The goal of physiology is to understand the function of living organisms and their parts. Study of function in living matter is called physiology.

Human Physiology

Study of specific characteristics and mechanisms of human body that make it a living being, is called human physiology. A distinguishing feature of physiology is that it seeks to integrate the functions of all of the parts of the body to understand the function of the entire human body.

Internal Environment/Milieu Interieur

ECF maintains same ionic and nutrient environment for all cells of body; so, ECF is also called internal environment.

Homeostasis

Homo = Same Stasis = Balance

The term *homeostasis* is used by physiologists to mean *maintenance of nearly constant conditions in the internal environment.* Maintenance of static or constant conditions in internal environment is called homeostasis.

BioFeedback

It can also be simply defined as *the process of furnishing an individual information of his body function, so as to get some control over it.*

Types

- **Negative Feedback**
  When final result is opposite to initial stimulus; it is called negative feedback.
- **Positive Feedback**
  When final result is more of initial stimulus; it is called positive feedback.

Vicious Circle

Positive feedback is also called vicious circle; because it is defective and fails to save life, and once started it leads to death.

Fluid

Intracellular Fluid (ICF)

Intra = internal

Fluid inside cell is called intracellular fluid.

Extracellular fluid (ECF)

Extra = Outside

Fluid outside cell is called extracellular fluid.

Divisions of ECF

(1) **Plasma**
Part of Extracellular Fluid present in blood.

(2) **Tissue Fluid or Interstitial Fluid**
Part of ECF present is spaces b/w cells.

Important Constituents and Physical Characteristics of Extracellular Fluid

	Normal value	Normal Range	Approximate Short-Term Nonlethal Limit	Unit
Oxygen	40	35-45	10-1000	mm Hg
Carbondioxide	40	35-45	5-80	mm Hg
Sodium ion	142	138-146	115-175	Mmol/L
Potassium ion	4.2	3.8-5.0	1.5-9.0	Mmol/L
Calcium ion	1.2	1.0-1.4	0.5-2.0	Mmol/L
Chloride ion	108	103-112	70-130	Mmol/L
Bicarbonate ion	28	24-32	8-45	Mmol/L
Glucose	85	75-95	20-1500	Mg/dL
Body temperature	98.4 (37.0)	98-98.8 (37.0)	65-110 (18.3-43.3)	°F (°C)
Acid-base	7.4	7.3-7.5	6.9-8.0	pH

Courtesy by Guyton & Halls physiology table 1-1

CELL

Smallest unit of life, Structural and functional unit of living matter, capable of carrying on all life processes independently, is called cell

Protoplasm

Different substances that make up cell are collectively called protoplasm.

Composition of cell : Composed mainly of five basic substances:

(1) Water
(2) Electrolytes
(3) Carbohydrates
(4) Proteins
(5) Lipids.

Organization of Cell

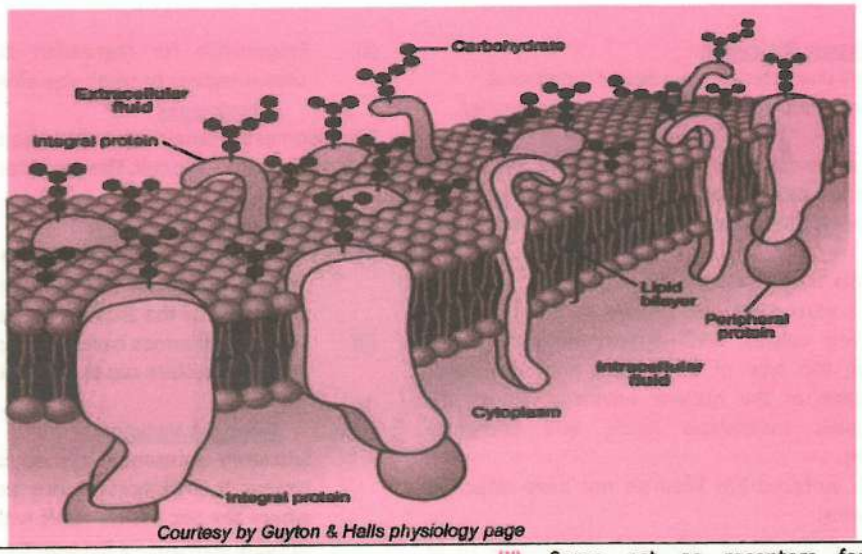
A typical cell is made up of four basic structures, which from outside to inside are:

(A) Cell membrane
(B) Cytoplasm
(C) Nuclear membrane and
(D) Nucleus.

(A) Cell Membrane

Outer covering of cell that isolates individual cell from its neighbours is called cell membrane. orroosstior

(1) Lipid Bilayer
(2) Proteins and
(3) Carbohydrates



Courtesy by Guyton & Halls physiology page

(1) Lipid Bilayer

Basic structure of cell membrane is a lipid bilayer (two molecules thick) composed of phospholipids and cholesterols. Their hydrophobic (fat-soluble) portion is directed towards center of lipid bilayer; while hydrophilic (water-soluble) portion is directed towards inner and outer surfaces of lipid bilayer.

Functions

Prevents free movements of water and water-soluble substances from one cell compartment to another.

(2) Proteins Of Cell Membrane

They are mostly glyco-proteins scattered in lipid bilayer.

Types

Two

(i) Integral Proteins

Penetrate all the way thru lipid bilayer.

Functions

(a) Provide channels or pores for passage of water-soluble substances, e.g. ions.

(b) Some act as carrier proteins that bind with specific substances and transport them through cell membrane.

(c) Enzymes: - catalyze reaction at the surface of membrane.

(d) Receptors:- Bind to neurotransmitter of hormones

(ii) Peripheral Proteins

Do not penetrate lipid bilayer; but are attached only to one surface of the membrane or to one of the end of integral proteins.

Function

Act as enzymes.

(3) Carbohydrates of Cell Membrane

They occur in combination with proteins and lipids forming glyco-proteins and glyco-lipids.

Function

(i) Some are negatively charged, so negative cell membrane repel other negative objects.

(ii) Some act as receptors for binding with hormones like insulin.

(iii) Glycocalyx attaches one cell to the adjacent cells.

(iv) Take part in immune reactions.

Glycocalyx

Entire outer surface of cell membrane has a carbohydrate coat called glyco-calyx.

(B) Cytoplasm

It is that portion of protoplasm which surrounds nucleus and is peripherally bounded by cell membrane.

Zones of Cytoplasm

Two,

(1) Ectoplasm or Cortex: Semi-solid. Immediately beneath cell membrane. Contains micro-tubules.

(2) Endoplasm: Liquified b/w ectoplasm and nuclear membrane.

Composition of Cytoplasm

(1) Cytosol

Clear fluid portion of cytoplasm in which inclusions or particles and organelles are dispersed.

(2) Inclusions or Particles

These are lifeless accumulations of metabolites.

(a) Stored food

(b) Secretion granules

(c) Pigments.

(3) Organ

These are intracellular minute organs or metabolic machineries.

Examples

(i) Endoplasmic reticulum

(ii) Golgi apparatus

(iii) Lysosomes

(iv) Peroxisomes

(v) Secretory Vesicles

(vi) Ribosomes

(vii) Microfilaments and microtubules &

(viii) Mitochondria.

i. Endoplasmic Reticulum

Eukaryotic cells are characterized by several membrane complexes that are interconnected by separate organelles.

Function

These organelles are involved in protein synthesis, transport, modification, storage and secretion. These membranes and the aqueous channels they enclose are called cisternae.

Types:

There are two kinds of endoplasmic reticulum (ER):

(i) **Rough surfaced ER,** also known as ergastoplasm. They are coated with Ribosomes. Near the nucleus, this type of ER merges with the outer membrane of the nuclear envelope. Rough ER synthesizes membrane lipids, and secretory proteins.

(ii) **Smooth surfaced ER:** They do not have attached ribosomes.
Smooth endoplasmic reticulum is involved: (i) In lipid synthesis and (ii) Modification and transport of proteins synthesized in the rough ER

ii. Golgi complexes (or Golgi apparatus)

They are also called Dictyosomes. Each eukaryotic cell contains a unique stack of smooth surfaced compartments or cisternae that make up the Golgi complex. The ER is usually closely associated with the Golgi complexes, which contain flattened, fluid filled golgi sacs.

Functions

(i) On the proximal or cis side, the Golgi complexes receive the newly **synthesized proteins** by ER via transfer vesicles.

(ii) The post-translational **modifications** take place in the golgi lumen (median part) where the carbohydrates and lipid precursors are added to proteins to form glycoprotein and lipoproteins respectively.

They **secrete** vesicles that move to and fuse with the plasma membrane where the contents may be expelled by a process called exocytosis..

Peroxisomes may be absent in inherited disorder Zellweger's syndrome

iii. Lysosomes

Lysosomes are cell organelles found in cells which contain packet of enzymes. They are surrounded by a lipoprotein membrane. Lysosomes are found in all animal cells, **except erythrocytes**, in varying numbers and types. pH inside the Lysosomes is lower than that of cytosol. The lysosomal enzymes have an optimal pH around

Function: Provide an intracellular digestive system.

(a) Contain nucleases for degrading DNA & RNA
(b) Contain lipases for degrading lipids.
(c) Contain glycosidases for degrading glycoprorein, proteoglycans & glycolipids.
(d) Contain proteases & peptidases for degrading proteins.
(e) Contain bactericidal agents, eg lysozyme and lysoferrin.
(f) Responsible for regression of various tissues, eg uterus regress to small size after childbirth.

iv. Peroxisomes

Peroxisomes are small organelles also called Microbodies, present in eukaryotic cell. The particles are approximately **0.5** μ in diameter.

Functions

(i) They carryout oxidation reactions in which toxic hydrogen peroxide (H_2O_2) is produced, which is destroyed by the enzyme catalase.

(ii) Liver peroxisomes have an unusually active β-oxidative system capable of oxidizing long chain fatty acids

v. Secretory Vesicles

Secretory substance formed by ER-Golgi apparatus system **is** Transported into secretory vesicles **from where the** Sec vesicle fuses with cell membrane upon suitable stimulus → Release its contents.

vi. Ribosomes

These are organelles containing rRNA & protein.

They consist of large (60S) & small (40S) subunits.

Ribosomes often form polysomes which consist of single messenger RNA (mRNA).

Form of Ribosomes

Free polysomes - are the site of synthesis for proteins destined for the nucleus, peroxisomes or mitochondria.

Membrane bounded polysomes are the site of synthesis of secretary proreins, membrane protein & lysosomal enzymes

vii. Mitochondrion:

Mitochondrion is the power house of cell.

- Number: The number of mitochondria in a cell varies dramatically. Some algae contain only one mitochondrion, whereas the protozoan Chaos contain half a million
- Size: They vary greatly in size.
- Shape: The shape of mitochondrion is not static.

Structure and Functions

The mitochondrion is bounded by two concentric membranes that have markedly different properties and biological functions.

Mitochondrial Membranes

(a) Outer mitochondrial membrane:

(b) Inner mitochondrial membrane:

- Cristae: The inner mitochondrial membrane is highly folded. The tightly packed inward folds are called "cristae".

(c) Intermembrane space:

The space between the outer and inner membranes is known as the intermembrane space.

(d) Mitochondrial matrix:

The region enclosed by the inner membrane is known as the mitochondrial matrix. It is specialized for the rapid oxidation of NADH and FAD.

(C) Nuclear Membrane

Nuclear envelope: A double membrane structure called the nuclear envelope separates the nucleus from the cytosol. It is covering of nucleus that separates it from cytoplasm

Composition

It is composed of two membranes, inner and outer. Outer membrane is continuous with endoplasmic reticulum. It has many nuclear pores.

Nuclear pore complexes:

These are embedded in the nuclear envelope. These complex structures control the movement of proteins and the nucleic acid ribonucleic acids (RNAs) across the nuclear envelope

Functions

(1) Prevents free mixing of cytoplasm with nucleoplasm.

(2) Nuclear pores allow protein molecules to pass.

(D) Nucleus

The nucleus contains more than 95 per cent of the cell's DNA and is the control centre of the eukaryotic cell.

- **Chromatin**: DNA in the nucleus is coiled into a dense mass called chromatin, so named because it is stained darkly with certain dyes.
- **Nucleolus**: A second dense mass closely associated with the inner nuclear envelope is called nucleolus.
- **Nucleoplasm**: Nucleoplasm of nucleus contain various enzymes such as DNA polymerases, and RNA polymerases, for m-RNA and t-RNA synthesis.

Number of chromosomes in Human

23 pairs (46) chromosomes.

Types

Two

(i) ***Somatic Chromosomes or Autosomes***

22 Pairs

(ii) ***Sex Chromosomes***

1 pair.

(a) ***Male*** XY

(b) ***Female*** XX

Functions

(i) Determine specific characteristics of cell.

(ii) Thru them hereditary qualities pass from one generation to next.

(iii) Responsible for mRNA formation which control protein synthesis.

Functions of nucleus

- DNA replication and RNA transcription of DNA occur in the nucleus.
- Nucleolus is the site of synthesis of ribosomal RNA (r-RNA).
- Nucleolus is also the major site where ribosome subunits are assembled.

Functions of Cell

(1) Ingestion

Occurs in four ways

(i) Diffusion

(ii) Facilitated diffusion

(iii) Active transport

(iv) Endocytosis

Endocytosis

It is a process in which substances are engulfed by forming vesicles at cell membrane.

Types

Two

1. **Pinocytosis**

It is formation of extremely minute vesicles to engulf protein molecules and ECF.

2. **Phagocytosis**

It is formation of large vesicles to ingest large particles, eg bacteria.

(2) Digestion

Brought about by lysosomes contain Hydrolysed enzymes

(3) Synthesis

(i) Granular ER synthesize proteins

(ii) Smooth ER synthesize lipids

(iii) Golgi apparatus synthesize galactose and sialic acid

(iv) Golgi apparatus also synthesize hyaluronic acid and chondroitin sulfate.

(4) Extraction of Energy

Brought about by mitochondria.

ATP

It is a high energy phosphate compound. (Adenosine Triphosphate).

Composition

Adenosine + Ribose + 3 phosphates.

Functions

Provides energy that helps in:

(1) Membrane transport

(2) Synthesis of chemical compounds

(3) Mechanical work

ATPase

It is an enzyme that cleaves ATP to ADP or AMP, thus releasing energy.

(5) Movement

(i) Ameboid Locomotion; exhibited by WBC and fibroblasts.

(ii) Ciliary movement; exhibited by cilia of ciliated epithelium. Flagellum of sperm is similar to cilium.

Nucleotides of DNA

(1) Deoxy-adenylic acid

(2) Deoxy-guanylic acid

(3) Deoxy-cytidylic acid

(4) Deoxy-thymidylic acid

Nucleotides Of RNA

(1) Adenylic acid

(2) Guanylic acid

(3) Cytidylic acid

(4) Uridylic acid Nucleic Acid

Courtesy by Guyton & Halls Physiology

GENETICS

Gene

It is a segment of long DNA molecule, that codes for a single protein (i.e., 1 gene → 1 protein).

Quantity

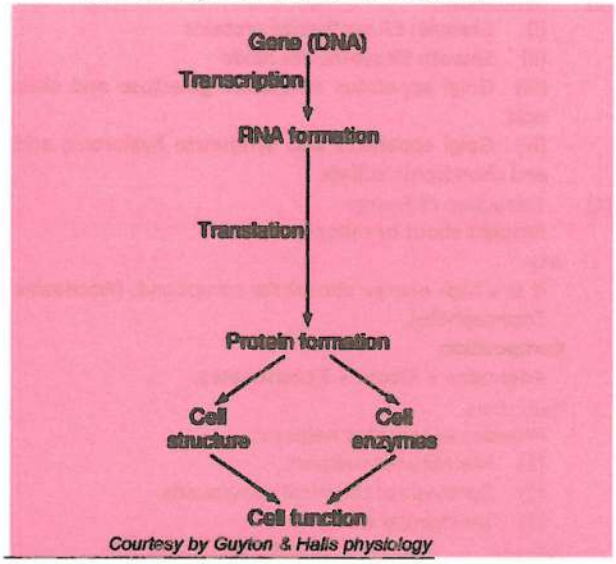
There are 30,000 essential genes which cause formation of 30,000 types of essential proteins. Functions: Genes (DNA molecules) control formation of mRNA which control formation of proteins.

Gene Regions

Exon : It is the coding region (expression sequences) of the gene (3% of human genome).

Introns: It is the non - coding region (intervening sequences) of the gene. (97% of human genome).

EXon are EXpressed, INtrons are INactive.



Courtesy by Guyton & Halls physiology

Nitrogenous Bases

These are bases which take part in formation of nucleic acids (DNA and RNA).

Types

Two,

(1) Purines

Have a 6-membered ring and a 5 membered ring. Include Adenine and guanine.

(2) Pyrimidines

Have only a 6-membered ring.

Include

Cytosine, uracil and thymine.

Nucleoside

Combination of a nitrogenous base with pentose sugar (deoxy-ribose or ribose) is called nucleoside.

Nucleotide

Combination of a nucleoside (nitrogenous base + pentose sugar) with phosphoric acid, is called nucleotide.

Nucleic Acids

Combination of many nucleotides (poly-nucleotide) is called nucleic acid.

Types

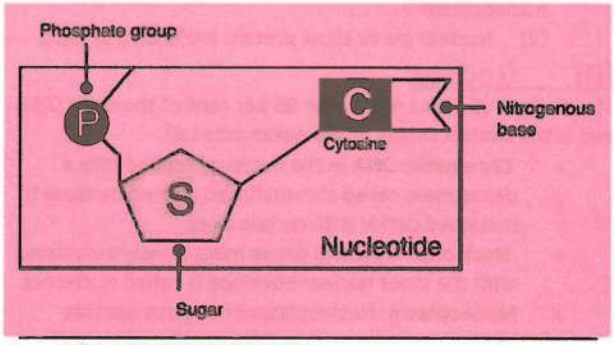
Two,

(1) DNA

Deoxy-ribo nucleic acid. Pentose sugar is deoxyribose.

(2) RNA

Ribo nucleic acid. Pentose sugar is ribose.



Deoxy-Ribo Nucleic Acid (DNA)

DNA is a poly-nucleotide formed by combination of four types of nucleotides in which pentose sugar is deoxy-ribose.

Structure

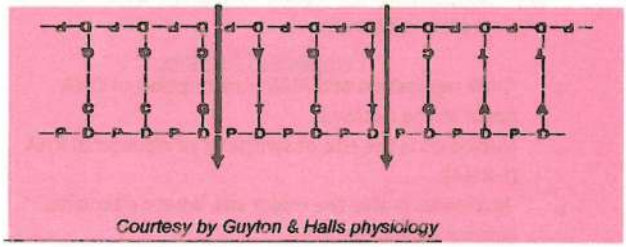
(1) Nucleotides are joined together to form strands of DNA molecule

(2) In DNA molecule, two such strands are held by loose bonds b/w nitrogenous bases

(3) While paralleling two strands, adenine binds with thymine (AT) & guanine with cytosine(GC). Two bond present between A = T while three bonds between G & C, unite by H-Bond.

(4) Two strands are coiled into a helix.

(5) DNA & a core of histone protein form nucleosome. A series of nucleosomes is sometimes called " beads on a string" [Nucleosome = DNA + Protein(Histone)]


Courtesy by Guyton & Halls physiology

Genetic Code

Three successive bases in DNA molecule are called a genetic code.

Function

Controls sequence of amino acids in protein molecule.

Ribo Nucleic Acid (RNA)

RNA is poly-nucleotide formed by combination of four types of nucleotides in which pentose sugar is ribose.

Function

Acts as intermediate compound thru which DNA (genes) of nucleus control chemical reactions of cytoplasm.

Types

Three,

1. ***Messenger RNA* (mRNA),**

which carries the genetic code to the cytoplasm for controlling the type of protein formed.

2. ***Transfer RNA* (tRNA),**

which transports activated amino acids to the ribosomes to be used in assembling the protein molecule.

3. ***Ribosomal RNA*,**

which, along with about 75 different proteins, forms *ribosomes*, the physical and chemical structures on which protein molecules are actually assembled

***MicroRNA* (miRNA),**

which are single-stranded RNA molecules of 21 to 23 nucleotides that can regulate gene transcription and translation.

Function

Forms ribosome upon which amino acids are assembled into protein molecule.

Codon

(1) Sequence of three successive nucleotides (triplet) in mRNA corresponding to genetic code of DNA is called a codon.
(2) There are 64 codons.
(3) 61 codons code for amino acids.
(4) The remaining 3 codons are stop codons (UAA, UGA, UAG).
(5) There is one start codon (initiation codon), AUG, coding for methionine. Protein synthesis begins with methionine (Met) in eukaryotes and with formylmethionine (fmet) in prokaryotes.

Anticodon

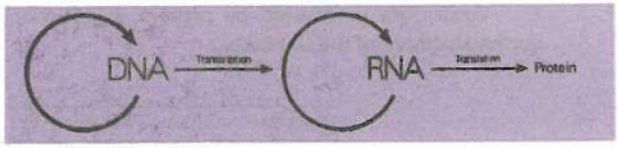
Sequence of three successive nucleotides in tRNA corresponding to codon, is called an anticodon.

Formation of Protein

Two steps,

(1) Transcription

Formation of mRNA from DNA is called transcription. During transcription genetic code of DNA (ie genetic information) is transferred to mRNA in form of codon, which will determine sequence of amino acids in protein molecule. It occurs in nucleus.



(2) Translation

Formation of protein molecule (with specific amino acid sequence) in ribosome with help of mRNA and tRNA is called translation. It occurs in cytoplasm.

Steps of Cell Reproduction

(1) DNA replication
(2) DNA proof-reading
(3) Chromosome replication
(4) Mitosis

Cell Cycle

Phases of Cell Cycle

(A) Gap Phase 0 (G_0) is the resting phase of the cell. During this phase, the cell cycle is suspended.

(B) **Gap phase 1 (G_1)**

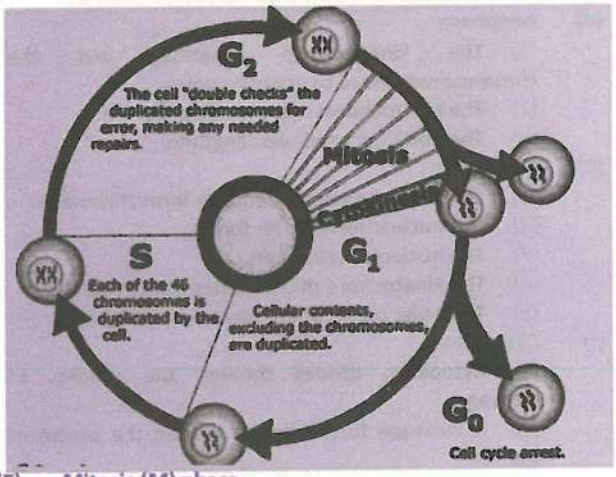
(1) G1 is the time between mitosis (M phase) and the synthesis of deoxyribonucleic acid (DNA) [S phase].
(2) RNA, protein, lipid & carbohydrate synthesis occurs.
(3) Duration is 5 hours in a typical mammalian cell with a 16 - hour cell cycle.

(C) **Synthesis (S) phase**

(1) DNA & chromosomal protein (e.g histones) synthesis occurs.
(2) Duration is 7 hours in a typical mammalian cell with a 16 - hour cell cycle.

(D) **Gap phase 2 (G_2),**

(1) G2 is the interval between DNA synthesis (S phase) & mitosis (M phase).
(2) Adenosine triphosphate (ATP) synthesis occurs.
(3) Duration is 3 hours in a typical mammalian cell with a 16 - hour cell cycle.



(E) **Mitosis (M) phase**

- Cell division occurs during this phase.
- In this one cell splits into two new cells.
- Occurs after replication of DNA & chromosome.
- The daughter cell contain same no. & type of chromosomes as in parent cell.

It has 6 stages:

(a) Prophase.
(b) Prometaphase.
(c) Metaphase.

(d) Anaphase.
(e) Telophase.
(f) Cytokinesis

- Duration is 1 hour in a typical mammalian cell with a 16 - hour cell cycle.

Stage of M phase

(a) Prophase

(1) Chromatin condenses to form well - defined chromosomes.
(2) The thickest phase of mitosis
(3) A centromere complex that acts as the microtubule organizing centre splits into two halves. The halves move to opposite poles of the cells.
(4) The mitotic spindle, which contain microtubules, forms between the centrosomes.

(b) Prometaphase

(1) The nuclear envelop is disrupted, giving the microtubules access to the chromosomes.
(2) The nucleolus disappears.
(3) Kinetochores (protein complexes) assemble at each centromere on the chromosomes.
(4) Certain microtubules of the mitotic spindle bind to the kinetochores (kinetochore microtubules).
(5) Other microtubules of the mitotic spindle are polar microtubules and astral microtubules.

(c) Metaphase

(1) Chromosomes allign at the metaphase plate.
(2) Cells can be arrested by microtubule inhibitors.
(3) Cells can be isolated for karyotype analysis.

(d) Anaphase

(1) The kinetochores separate, and the chromosomes move to opposite poles.
(2) The kinetochores microtubules shorten.
(3) The polar microtubules lengthen.

(e) Telophase

(1) Chromosomes decondense to form chromatin.
(2) The nuclear envelop re- forms.
(3) The nucleolus reappears.
(4) The kinetochore microtubules disappears.
(5) The polar microtubule continue to lengthen.

(f) Cytokinesis

(1) Cytoplasm divides through the process of cleavage.
(2) A cleavage furrow forms around the centre of the cell.
(3) A contractile ring forms at the cleavage furrow. The ring is composed of actin and myosin filament.

Mitotic Apparatus

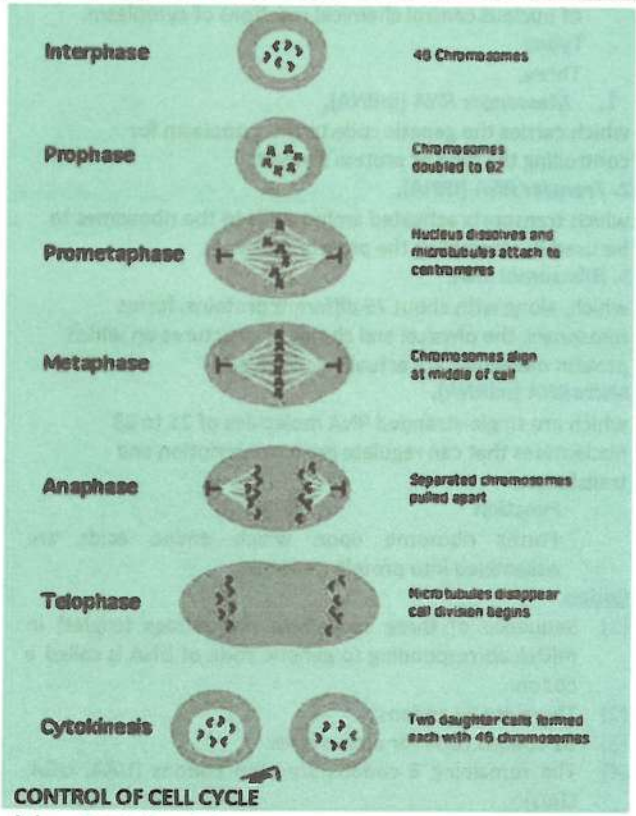
Consists of two centrioles at opposite poles of nucleus & microtubes connecting them.

Function

Causes movement of chromosomes to opposite poles during mitosis.

Interphase

Period from end of one mitosis to onset of next, is called interphase.



CONTROL OF CELL CYCLE

(A) Control proteins

The two main protein families that control the cell cycle are cyclin - dependent protein kinases (Cdks) & cyclin. These proteins forms Cdk - cyclin complexes.

(B) Cdk - cyclin complexes

The ability of Cdk to phosphorylate target proteins is dependent on the cyclin that forms a complex with it .

(C) Check points

Are points in the cell cycle where cdk - protein complexes mediates control.

(1) G_1 checkpoint

- Occurs at the $G_1 \rightarrow S$ phase transition.

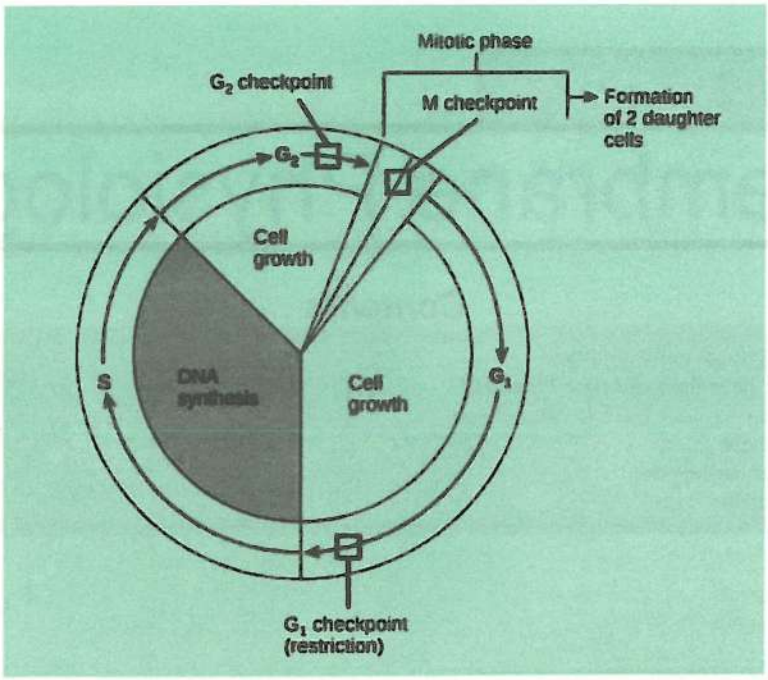
(2) G_2 check point

- Occurs at the $G_2 \rightarrow M$ phase transition.

(D) Inactivation of Cl/dins

- Cyclins are inactivated by protein degradation during anaphase of the M phase.

Courtesy by Guyton & Halls Physiology



Mutation

A mistake in transcription process during DNA replication, causing appearance of inappropriate nucleotides in DNA molecule, is called mutation.

Cancer

Uncontrolled mitosis resulting in excess cell growth (tumor) due to mutated genes (or oncogenes) is called cancer. Cancer is caused in all or almost all instances by *mutation* or by some other *abnormal activation* of cellular genes that control cell growth and cell mitosis.

Basic Cause

Cancer occurs because mutated cells lose normal feedback control for preventing excess growth cause the abnormal cell growth.

Factors Responsible

(1) Ionizing radiations, eg X-rays, gamma rays, etc.
(2) Chemical substances (carcinogens), eg aniline dye derivatives & cigarette
(3) Physical irritants
(4) Viruses
(5) Genetic (parental)

Properties Of Cancer Cells

(1) They need no growth factor, so they have no growth limits.
(2) They are not attached to each other,
(3) They compete with normal tissues for nutrition; so, as cancer cells grow, normal cells suffer nutritional death.
(4) They are large in size

Cell Death

Types

There are two types

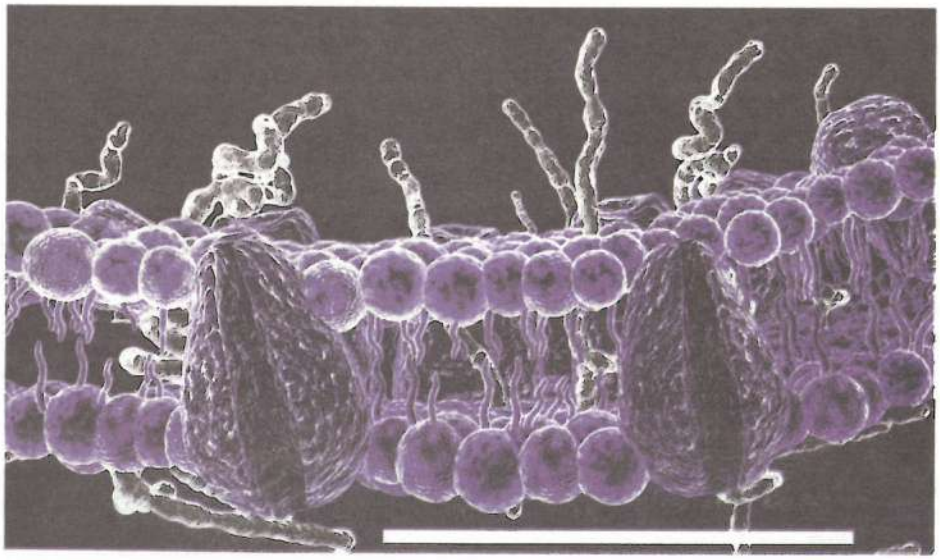
Contrasting Features of Apoptosis and Necrosis.

Feature	Apoptosis	Necrosis
1. *Definition*	Programmed and coordinated cell death	Cell death along with degradation of tissue by hydrolytic enzymes
2. *Causative agents*	Physiologic and pathologic processes	Hypoxia, toxins
3. *Morphology*	i) No inflammatory reaction ii) Death of single cells iii) Cell shrinkage iv) Cytoplasmic blebs on membrane v) Apoptotic bodies vi) Chromatin condensation vii) Phagocytosis of apoptotic bodies by macrophages	i) Inflammatory reaction always present ii) Death of many adjacent cells iii) Cell swelling initially iv) Membrane disruption v) Damaged organelles vi) Nuclear disruption vii) Phagocytosis of cell debris by macrophages

Chapter # 2

Membrane Physiology

Contents



Transport Through Cell Membrane

	Extracellular Fluid	Intracellular Fluid
Na^+	142 mEq/L	10 mEq/L
K^+	4 mEq/L	140 mEq/L
Ca^{++}	2.4 mEq/L	0.0001 mEq/L
Mg^{++}	1.2mEq/L	58 mEq/L
Cl^-	103 mEq/L	4 mEq/L
HCO_3^-	28 mEq/L	10 mEq/L
Phosphates	4 mEq/L	75 m Eq/L
SO_4^-	1 m Eq/L	2 m Eq/L
Glucose	90 mg/dl	0 to 20 mg/dL
Amino acids	30 mg/dl	200 mg/dl?
Cholesterol Phospholipids Neutral fat	0.5g/dl	2 to 95 g/dl
PO_2	35 mm Hg	40 mm Hg?
PCO_2	46 mm Hg	50 mm Hg?
PH	7.4	7.0
Proteins	2 g/dl (5 m Eq/L)	16 g/dl (40 m Eq/L

Courtesy by Guyton & Halls physiology Figure 4-1,

Structure of Cell Membrane

Cell membrane consists of :

(1) Lipid Bilayer

(2) Proteins

(i) Integral or Transport Proteins

Protrude all the way through cell membrane. Two types:

(a) *Channel Proteins*: Have pores or channels

(b) Carrier Proteins: Bind with substance **that make** conformational change **and** Transport substance across cell mem.

(ii) Peripheral Proteins

Attached to integral protein on inner side. Act as enzyme.

Transport Through Cell Membrane

By Two methods

(1) Diffusion or Passive Transport.

(a) Simple Diffusion

(b) Facilitated Diffusion

(2) Active Transport

Diffusion or Passive Transport

(Random molecular) Movement of substances down their concentration gradient either through opening in cell membrane or in combination with carrier protein, caused by simple kinetic motion of molecule is called diffusion or passive transport.

Simple Diffusion

Movement of substances through opening in cell membrane without binding with carrier protein caused by simple kinetic motion, is called simple diffusion.

Simple diffusion can occur through the cell membrane by two pathways:

(1) through the interstices of the lipid bilayer

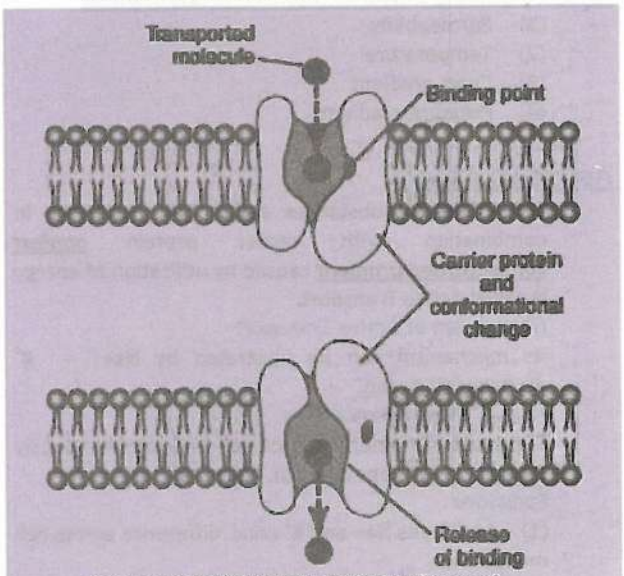
(2) through watery channels that penetrate all the way through some of the large transport proteins

Facilitated Diffusion/Carrier Mediated Diffusion

Movement of substance across cell membrane in combination with carrier protein towards conc. gradient without utilization of energy, is called facilitated diffusion.

Example

Glucose and Amino acid.



Courtesy by Guyton & Halls physiology Figure 4-6,

Diffusion Through Lipid Bilayer

1. Lipid soluble substances can easily diffuse through lipid bilayer.

Example O_2, N_2, Alcohol, CO_2

2. Water, although lipid insoluble, can diffuse through lipid bilayer by penetrating it like bullet due to its small size and high KE.

Failure of Ions to Diffuse Through Lipid Bilayer

Reason

Electrical charge on ions impede their diffusion through lipid bilayer in two ways :

(1) Water molecules attach to ions that **become** hydrated ions - big size **ultimately** cannot diffuse.

(2) Lipid bilayer is polar -ve on surface and +ve in center, so ions (+ve or -ve) are repelled **and** cannot diffuse.

Properties of Protein Channels

(1) **Selective Permeability examples**

(2) **Gates of Protein Channels examples**

(a) For Na^+ Channels → on outside of membrane

(b) For K^+ Channels → on inside of membrane

Gating of Protein Channels

"Opening or closing of protein channels is called gating". Two types :

(i) ***Voltage - Gating*** In this gates are opened or closed due to electrical potential changes across cell membrane. Examples are

a. Natgates open when inside of membrane becomes less negative or '+ve'.

b. Ktgates open when inside of membrane becomes +ve but very slowly.

(ii) **Ligand-Gating** In this, gates are opened or closed due to binding of another molecule with channel protein (binding substances. = ligand). Example Acetyl choline binds with Achchannels and opens it.

Factors Increasing Diffusion Through Protein Channel

(1) Permeability
(2) Temperature
(3) Conc. gradient
(4) Pressure gradient

Active Transport

Movement of substances across cell membrane in combination with carrier protein ***against concentration gradient*** caused by utilization of energy is called Active Transport.

Mechanism of Active Transport

Its mechanism can be illustrated by Na+ - K^+ electrogenic pump.

Na^+ - K^+ Electrogenic Pump

Transports 3 Cations out of cell and simultaneously transports 2 K^+ ions into cell.

Functions

(1) Maintains Na+ and K^+ conc. difference across cell membrane.

(2) Contributes → mV to resting membrane potential (-90 mV)

(3) Controls cell volume

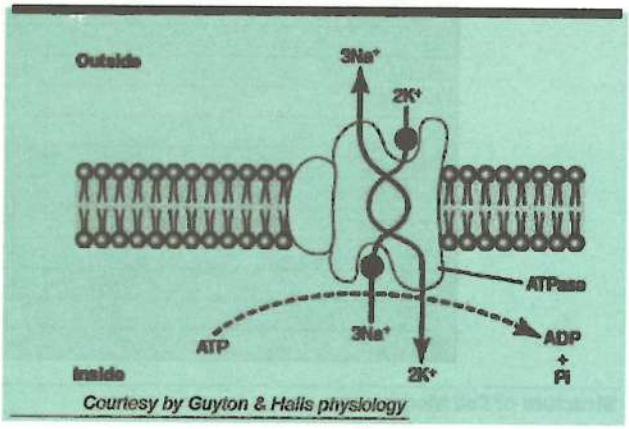
Carrier Protein of Na Cl Pump

Has two globular proteins, smaller one has unknown functions, but larger one has three functions :

When two K^+ ions bind on the outside of carrier protiens & three Na^+ ions on inside, the ATPase becomes activated, liberating energy from ATP. This energy causes a conformational change in pump, expelling three Na^+ ions to the outside & two K^+ ions to the inside of membrane.

Why Called Electrogenic?

Na^+ - K^+ pump, pumps 3 Na+ out of cell and 2 K^+ into cell. It creates negativity inside cell membrane. So it is called electrogenic pump.



Courtesy by Guyton & Halls physiology

(a) 3 receptors for Na+ ions on inside

(b) 2 receptors for K^+ ions on outside

(c) Inside portion has ATP ase activity

Calcium Pump

Two Ca^{++} pumps

(a) One in cell membrane → pumps Ca^{++} to outside.

(b) Other pumps Ca^{++} into vesicular organelles of cells. So Ca^{++} conc. in cytoplasm is 10,000 times less than E.C.F.

Hydrogen Pump

Present in:

(a) Parietal cells of gastric glands.

(b) Late distal tubule & cortical collecting ducts of kidney.

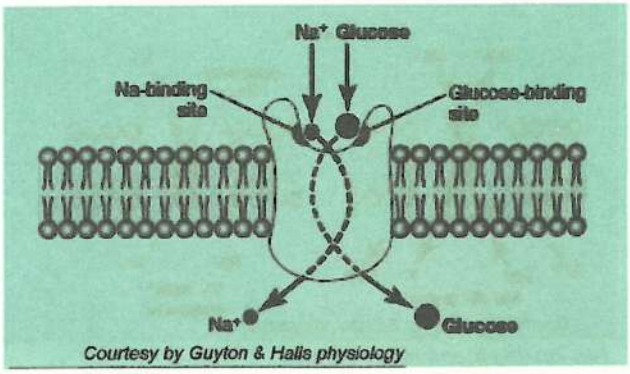
Secondary Active Transport

In secondary active transport energy is not provided by ATP, but it is provided by conc. gradient of Na^+ ions across cell membrane.

For sodium to pull another substance along with it, a coupling mechanism is required. This is achieved by means of still another carrier protein in the cell membrane.

(a) **Na-Cotransport of Glucose and Amino Acid**

Carrier protein has two sites on outside, one for Na and other for glucose or amino acid → when both bind → conc. gradient of Na cause conformational change in carrier protein → Glucose or amino acid co-transported with Na to inside.



Courtesy by Guyton & Halls physiology

Found in

Epithelium of GIT and renal tubules.

Used for

Exchange of Na^+ with K^+, Ca^{++}, H^+

Osmosis

Diffusion of water from higher water conc. to lower water conc. ie from dilute solution to concentrated solution through a semipermeable membrane, is called osmosis.

Osmotic Pressure

"Pressure required to stop osmosis completely is called osmotic pressure"

Dependence

Osmotic pressure depends upon No. of particles per unit volume of conc, solution.

Osmole

(a) No. of particles in one mole (gram mol.wt.) of undissociated solute is called one osmole.

Value 1 osmole = 6.02×10^{23} particles; eg 180 gm. of glucose (1 mole) = 6.02 x 1023 particles = 1 osmole.

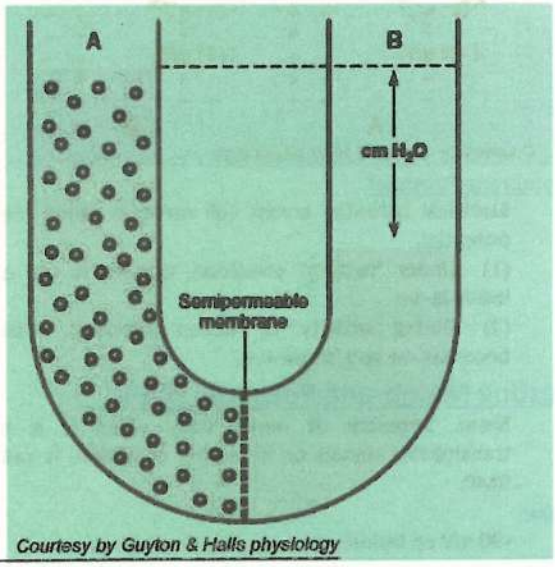
(b) If a solute dissociates into two ions, its 1 gm mol. weight will be equal to 2 osmoles; eg $Na^+ C1^-$.

Osmolality

No. of osmoles of solute per liter of water is called osmolality; eg, normal osmolality of ECF is 300 MOs/ kg.

Osmolarity

Osmoles per litter of solution



Courtesy by Guyton & Halls physiology

Bulk Flow of Water

Tremendous movement of water across cell membrane due to hydrostatic and osmotic pressure gradients is called bulk flow of water. *the red cell membrane per second to equal about 100 times the volume of the cell*

Membrane Potential

Action Potential

Channels in Cell Membrane

(1) K^+- Na^+ Leak Channels [These are channel proteins in cell membrane through which K^+ and Nat can normally leak towards conc, gradient. They are 100 times more permeable to K^+ than Na. Responsible for RMIA]

(2) Voltage-Gated Na^+-Channels [Has two gates]

Increased Permeability of Na^+-Channels when Ca^{++} Decreases Ca^{++} binds to exterior of Na-channel protein molecule - Difficult to open. So, when Ca^{++} conc. decrease, permeability of Na-channels inc.

(3) Voltage-Gated K^+-Channels Has only one activation gate on inside that ***remains closed*** at RMP (-90 mV). Slowly activated or opened when membrane potential rises from -90 mV towards zero. So, K ions outflux to cause repolarization.

(4) Slow Ca^{++} - Na^+ Channels These are present in heart muscle and smooth muscle. Slow to be activated and they allow diffusion of Ca^{++} and Na ions. Their slow but prolonged activation for causes plateau in action potentials of those muscles where they are present.

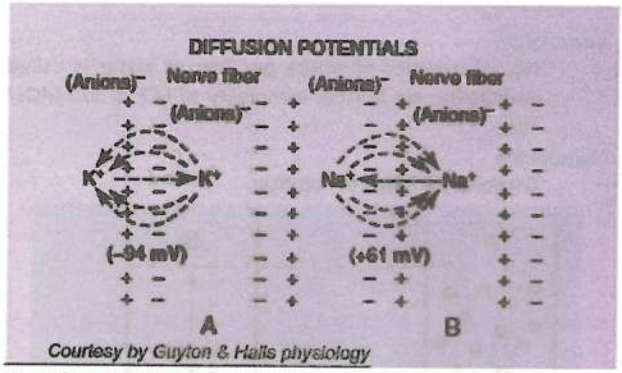
Activation Gate: On outside. Remains closed at normal resting membrane potential (-90 mV). Activated or opened when mem. potential becomes less -ve b/w -70 and -50 mV. So, Na ions influx to cause depolarization.

Inactivation Gate: On inside. Remains opened at normal RMP (-90 mV). Inactivated or closed when mem. potential becomes +35 mV. So, Nat ions influx is blocked.

Pumps in Cell Membrane

(1) Na^+- K^+ Electrogenic Pump Transports 3 Na^+ out of cell and at the same time 2 K^+ into cell, thereby creating negativity inside cell mem. Contributes → mV in RMP (-90 mV).

(2) Calcium Pump Transports Ca^{++} out of cytoplasm into ECF or into cytoplasmic organelles.



Courtesy by Guyton & Halls physiology

Membrane Potential

Electrical potential across cell mem. is called mem. potential.

(1) Under "resting" condition, outside is +ve and inside is -ve.

(2) During "activity" or "action potential", outside becomes -ve and inside +ve.

Resting Membrane Potential (RMP)

Mem. potential of nerve fiber when it is not transmitting signals or in resting condition, is called RMP.

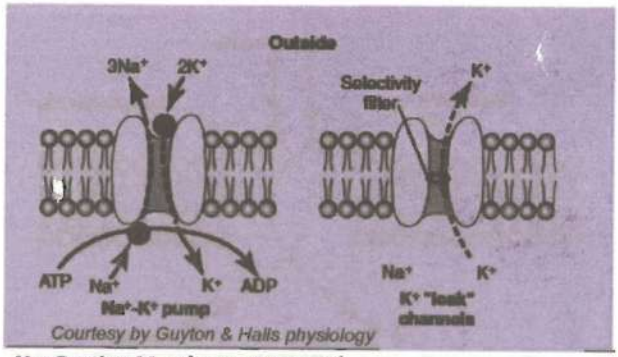
Value

-90 mV on inside.

Origin of Normal RMP -90 MV

The Resting Membrane Potential Is Established by the Diffusion Potentials, Membrane Permeability, and Electrogenic Nature of the Na - K Pump

- ***Potassium diffusion potential.*** A high ratio of potassium ions from inside to outside the cell, 35:1, produces a Nernst potential of -94 millivolts
- ***Sodium diffusion potential.*** The ratio of sodium ions from inside to outside the membrane is 0.1, which gives a calculated Nernst potential of +61 millivolts.
- ***Membrane permeability.*** The permeability of the nerve fiber membrane to potassium is about 100 times as great as that to sodium, so the diffusion of potassium contributes far more to the membrane potential. The use of this high value of permeability in the Goldman equation gives an internal membrane potential of -86 millivolts, which is near the potassium diffusion potential of -94 millivolts.
- ***Electrogenic nature of the Na^+- K^+ pump.*** The Na^+- K^+ pump transports three sodium ions to the outside of the cell for each two potassium ions pumped to the inside, which causes a continual loss of positive charges from inside the membrane. Therefore the Na^+- K^+ pump is electrogenic because it produces a net deficit of positive ions inside the cell; this causes a negative charge of about _4 millivolts inside the cell membrane.



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Net Resting Membrane Potential

(1) K^+ diffusion potential = -94 mV

(2) Na^+ diffusion potential = +8 mV

(3) Contribution by Na^+- K^+ electrogenic Pump = -4 mV.

(4) Net resting mem. potential = -90 mV.

Cause of Negativity Inside

Proteins, organic phosphate compounds and sulfates cannot diffuse out of cell. So, they cause negativity inside cell membrane when positive ions are removed from interior of cell.

Nernst Potential

The Nernst Equation Describes the Relation of Diffusion Potential to Concentration Difference. The membrane potential that prevents net diffusion of an ion in either direction through the membrane is called the Nernst potential for that ion. Examples

Nernst Equation

It is used to calculate Nernst potential for any univalent ion:

- EMF (mV) = ± 61 log conc. inside = $\frac{conc.inside}{conc.outside}$
- Sign is +ve for -ve ions & vice versa.

Condition

For NP to develop by diffusion of ions, two conditions are required.

(1) Selective permeability.

(2) Concentration gradient.

Goldman Equation

The Goldman Equation Is Used to Calculate the Diffusion Potential When the Membrane Is Permeable to Several Different Ions.

$$EMF\ (mV) = -61 \log\left(\frac{C_{Na^+i}P_{Na^+} + C_{K^+i}P_{K^+} + C_{Cl^-o}P_{Cl^-}}{C_{Na^+o}P_{Na^+} + C_{K^+o}P_{K^+} + C_{Cl^-i}P_{Cl^-}}\right)$$

Action Potential

(1) Transport of ions across cell mem. due to a stimulus to change mem. potential from normal -ve value to +ve value and then back to -ve value, giving rise to an impulse, is called action potential. OR

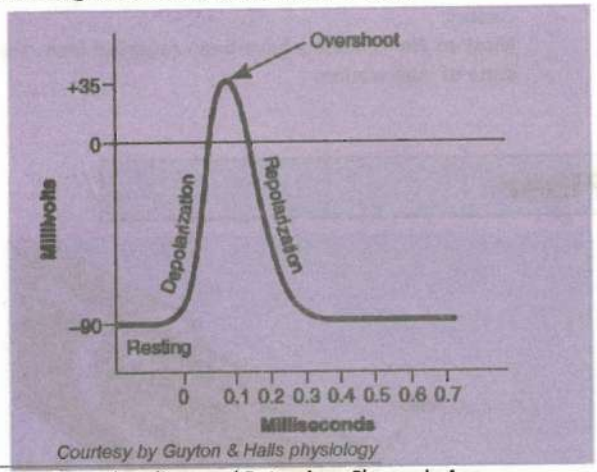
(2) Changes in mem. potential that occurs during activity are collectively called action potential.

(3) Rapid changes in membrane potential resulting in generation of an impulse.

Stages of Action Potential

The successive stages of the action potential are as follows:

- ***Resting stage***. This is the resting membrane potential before the action potential occurs.
- ***Depolarization stage***. At this time, the membrane suddenly becomes permeable to sodium ions, allowing tremendous numbers of positively charged sodium ions to flow to the interior of the axon, and the potential rises rapidly in the positive direction.
- ***Repolarization stage***. Within a few 10,000ths of a second after the membrane becomes highly permeable to sodium ions the sodium channels begin to close and the potassium channels open more than they normally do. Then rapid diffusion of potassium ions to the exterior re-establishes the normal negative resting membrane potential.



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Voltage-Gated Sodium and Potassium Channels Are Activated and Inactivated during the Course of an Action Potential.

- The necessary factor for both depolarization and repolarization of the nerve membrane during the action potential is the voltage-gated sodium channel.
- The voltage-gated potassium channel also plays an important role in increasing the rapidity of repolarization of the membrane.
- These two voltage-gated channels are present in addition to the Na^+- K^+ pump and the Na^+- K^+ leak channels that establish the resting permeability of the membrane.

Spike Potential

Initial very large change in mem, potential is called spike potential. Also called nerve impulse.

Negative After Potential/After Depolarization

At termination of spike potential mem. potential returns slowly to its resting level this is called negative after potential.

Occurs → After a series of repeated action potentials.

Causes → Build-up of K^+ immediately outside cell mem. after repeated action potential that slows down K^+ outflux.

Positive After Potential (Hyperpolarization)

After action potential is over, mem. potential becomes more negative; this is called positive after potential or hyperpolarization.

Causes

(1) First part is due to K^+ channels remain open for several minutes that causes more K^+ outflux and more negativity inside.

(2) Prolonged continuation is due to excess Na^+ pumped out by Na^+- K^+ electrogenic pump that causes negativity inside.

Compound Action Potential

Action potential recorded from a group of nerve fibers, eg sciatic nerve, is called compound action potential.

Consists of:

A, B & C waves.

Threshold For Initiation Of Action Potential

Minimum rise in RMP that can initiate action potential is called threshold for initiation of action potential.

Value → threshold is -65 mV.

Stimuli For Initiation Of Action Potential

Stimulus

Any factor that causes Na+ influx

(1) Chemical stimuli, eg
  (a) Acetylcholine
  (b) Norepinephrine and epinephrine (ie noradrenaline and adrenaline)
  (c) Other neurotransmitters.

(2) Mechanical stimuli, eg
  (a) Crushing
  (b) Pinching

(c) Pricking

(3) Electircal Stimuli, eg
  (a) Cathode current excites AP
  (b) Anode current inhibits AP

(4) Thermal stimuli

Subthreshold Potential

Potential below threshold level that cannot initiate action potential is called subthreshold potential.

All-or-Nothing Principle (All-or-None Law)

Once an action potential has been elicited at any point on the membrane of a Normal fiber, the depolarization process travels over the entire membrane if conditions are right, or it does not travel at all if conditions are not right. This is called the *all-or-nothing principle,* and it applies to all normal excitable tissues.

Safety Factor

Ratio of action potential to threshold for excitation, is called safety factor.

Note

For normal propagation of impulse safety factor should be greater than 1.

Plateau in Some Action Potentials

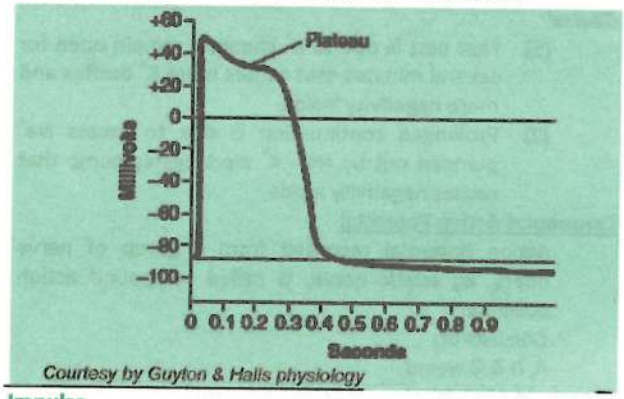
Cause

Voltage-gated slow Ca^+ -Na^+ channels.

Function

Plateau in action potential prolongs duration of action potential and muscle contraction.

Found in Cardiac muscle and smooth muscle.



Courtesy by Guyton & Halls physiology

Impulse

Transmission or propagation of depolarization wave along a nerve or muscle fiber is called impluse.

Refractory Period

Period during which a second action potential cannot occur in presence of first action potential, is called refractory period.

Types

Two

- ***Absolute refractory period***. An action potential cannot be elicited during the absolute refractory period, even with a strong stimulus. This period for large myelinated nerve fibers is about 1/2500 second, which means that a maximum of about 2500 impulses can be transmitted per second.
- ***Relative refractory period.*** This period follows the absolute refractory period. During this time, stronger than normal stimuli can excite the nerve fiber, and an action potential can be initiated.

Occurs

When stimulus is given during repolarization.

Causes

Most of Na^+ channels have been reversed from their state of inactivation.

Nerve Fiber

Nerve Fiber

Axon of neuron is called nerve fiber.

Kinds → Two,

(1) Unmyelinated Axon or nerve fiber is not covered by myelin sheath.

(2) Myelinated Axon or nerve fiber is covered by myelin sheath.

Myelin Sheath

It is a lipoprotein layer that acts as insulator and prevents flow of ions across nerve fiber (axon) mem.

Consists of:

Multiple concentric layers of Schwann cell mem. Each layer of Schwann cell mem. is composed of

(1) Outer and inner protein layers and

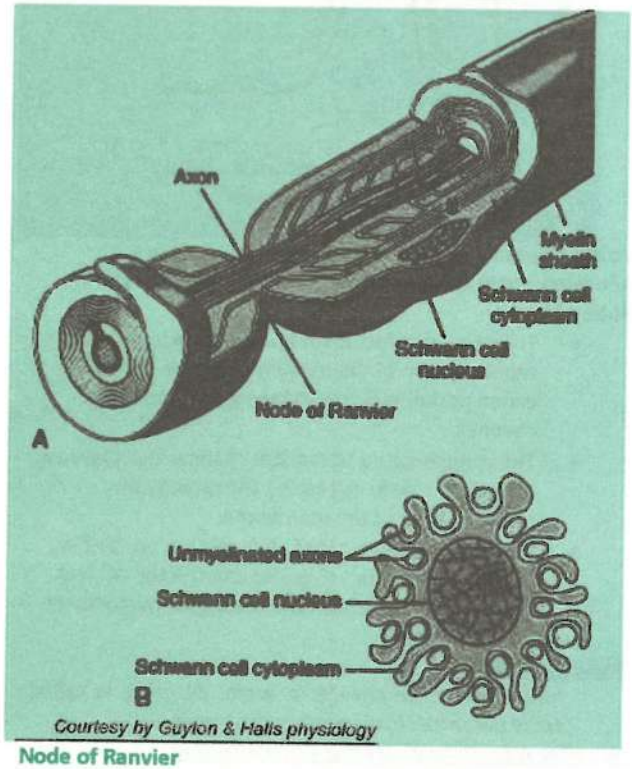
(2) Sphingomyelin in between.

Myelination

Manner is which myelin sheath is formed is called myelination.

Mechanism

Schwann cell takes several turns around axon. Later, cytoplasm of Schwann cell disappears leaving multiple concentric layers of cell mem. of Schwann cells, which together constitute myelin sheath.



Courtesy by Guyton & Halls physiology

Node of Ranvier

Myelin sheath is interrupted at intervals by constricted uninsulated areas where myelin sheath is absent and allow ionic exchange for action potential to take place; these are called nodes of Ranvier.

Neurolemma or Sheath of Schwann

It is a sheath of Schwann cells (not Schawnn cell mem.) that closely invests peripheral nerves, both myelinated and unmyelinated.

Function

Responsible for regeneration of nerve fiber.

Note

Absent in CNS.So, if nerve fiber is damaged within CNS, it cannot be regenerated.

Saltatory Conduction

Conduction of action potential in myelinated nerve fibers in jumping manner from one node of Ranvier to another, is called saltatory conduction.

Importance

(1) Velocity of transmission is inc.
(2) Conserves energy as only nodes depolarize.

Rheobase

Minimum current needed to stimulate a nerve or muscle is called rheobase.

Utilization Time

Time needed for stimulation by rheobase is called utilization time.

Chronaxie

Time needed for stimulation by a current double the rheobase, is called chronaxie.

Muscles

Types

There are three types of muscles

1.Smooth
2.Cardiac
3.Skeletal

Courtesy by Guyton & Halls Physiology

Comparsion Between them

Skeletal	Cardiac	Smooth
Stiated	Stiated	Non striated
Actin and myosin form sarcomeres	Actin and myosin form sarcomeres	Actin & myosin not organized into sarcomeres
Sarcolemma lacks junctional complexes between fibers	Junctional complexes between fibers including Gap junctions	Gap junctions
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

Skeletal Muscle

Muscle

Contractile tissue of body is called muscle.

Types

(1) Striated Muscle
  (a) Skeletal muscle (Voluntary)
  (b) Cardiac muscle (Involuntary)
(2) Unstriated Muscle (involuntary) smooth muscle, present in viscera.

Skeletal Muscle

That type of muscle, which is present in skeleton, voluntary in action and striated in appearance, is called skeletal muscle.

Skeletal Muscle Fiber

Functional and structural unit of muscle is called muscle fiber.

Composition

(1) Sarcolemma: It is cell mem. of muscle fiber that surrounds it.
(2) Sarcoplasm: It is matrix present in muscle fiber
(3) Sarcoplasmic Reticulum. It contain a protein called "calsequestrin". Which can bind up to 40 times more Cal,
(4) Myofibrils
(5) Each muscle fiber is innervated by one nerve ending in center

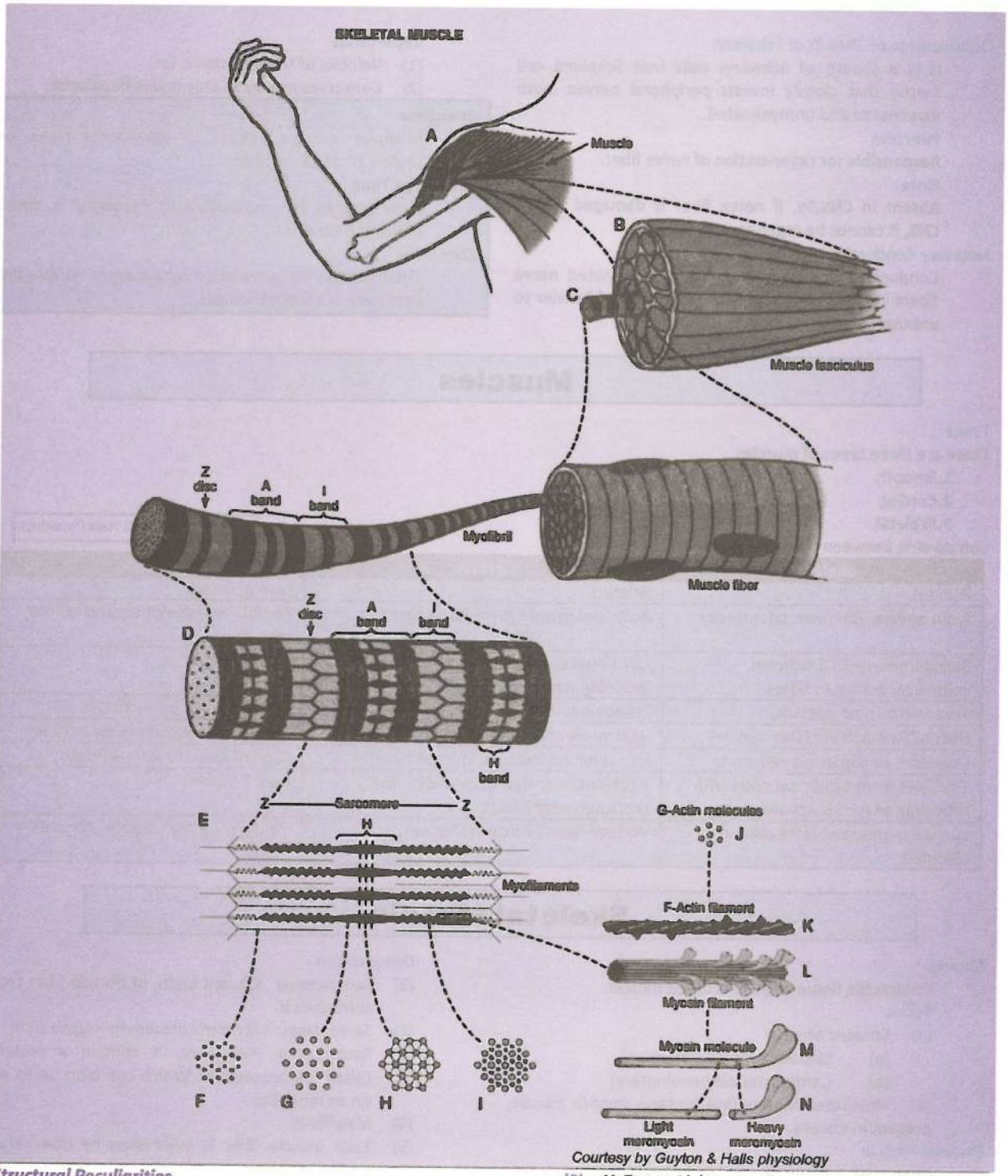
Myofibrils

Each muscle fiber contains in its sarcoplasm hundreds of myofibrils.

Composition

Each myofibril contains:

(1) 1500 myosin (thick) filaments
(2) 3000 actin (thin) filaments



Courtesy by Guyton & Halls physiology

Structural Peculiarities

Actin and myosin filaments partly interdigitate, causing alternate dark and light bands:

(1) **I Band**: Light band containing only actin filament. Isotropic to polarized light.

(2) **A Band:** Dark band containing actin and myosin filaments where they overlap. Anisotropic to polarized light.

(3) **H Zone**: Light area in center of A band. Seen when muscle is stretched beyond its resting length, due to pulling apart of actin filaments.

(4) **M Line**: Dark line in the center of H zone.

Z Disc

It is a disc (plate) of filamentous protein to which actin filaments are attached.

Function

Z disc passes from myofibril to myofibril and attach them together.

SARCOMERE:

Portion of myofibril b/w two successive Z discs is called sarcomere.

Resting Length: of sarcomere is 2g.

Myosin Filament

It consists of 200 myosin molecules. Each myosin molecule consists of two heavy chains and four light chains.

Structural Peculiarities

(1) **Tail** Formed by two heavy chains which coil into a helix.

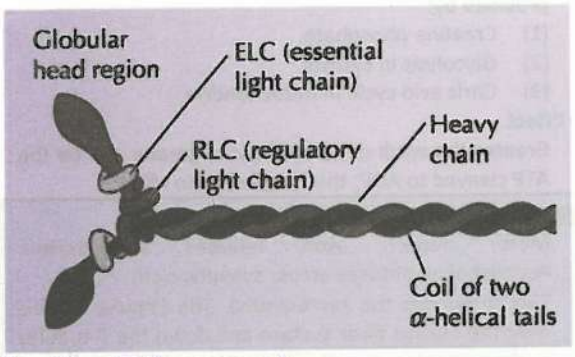
(2) **Head** Formed by the other end of helix together with four light chains. It has ATP-ase activity.

(3) **Body** Formed by tails of all myosin molecules.

(4) **Arm** Part of tail that protrude out from body is called arm

(5) **Cross Bridge** Arm and head together are called cross bridge. Absent in center.

(6) **Two Hinges** Movable point of myosin filament is called hinge. One hinge is present where arm leaves body and other where head is attached to arm.



Actin Filament

Composed of:

(1) **F-Actin Strands** (F = filamentous). Two F-actin strands are wound into helix. Each strand of F-actin molecules is made by polymerization of G-actin (G = globular) protein molecules. Each G-actin molecule has one ADP that is active site, which interacts with cross bridge during sliding process.

(2) **Tropomyosin** Strands Two strands of tropomyosin are coiled into helix that is attached to F-actin strands. Each strand is made by polymerization of tropomyosin molecules.

Function In resting state tropomyosin strands physically cover active-sites of F-actin strands, preventing muscle contraction.

(3) **Troponin Complex** It is attached 2/3 distance along each tropomyosin molecule

Consists of 3 globular proteins

(a) Troponin I; to attach with actin

(b) Troponin T; to attach with tropomyosin

(c) Troponin C; to attach with Ca^{++}

Function Troponin complex attaches F-actin strands with tropomyosin strands.

Inhibition of Actin Filament

Under resting condition, tropomyosin strand physically covers active site (ADP) of actin strand. Thus, no interaction occurs b/w actin and myosin to cause muscle contraction.

Activation of Actin Filament By

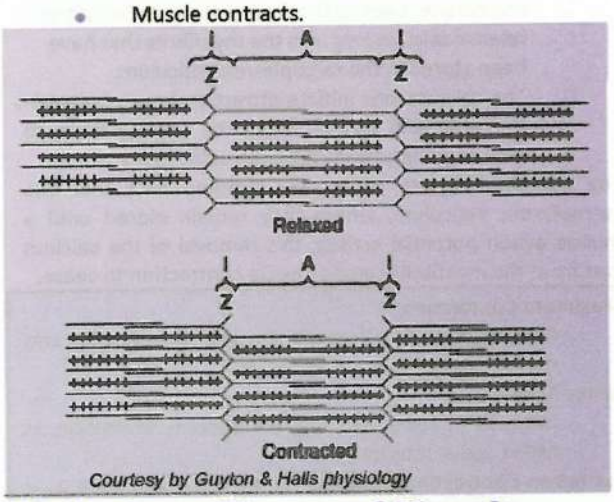
Action potential in muscle mem. → Ca^{++} released from sarcoplasmic reticulum → Ca^{++} binds with troponin C → Conformational change → Pushes tropomyosin strand deeper into groove b/w two F-actin strands → Active site (ADP) on F-actin strands uncovered → Interaction b/w actin and myosin → Muscle contraction.

Contraction will produce the following:

- A band: no change in length.
- I band: shortens.
- H zone (band): shortens.

Sliding Filament Mechanism of Muscle Contraction

- Action potential over muscle membrane
- Ca^{++} released from SR
- Active site on actin filament uncovered
- Interaction b/w active site (ADP) of actin and cross bridge of myosin (they walk along)
- Actin filament is pulled inward over myosin filament, ie they slide over each other
- Z discs pulled closer
- Sarcomere shorten
- Muscle contracts.



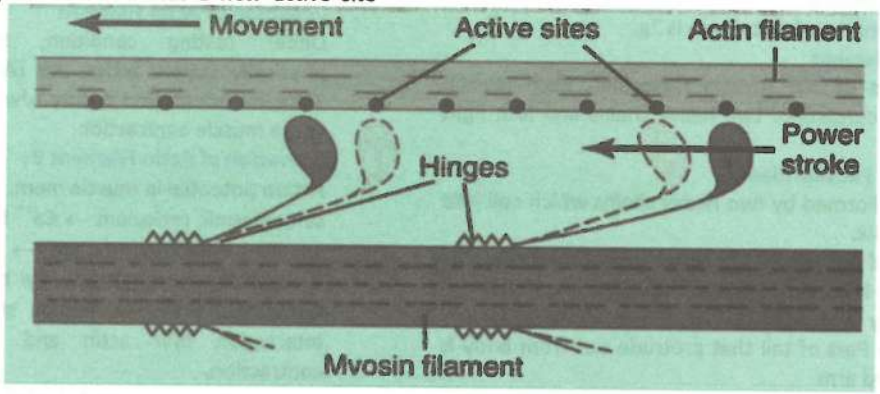
Courtesy by Guyton & Halls physiology

Walk along Theory of Muscle Contraction

- When a myosin head attaches to an active site, the head tilts automatically toward the arm that is

dragging along the actin filament. This tilt of the head is called the **power stroke.**

- Immediately after tilting, the head automatically breaks away from the active site. The head then returns to its normal perpendicular direction. In this position, it combines with a new active site farther along the actin filament. Thus, the heads of the cross-bridges bend back and forth and, step by step, walk along the actin filament, pulling the ends of the actin filaments toward the center of the myosin filament.



Process of Muscle Contraction

The initiation of muscle contraction occur in the following sequential steps:

1. An action potential travels along a motor nerve to its endings on muscle fibers, and each nerve ending secretes a small amount of the neurotransmitter substance acetylcholine.
2. The acetylcholine acts on a local area of the muscle membrane to open acetylcholine-gated cation channels, which allows mainly sodium ions but also calcium ions to flow into the muscle fiber causing a
3. local depolarization. The local depolarization in turn leads to opening of voltage-gated sodium channels resulting in an action potential.
4. The action potential travels along the muscle fiber membrane, causing the sarcoplasmic reticulum to
5. release calcium ions into the myofibrils that have been stored in the sarcoplasmic reticulum.
6. The calcium ions initiate attractive forces between the actin and myosin filaments, causing them to slide together; this is the contractile process.

The calcium ions are continually pumped back into the sarcoplasmic reticulum, where they remain stored until a muscle action potential arrives; this removal of the calcium ions from the myofibrils causes muscle contraction to cease.

Maximum Contraction
Occurs when there is maximum overlap b/w actin and myosin filaments.

Active Tension
Increase in tension during contraction of muscle, is called active tension.

Excitation-Contraction Coupling Contraction of muscle as a result of excitation by a nerve action potential, is called excitation-contraction coupling

Energy Source For Muscle Contraction

Energy for muscle contraction is derived from ATP that is cleaved into ADP, which must be rephosphorylated for continued muscle contraction.

Rephosphorylation of ADP

For rephosphorylation of ADP into ATP, energy is provided by:

(1) Creatine phosphate.
(2) Glycolysis in cytosol.
(3) Citric acid cycle in mitochondria.

Fenn Effect

Greater the work done by muscle, greater will be the ATP cleaved to ADP; this is called Fenn effect.

Molecular Events in Muscle Contraction

- Motor neuron axon releases acetylcholine. Acetylcholine diffuses across synaptic cleft.
- This stimulates the sarcolemma. The impulse travels over the muslce fiber surface and down the T-tubules to the sarcoplasmic reticulum (SR).
- Calcium ions diffuse out of the SR into the sarcoplasm and bind to troponin.
- Tropomyosin moves and exposes sites on actin filaments. Actin and myosin form linkages.
- Actin filaments are pulled inward by myosin cross-bridges (Sliding filament theory Muslce fibers shorten as contraction occurs.

Muscle Action Potential

Almost same as nerve action potential:

(1) RMP =-90 mV.
(2) Duration = 1-5 ms.
(3) Velocity = 3-5 m/s.

Transverse (T) Tubule

These are inward extension of sarcolemma in the form of penetrating tubules in direction transverse to length of muscle fiber.

Function

Conduct action potential from sarcolemma to deep interior of muscle fiber.

Sarcoplasmic Reticulum

It is an extensive endoplasmic reticulum present in sarcomplasm, contaninig large amount of Ca -.

Composed of:

(1) Longitudinal tubules

(2) Terminal cistemae that adjoin T-tubules, forming a triad.

Release of Ca^{++}

Action potential over sarcolemma and T-tubules open Ca^{++} channels in cistemae and longitudinal tubules to release Ca^{++}.

Removal of Ca^{++}

Ca^{++} is removed from sarcoplasm by continually active Ca^{++} pump in mem. of SR.

Excitatory Pulse of Ca^{++}

Time for which Ca^{++} remains in sarcoplasm to cause muscle contraction, is called excitatory pulse of Ca^{++}.

CHARACTERISTICS OF WHOLE MUSCLE CONTRACTION

Isometric contraction	Isotonic contraction
muscle is said to be isometric when it does not shortens	Muscle it isotonic when it shortens against a fix tension
Length remains constant	Tension or load applied is constant
Records changes in force of contraction in the muscle itself	Depends upon the load plus the inertia of the load

Series Elastic Component Of Muscle

Elements of muscle that stretch during contraction, are called series elastic component of muscle.

Include

(1) Tendon.

(2) Sarcolemmal end.

(3) Hinged arms of cross bridges.

Macromotor unit

- When some but not all the nerve fibres are destroyed, the remaining fibres tend to branch off and supply many of the paralyzed muscle. This leads to formation of larger motor units, which are called as Macromotor units.
- There is decrease fitness control over the muscle but it allows a muscle to regain strength.

Fast V/S Slow Fibers

Type 1 (slow fibres)	Type 2 (fast fibres)
Small fibres	Large fibres for greater strength of contraction
Smalller	Longer
Reddish appearance due to large amount of myoglobin	Whitish due to deficient myoglobin
More extensive Blood vessels to supply extra oxygen	Less vessels because oxidative mechanism is of secondary importance
Extensive mitochondria supporting oxidative process	Fewer mitochondria
Contains large amount of myoglobin for extensive oxygen storage	Extensive SR for rapid release of Ca++ ions to initiate contraction
Example: soleus	Example: Tibialis anterior

Motor Unit

All the muscle fibers supplied by a single motor neuron, are collectively called motor unit.

Summation of Muscle Contraction

Summation means adding together of individual twitch contractions to increase the intensity of overall muscle contraction it can be through

Types

Two,

(1) Multiple Motor Unit Summation

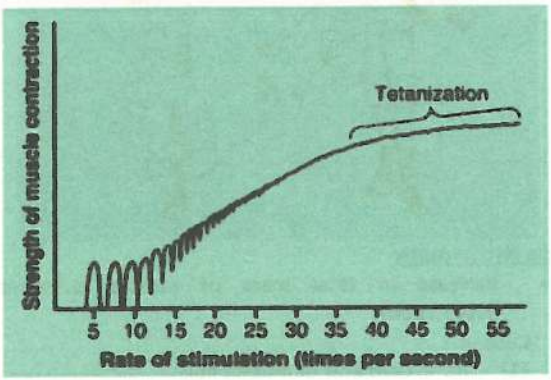
In this no. of motor units contracting simultaneously is increased.

(2) Wave or Frequency Summation

In this frequency of contraction of individual motor unit is increased.

Tetanization

When muscle is stimulated at progressively greater frequency, at a certain higher freqeuency successive contractions fuse together and cannot be distinguished from one another; this state is called tetanization.



Critical Frequencey

Lowest frequency at which tetanization occurs is called critical frequency.

Asynchronous Summation Of Motor Units

Incoordinate summation of motor units is called asynchronous summation of motor units.

Importance

Due to asynchronous summation tetanization does not occur even when frequency is great enough.

Staircase Effect or Treppe

When a muscle begins to contract after a long period of rest initially its strength may be little (almost half of the original) but on repeated stimulus it increases till it reaches a plateau. This is called staircase effect or treppe.

It is due to the release of more than normal amount o Ca+ ions and failure of the SR to pump them back.

Cause

Some Ca^{++} of first contraction remains in sarcoplasm when second contraction begins, thereby causing second contraction to be stronger than first.

Skeletal Muscle Tone

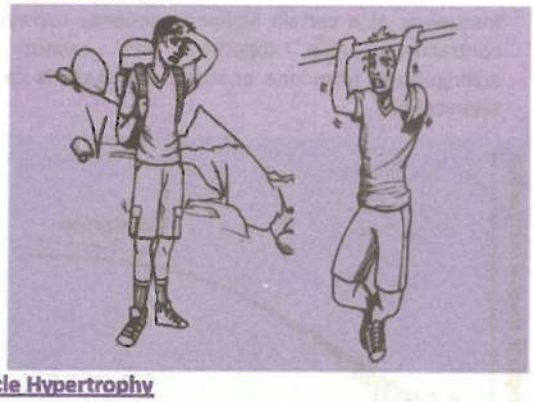
* The tautness in a muscle even at rest is called muscle tone.
* This is due to low rate of nerve impulses coming from the spinal cord that are controlled by brain and the muscle spindles in the muscle itself..

Muscle Fatigue

Loss of capacity of muscle to respond to stimulus is called muscle fatigue.

Decline in ability of a muscle to generate force. It depends upon

- Rapid Depletion of glycogen
- Diminish nerve signal NMJ
- After Prolonged exercise
- Interruption of blood flow
- Lactic acid accumulation
- Dec. blood flow



Muscle Hypertrophy

* Increase in total mass of muscle is called hypertrophy.

Causes

(1) Inc. in diameter of muscle fiber
(2) Inc. in no. of muscle fiber (hyperplasia)

Muscle Atrophy

Dec. size of muscle is called muscle atrophy.

Causes

(1) Muscle not used or used for weak contractions
(2) Muscle placed in cast
(3) Muscle denervated

Rigor Mortis

The ability of muscles to go in state of contracture formation after death is called rigor mortis.

* This is due to the loss of ATP that is required to separate the cross bridges from actin during contraction.
* It remains until after 15 to 20 hours, when the muscle protein detoriates.

Disappearance

When muscle protein is autolyzed by lysosomal enzymes.

Electro-Myogram

Graphical record of electrical potential changes in muscle, is called electro-myogram.

Muscle Fasciculation

An abnormal impulse in motor nerve causes whole of its motor unit to contract that is seen as a ripple (wave) over skin of motor unit; this is called muscle fasciculation.

Cause

Destruction of anterior motor neuron (as in poliomyelitis).

Muscle Fibrillation

Inc. frequency of contraction of skeletal muscle after its denervation, is called muscle fibrillation.

Cause

Spread of acetylcholine over muscle mem.

Starling Law For Skeletal Muscle

It states "within physiological limits, greater the initial length of skeletal muscle, stronger will be the force of contraction."

Neuro-Muscular Junction

Synapse

Junction b/w excitable cells that allows transmission of a signal from first cell to next, is called synapse.

Example

Neuro muscular junction.

Neuro-Muscular Junction

Junction (synapse) b/w a nerve ending and muscle mem. is called neuro-muscular junction.

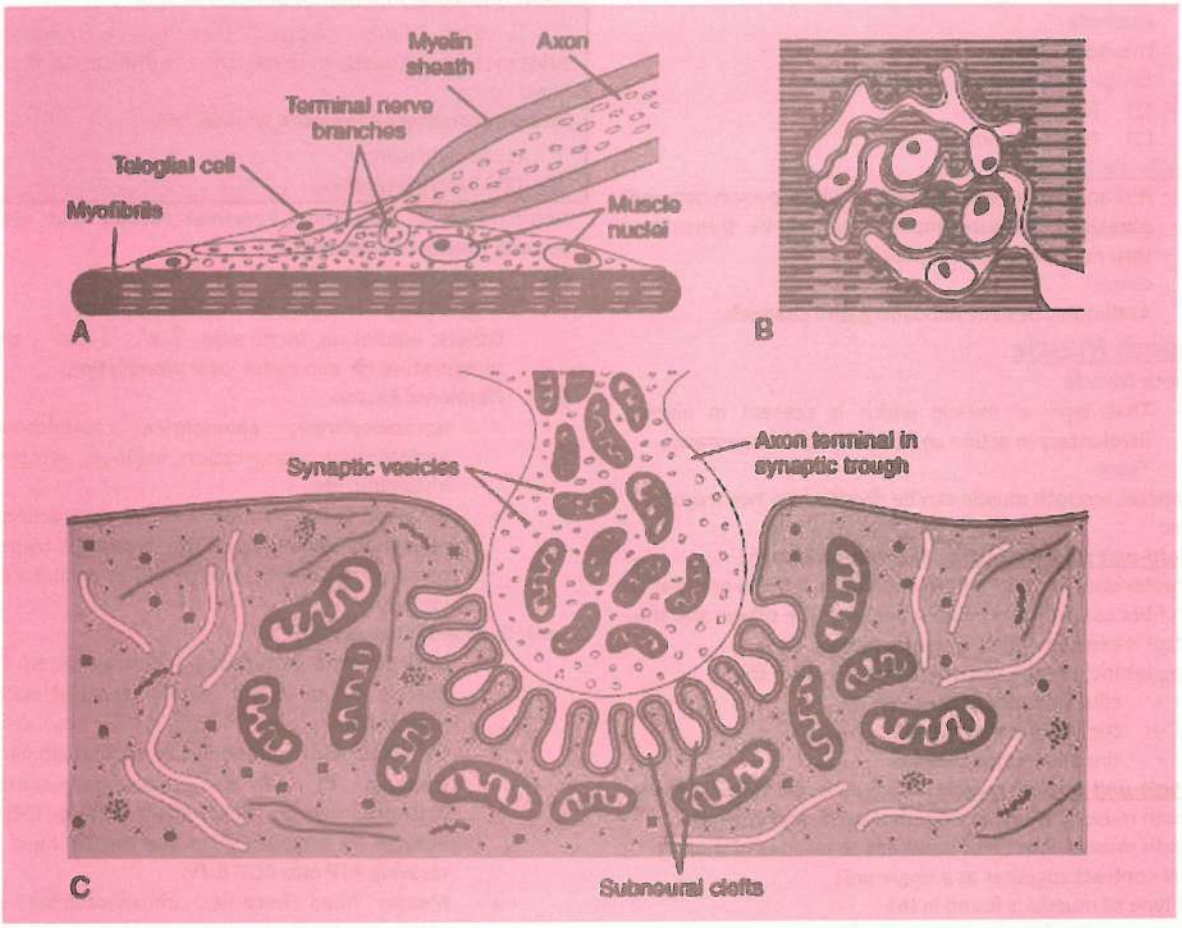
Neuro-Muscular Transmission

Transmission of nerve impulse (action potential) from nerve ending to muscle thru neuromuscular junction, is called neuro-muscular transmission.

Physiologic Anatomy Of Neuro-Muscular Junction

(1) End plate = Nerve terminal
(2) Synaptic gutter or trough = Invagination of muscle mem.
(3) Synaptic cleft = space b/w nerve terminal and muscle mem.

(4) Sub-neural cleft = small folds of muscle mem. at bottom of gutter.
(5) Mitochondria = Present in axon terminal. Provide energy for synthesis of acetyl-choline (Ach).
(6) Acetylcholine = Neurotransmitter
(7) Basal lamina = Thin layer of spongy reticular fibers in synaptic cleft
(8) Acetylcholinesterase = Enzyme that destroys Ach released in basal lamina.



Courtesy by Guyton & Halls physiology

End Plate Potential

When Ach-gated channels open due to arrival of nerve action potential, sudden Na+ influx into muscle fiber causes mem. Potential to rise by 50 to 70 mV in the +ve direction; this is called end plate potential that initiate and propagate action potential.

Miniature End Plate Potential

Under resting conditions, occasional Ach vesicles fuse with mem. and release small amounts of Ach that causes a small potential; this is called miniature end plate potential.

Acetylcholine

- Ach is a neurotransmitter.

Synthesis

- Ach is synthesized in cytosol of axon terminal.

Storage

- Ach is stored in small vesicles formed by Golgi apparatus in cell body of motor neuron of spinal cord, that have been transported from cell body to axon terminal.

Secretion

- Action potential reach axon terminal → Ca++ enter cytosol → Cause Ach vesicle to fuse with mem. → Ach is secreted by rupturing of vesicle.

Function

- Ach bind with receptor of Ach-gated channels on muscle mem. and open them to cause tremendous Na+ influx, giving rise to muscle action potential.

Destruction

- Released Ach is destroyed by acetylcholinesterase in basal lamina; this prevents re-excitation.

Fatigue Of Neuro-Muscular Junction

After repeated stimulation no. of Ach vesicles dec., causing failure of impulses to pass into muscle fiber; this is called fatigue of neuromuscular junction.

Ach-Like Drugs

(1) Methacholine
(2) Carbachol
(3) Nicotine

Drugs That Block Ach-Gated Channels

Curariform drugs

Example

D-tubo-curarine.

Drugs That Inactivate Ach-Esterase

(1) Neostigmine
(2) Physostigmine

Myasthenia Gravis

It is an autoimmune disease in which person becomes paralysed, because impulses cannot be transmitted thru neuro-muscular junction.

Cause

Antibodies destroy Acholine-gated channels.

Smooth Muscle

Smooth Muscle

That type of muscle which is present in viscera, involuntary in action and unstriated in appearance.

Types

In general, smooth muscle can be divided into two major types:

• ***Multi-unit smooth muscle***. The most important characteristics of multi-unit smooth muscle fibers are that each fiber can contract independently of the others and the control is exerted mainly by nerve signals.

Examples include the smooth muscle fibers of the

- ciliary muscle of the eye,
- the iris of the eye, and
- the piloerector muscles

• ***Single-unit smooth muscle***. This type is also called unitary smooth muscle, syncytial smooth muscle, and visceral smooth muscle. A mass of hundreds to millions of muscle fibers contract together as a single unit

This type of muscle is found in the

- walls of the gastrointestinal tract,
- bile ducts,
- ureters,
- uterus,
- oviducts, and blood vessels.

Structure Of Smooth Muscle

Smooth musde fiber consists of :

(1) **Actin Filaments**:- That are attached to dense bodies. Do not contain troponin complex.

(2) **Myosin Filaments**: That are scattered among actin filaments.

RMP Of Smooth Muscle

Value

= -50 to -60 mV

Action Potential In Smooth Muscle Types

Two,

(1) Spike potentials
(2) Action potentials with plateau

Ca^{++} Channels In Smooth Muscle Functions

(1) Responsible for action potential
(2) Slow to open, so action potential and smooth muscle contraction are also slow.
(3) ca- ions that enter muscle fiber during action potential also cause muscle contraction.

Neuro-Muscular Junction Of Smooth Muscle

is called "diffuse junction" that secretes transmitter substance into interstitial space, then it diffuses to muscle fiber.

Neurotransmitters At Smooth Muscle NMJ

(1) Acetylcholine
(2) Norepinephrine

Non-nervous & non-action Potential Factors that Affect Smooth Muscles Contraction

(1) Local Chemical Factors

$\downarrow O_2$ $\uparrow CO_2$, $\uparrow H^+$ conc. ➔ cause vasodilation.

Others: adenosine, lactic acid, $\uparrow K^+$, $\downarrow Ca^{2+}$, body temperature ➔ can cause local vasodilation.

(2) Hormonal Factors

- Norepinephrine, epinephrine, acetylcholine, angiotension, vasopression, oxytocin, serotonin, histamine, etc.
- Whether these hormones cause contraction or relaxation depends on the type of receptors present on smooth muslce either excitatory or inhibitory.

Smooth Muscle Contraction

- During action potential → voltage gated Ca^{2+} channels open → Ca^{2+} enter cytosol of smooth muscle fiber
- Ca^{2+} bind with calmodulin (a protein similar to troponin C) → Ca^{2+} calmodulin-complex activates myosin light chain kinase (MLCK) enzyme → provides Pi to the myosin head (by cleaving ATP into ADP & Pi)
- Myosin head becomes phosphorylated and active → leads to walk → along contractile process → cross bridge formation and smooth muscle contraction.

Caveoli → Small invagination of cell membrane of smooth muscle fiber, analogous to the T- tubule of skeletal muscle fiber.

Smooth Muscle Tone

A state of longterm steady contraction in smooth muscle is called smooth muscle tone.

Cause

(1) Summation of individual contractions
(2) Prolonged direct smooth muscle excitation by local tissue factors or circulatory hormones.

Stress Relaxation Of Smooth Muscle

When smooth muscle is stretched, its tension first rises, but after some time, tension dec. to normal; this is called stress relaxation.

Cause

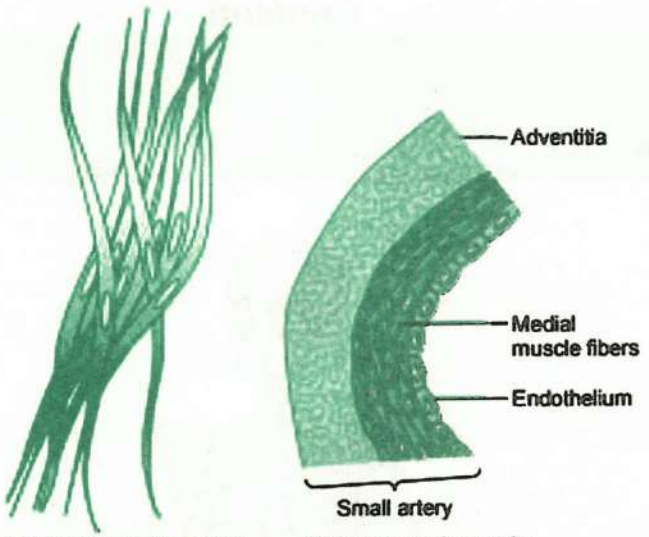
Loose arrangement of actin and myosin filaments rearrange their bonds and gradually allow sliding process to take place, thus allowing tension to return to normal.

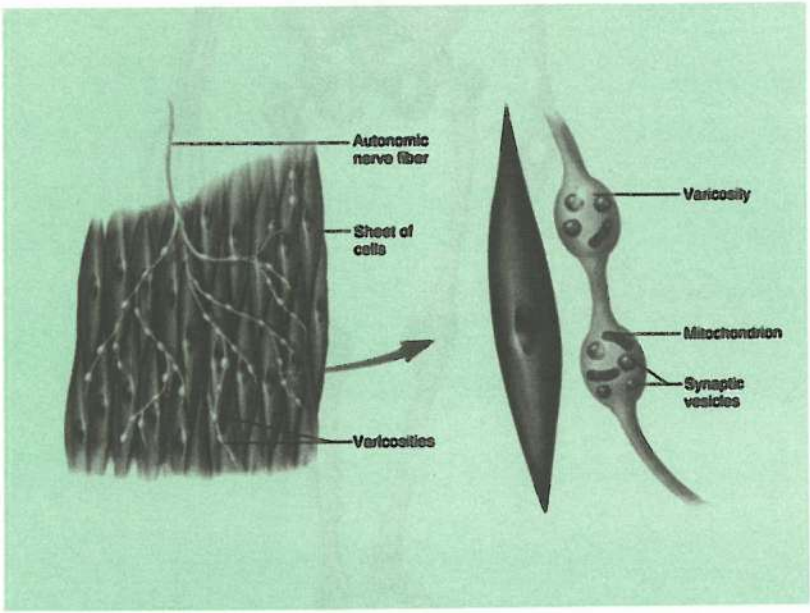
Reverse Stress Relaxation

When smooth muscle is shortened, its tension first dec., but after some time, tension rises to normal; this is called reverse stress relaxation.

Latch Mechanism

- Once smooth muscle has developed full contraction, the degree of activation of the muscle can usually be reduced to far less than the initial level, yet the muscle can maintain its full force of contraction. This is called the "latch mechanism."
- The importance of the latch mechanism is that it can maintain prolonged tonic contraction in smooth muscle for hours with little use of energy.

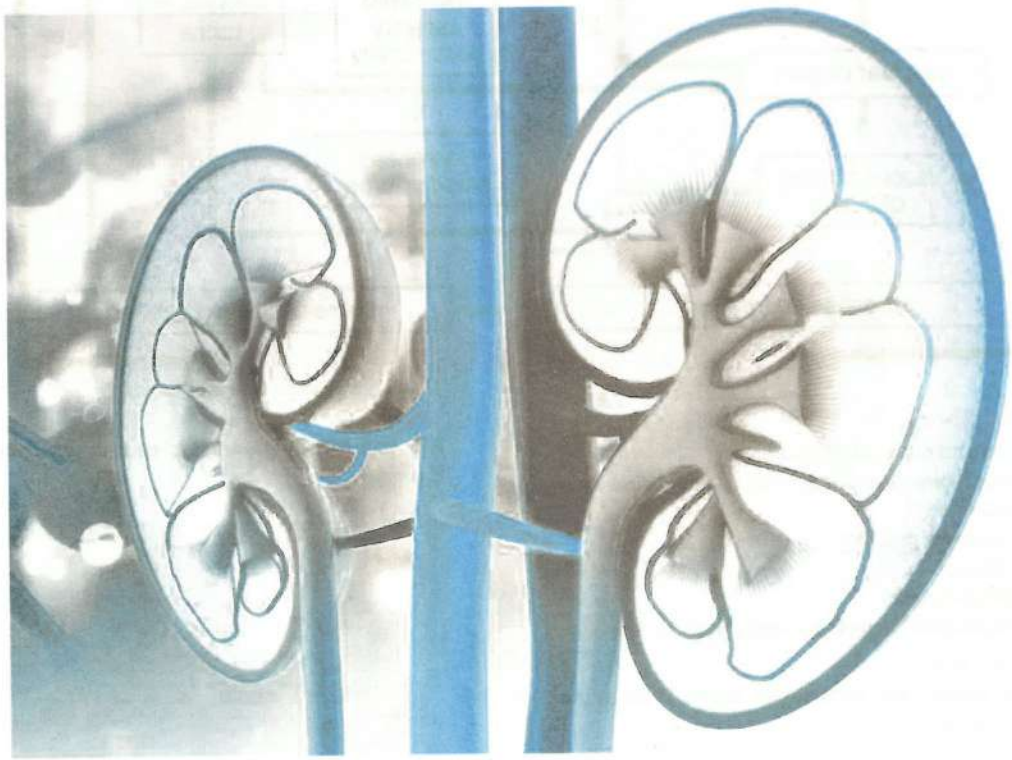




Chapter # 7

Renal Physiology

Contents



Body Water

The total amount and composition of the body fluids are maintained relatively constant under most physiological conditions, as required for homeostasis

Total Body Water

60% of body wt. or 42 L in 70 kg adult human.

Daily intake of Water

2300 ml/day (including 150-250 ml/day yielded in body metabolism).

Daily Loss of Body Water

(1) Urine = 1400 ml/day
(2) Sweat = 100 ml/day
(3) Feces = 100 ml/day
(4) Insensible water Loss, ie
  (a) Skin = 350 ml/day
  (b) Resp. tract = 350 ml/day

Daily intake and output of water (ml/day)

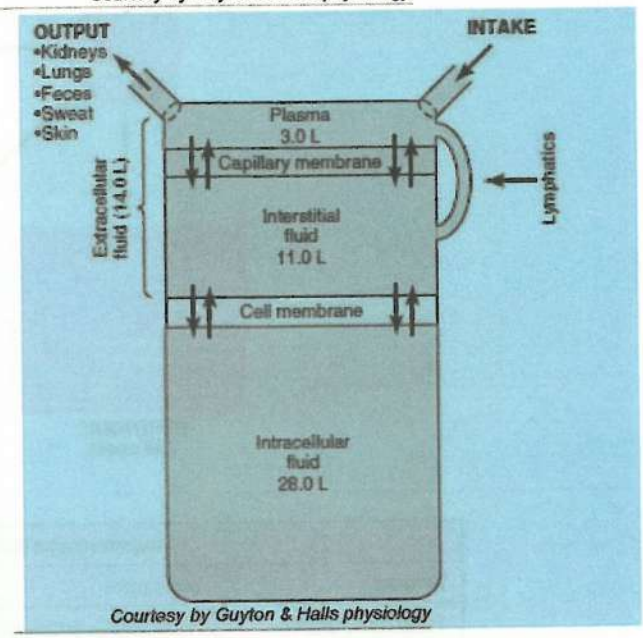
	Normal	Prolonged Heavy Exercise
Intake		
• Fluids ingetsted	2100	?
• From metabolism	200	200
• Tota intake	2300	?
Output		
• Insensible – skin	350	350
• Insensible – lungs	350	650
• Sweat	100	5000
• Feces	100	100
• Urine	1400	500
Total output	2300	6600

Body Fluid Compartments

(1) Intracellular Fluid Compartment = 28 lit.
(2) Extracellular Fluid Compartment = 14 lit.
(a) Plasma = 3 lit.
(b) Interstitial fluid
(c) Cerebrospinal fluid
(d) Intraocular fluid
(e) Fluids of GIT
(f) Fluids of potential spaces

Constituents of Extracellular Fluid	Constituents of Intracellular Fluid
(1) Large quantities of Na+, Cl- & HCO_3-ions	(1) Large amounts of K^+ & phosphate ions & proteins
(2) Small quantities of Ca^{++}, Mg^{++}, phosphatase, sulfate & organic acid ions	(2) Moderate amounts of Mr^{++} & sulphate ions
(3) Plasma contains large amounts of proteins	(3) Small amounts of Na^+ & Cl^- ions
(4) Interstitial fluid contains small amount of proteins	(4) Almost no Ca^{++} ions

Courtesy by Guyton & Halls physiology



Courtesy by Guyton & Halls physiology

Osmotic Pressure

(1) Amount of pressure required to oppose osmosis exactly, is called osmotic pressure
(2) Sucking pressure of concentrated solution that causes movement of water molecules from dilute solution to concentrated solution, is called osmotic pressure.

Dependence

Osmotic pressure depends upon no. of non-permeant molecules dissolved in water.

Relationship b/w Osmotic Pressure & Osmolality

Osmotic Pressure = 19.3 x Osmolality

Osmosis

Movement of solvent molecules (H_2O) from solution of lesser solute conc. thru a semipermeable membrane to solution of greater solute conc., is called osmosis

Osmole

(1) No. of particles in one mole (gm mol. wt.) of a non-permeant & non-ionizable substance, is equal to 1 osmole; eg, 1 osmole of glucose = 180 gm (ie 1 mole)

(2) If a substance ionizes into two ions, its 1 gm mol. wt. will be equal to 2 osmoles; eg, $Na^+ Cl^-$.

Milliosmole

1 Milliosmole = 1/1000 osmole

Osmolality

Osmoles per kg of water, is called osmolality.

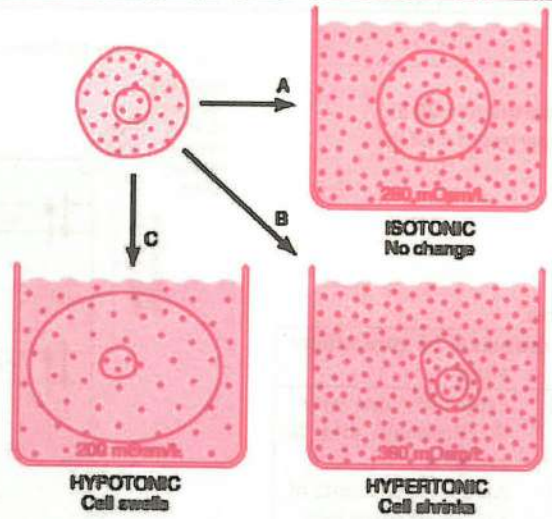
Example

Osmolality of plasma = 282.5 mosm/kg.

Types of Solutions

Three types of solution

(1) Isotonic Solution	(2) Hypotonic Solution	(3) Hypertonic Solution
A solution whose osmolality is same as that of extracellular fluid is called isotonic solution.	A solution whose osmolality is less than that of extracellular fluid, & cause body cells to swell, is called Hypotonic solution.	A solution whose osmolality is greater than that of extracellular fluid, & cause body cells to shrink, is called hypertonic solution.
0.9% NaC1 solution 5% Glucose solution	NaCl solution Of less than 0.9% conc	NaCl solution of greater than 0.9% conc.



Courtesy by Guyton & Halls physiology

Measurement of Body Fluid Volume	
Volume	Indicators
Total body water	^3H_2O, ^2H_2O, antipyrine
Extracellular fluid	^{22}Na, ^{125}I-iothalamine, thiosulfate, inulin
Intracellular fluid	(Calculated as Total body water-Extracellular fluid volume)
Plasma volume	^{125}I-albumin, Evans blue dye (T-1824)
Blood volume	^{51}Cr=labeled ared blood cells, or calculated as Blood volume = Plasma volume/ (1-Hematocrit)
Interstitial fluid	(calculated as Extracellular fluid volume – Plasma volume)

Abnormalities of Body Fluid Volume Regulation: Hyponatremia and Hypernatremia				
Abnormality	Cause	Plasma Na+ Concentration	Extracellular Fluid Volume	Intracellular Fluid Volume
Hypo-osmatic dehydration	Adrenal insufficiency; overuse of diuretics	↓	↓	↑
Hypo-osmotic overhydration	Excess ADH; bronchogenic tunor	↓	↑	↑
Hyper-osmotic dehydration	Diabetes insipidus; excessive sweating	↑	↓	↓
Hyper-osmotic overhydration	Cushing's disease; primary aldosteronism	↑	↑	↓

Edema

Presence of excess fluid in tissues of body, is called edema.

Types

Intracellular Edema: Increased Intracellular Fluid

Three conditions especially likely to cause intracellular swelling are hyponatremia, depression of the metabolic systems of the tissues, and lack of adequate nutrition to the cells

When the cell's metabolic systems are depressed or they receive inadequate nutrition, ➔ sodium ions that normally leak into the interior of the cells can not pumped out of the cells, ➔ and the excess sodium ions cause osmosis of water into the cells.

Extracellular Edema: Increased Fluid in Interstitial Spaces

The two general causes of extracellular edema are

abnormal leakage of fluid from the plasma to the interstitial spaces across the capillaries and

failure of the lymphatics to return fluid from the interstitium to the blood, often called lymphedema.

Factors Can Increase Capillary Filtration and Cause Interstitial Fluid Edema.

To understand the causes of excessive capillary filtration, it is useful to review the determinants of capillary filtration,

$$\text{Filtration} = K_f \times (P_c - P_{if} - \pi_c + \pi_{if})$$

- where K_f is the capillary filtration coefficient (the product of the permeability and surface area of the capillaries),
- P_{if} is the interstitial fluid hydrostatic pressure,
- Π_c is the capillary plasma colloid osmotic pressure, and
- Π_{if} is the interstitial fluid colloid osmotic pressure.

Causing Factors

(i) Inc. capillary pressure

(ii) Decrease Plasma colloid osmotic pressure caused by decrease plasma proteins.

(iii) Increase capillary permeability

(iv) Blockage of lymphatic return

Examples

(i) Heart Failure: Edema is caused by decrease pumping by heart & damping of blood in veins

(ii) Nephrosis: Edema is caused by damage to renal glomeruli & leakage of plasma proteins into urine

(b) Edema caused by Renal Retention of Salt & water.

Edema Safety Factor

1. The compliance of the tissues is low so long as interstitial fluid hydrostatic pressure is in the negative range.
   - Low compliance (defined as the change in volume per millimeter of mercury pressure change) means that small increases in interstitial fluid volume are associated with relatively large increases in interstitial fluid hydrostatic pressure.
   - When theinterstitial fluid volume increases, the interstitial fluid hydrostatic pressure increases markedly, which opposes further excessive capillary filtration.
   - The safety factor that protects against edema for this effect is about 3 mm Hg in many tissues such as skin.
2. Lymph flow can increase as much as 10- to 50-fold.
   - Lymph vessels carry away large amounts of fluid and proteins in response to increased capillary filtration.
   - The safety factor for this effect has been calculated to be about 7 mm Hg.
3. There is a "wash-down" of interstitial fluid protein as lymph flow increases.
   - As increased amounts of fluid are filtered into the interstitium the interstitial fluid pressure increases, causing greater lymph flow. This decreases the protein concentration of the

interstitium because more protein is carried away than can be filtered by the capillaries.

- The safety factor for this effect has been calculated to be about 7 mm Hg in most tissues.

Combining all of the safety factors, the total safety factor that protects against edema is about 17 mm Hg.

Potential Spaces of Body

These are small spaces in body having surfaces that are close to each other with a thin layer fluid in between. They are drained by lymphatics.

Include

(1) Pleural cavity
(2) Pericardial cavity
(3) Peritoneal cavity
(4) Synovial cavities, ie joint cavities & bursae.

Edema in Potential Spaces (1).

(1) Effusion

When edema fluid collects in potential space, it is called effusion. This occurs when fluid accumulates in subcutaneous tissue adjacent to a potential space.

(2) Ascrtes

Excess effusion fluid in peritoneal cavity is called ascites

KIDNEY

Urine Formation I

Urine

It is an amber color fluid of slight acidic reaction excreted by kidneys.

Volume

600 - 2500 ml/day

Color

Pale yellow or amber; depends upon pigment urochrome

pH

Mean = 6.0; Range = 4.5 - 8.2

Reaction

Acidic

Specific gravity

1.015 to 1.025

(1) Decrease in diabetes insipidus
(2) Increase in diabetes mellitus due to presence of glucose.

Normal Constituents of Urine		Pathological Urine
		Urine having abnormal constituents is called pathological urine.
(A) Organic	**(B) Inorganc**	**Abnormal Constituents of Urine**
(1) Urea	(1) Chloride	(1) Proteins: Albumin, Globulin and Bence Jones Protein (An abnormal protein excreted in urine of multiple myeloma patients; coagulates at 60.0 and dissolves at 80.0 when urine is heated)
(2) Uric acid	(2) Phosphate	(2) Sugars: Glucose, Fructose, Galactose, Lactose and Pentose
(3) Creatine	(3) Sulphate	(3) Ketone bodies
(4) Creatinine	(4) Potassium	(4) Indican
(5) Ammonia	(5) Sodium	(5) Blood
(6) Hippuric acid	(6) Calcium	(6) Pigments: bilirubin, urochromogen, poryphyrin & melanin
(7) Oxalic acid	(7) Magnesium	(7) Casts
(8) Amino acid	(8) Iodine	(8) Calculi
(9) Allantoin	(9) Arsenic	(9) Pus
(10) Vitamins	(10) Lead	(10) Hormones
(11) Hormones		
(12) Enzymes		

Functions of Kidney

The kidneys serve many important homeostatic functions, including the following:

- Excretion of metabolic waste products and foreign chemicals
- Regulation of water and electrolyte balances
- Regulation of body fluid osmolality and electrolyte concentrations
- Regulation of arterial pressure
- Regulation of acid-base balance
- Secretion, metabolism, and excretion of hormones
- Gluconeogenesis

Structure of Kidney

(1) Cortex → outer zone
(2) Medulla → inner zone
(3) Pyramid containing straight collecting tubules
(4) Papilla or apex of pyramid is perforated by openings of collecting tubules into minor calyx of Pelvis (5) Pelvis leads into ureter.

Nephron

Structural & Functional unit of kidney which is capable of forming urine by itself is called Nephron

Number

2.4 millions/two kidneys

Parts of Nephron

(1) Glomerulus

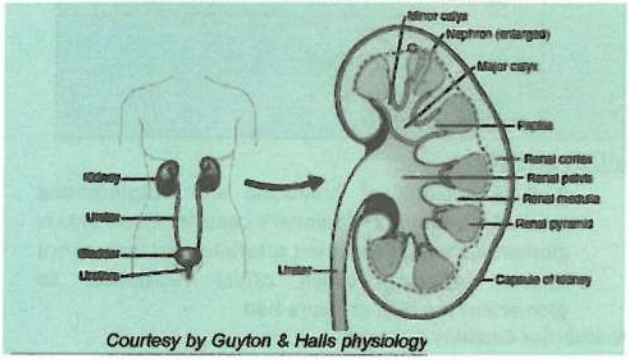
(2) Bowman's capsule

(3) Renal tubule consist of

(a) Proximal convoluted tubule

(b) Loop of Henle having ascending and descending limbs

(c) Distal tubule with diluting segment (first 1 /2) and late distal tubule (remaining 1/2)



Courtesy by Guyton & Halls physiology

(a) Early Proximal Convoluted Tubule

"Workhouse" of the nephron. Reabsorbs all of the glucose and amino acids and most of the bicarbonate, sodium, and water. Secretes ammonia, which acts as a buffer for secreted H^+

(b) Thin Descending Loop of Henle

Passively reabsorbs water via medullary hypertonicity (impermeable to sodium)

(c) Thick Ascending Loop of Henle

Actively reabsorbs Na^+, Cl^- and indirectly induces the reabsorption of Mg^{2+} and Ca^{2+}. Impermeable to H_2O.

(d) Early nictal Convuluted Tubule

Actively reabsorbs Na^+, Cl^-. Reabsorption of Ca^{2+} is under the control of PTH.

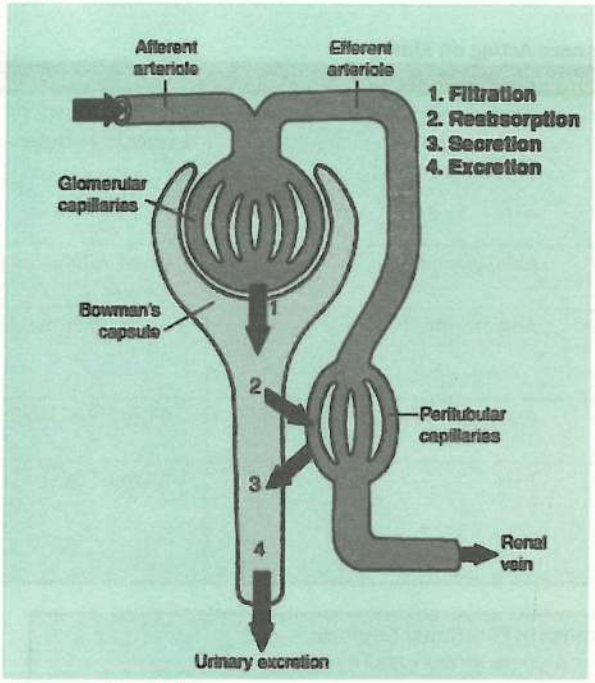
(e) Collecting Tubules;

Reabsorbs Na+ in exchange for secreting K+ or H+ (regulated by aldosterone). Reabsorption of water is regulated by ADH (vasopressin). Osmolarity of medulla can reach 1200 mOsm..

Thin Segment and Thick Segment of Loop of Henle

(1) Thin Segment Descending limb plus lower part of ascending limb have thin wall, and are called thin segment.

(2) Thick Segment Upper part of ascending limb has thick wall like other portions of tubule, so it is called thick segment.



Passage Way of Urine

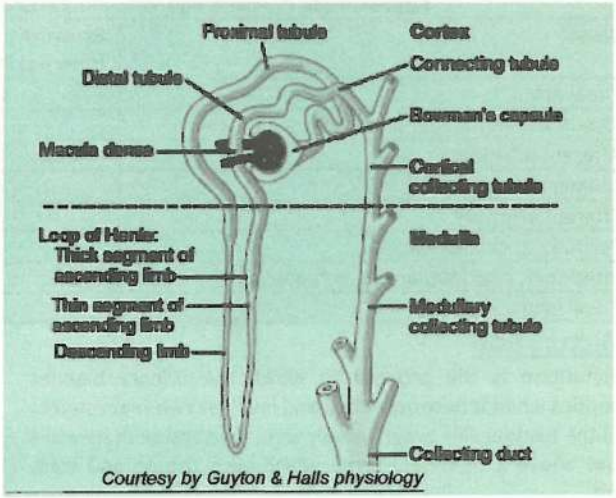
Urine formed in nephron → Collecting tubule → Major Calyx → Pelvis → Ureter → Urinary bladder → Urethra → Excreted

Kind of Nephron

Two kinds

(1) **Cortical Nephrons** Those nephrons of which glomeruli lie close to surface of kidney, are called cortical Nephrons. They have short thin segments and loops of Henle penetrate short distance into outer portion of medulla.

(2) **Juxtamedullary Nephrons** Those nephrons of which glomeruli lie deep in renal cortex near medulla are called juxtamedullary nephrons. They have long thin segments and loops of Henle penetrate deeply into inner portion of medulla.



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Hormones Acting on Kidney

Hormone	Stimulus for secretion	Actions on Kidney
• Vasopressin (ADH)	↑ plasma osmolarity ↓↓ blood volume	↑ H_2O permeability of principal cells in collecting ducts. ↑ urea absorption in collecting duct ↑ $Na^+/K^+/2\ Cl^-$ transporter in thick ascending limb.
• Aldosterone	↓ blood volume (via A-II) ↑ plasma $[K^+]$	↑ Na^+ reabsorption ↑ K^+ secretion, ↑ H^+ secretion in distal tubule
• Angiotensin II	↓ blood volume (via rennin)	Contractino of efferent arteriole → ↑ GFR. ↑ Na^+ and HCO_3^- reabsorption in proximal tubule
• Atrial natriuretic peptide (ANP)	↑ ATRIAL PRESSURE	↓ Na+ reabsorption ↑ GFR
• PTH	↓ plasma $[Ca^{2+}]$	↑ Ca^{2+} reabsoption ↓ $(PO4)3^-$ reabsoprtion ↑ 1, 25 $(OH)^2$ vitamin D production

Pressures in Functional Nephron

(1) Arcuate artery = 100 mm Hg
(2) Afferent arteriole and glomerulus = 60 mm Hg
(3) Efferent arteriole = 18 mm Hg
(4) Peritubular capillary network and vasa recta = 13 mm Hg
(5) Venous end = 10 mm Hg
(6) Arcuate vein = 8 mm Hg
(7) Proximal tubule =18 mm Hg
(8) Distal tubule = 10 mm Hg
(9) Renal Interstitial fluid pressure = 6 mm Hg

Rate of Renal Blood Flow

Value

1100 ml/min/both kidneys

Renal Fraction

Percent of total cardiac output that passes through kidneys is called renal fraction.

Glomerulus

It is a network of branching and anastomosing capillaries present in Bowman's capsule. Blood enters glomerulus through afferent arteriole, and leaves thru efferent arteriole which offers resistance. So glomerulus is a high pressure bed.

Peritubular Capillary Network

It is an extensive network of capillaries around proximal tubule, distal tubule and collecting tubule in renal cortex. Blood enters it through efferent arteriole.

Vasa Recta

These are long and straight capillary loops that arise from deeper portion of peritubular capillary network and extend downward into medulla to lie side by side with loops of Henle.

Approximate Pressure and Vascular Resistances in the Circulation of a Normal Kidney

Vessel	Pressure in Vessel (mm Hg) Beginngin	End	Per Cent of Total Ranal Vasular Resistance
Renal artery	100	100	-0
Interlobar, arcuate, and interlobular arteries	-100	85	-16
Afferent arteriole	85	60	-26
Glomerular capillaries	60	59	-1
Efferent arteriole	59	18	-43
Peritubular capillaries	18	8	-10
Interlobar, interlobular and arcuate veins	8	4	-4
Renal vein	4	-4	-0

Micturation

Micturition is the process by which the urinary bladder empties when it becomes filled and involves two main steps: (1) the bladder fills progressively until the tension in its walls rises above a threshold level, which elicit the second step, and (2) a nervous reflex, called the micturition reflex, is activated and empties the bladder or, if this fails, at least causes a conscious desire to urinate.

Physiologic Anatomy and Nervous Connections of the Bladder

The ureters carry the urine from the renal pelvis to the bladder, where they pass obliquely through the bladder wall

before emptying into the bladder chamber. There are no major changes in the composition of the urine as it flows through the ureters into the bladder. Peristaltic contractions of the ureter, which are enhanced by parasympathetic stimulation, force the urine from the renal pelvis toward the bladder.

The urinary bladder is a smooth muscle chamber composed of two main parts:

(1) the body, which is the major portion of the bladder in which urine collects, and

(2) the neck, which is a funnel-shaped extension of the body that connects with the urethra

The smooth muscle of the bladder is called the detrusor muscle. When the fibers contract, they can increase the pressure of the bladder to 40 to 60 mm Hg and therefore play a major role in emptying the bladder. The bladder neck (posterior urethra) is composed of detrusor muscle interlaced with a large amount of elastic tissue. The muscle in this area is called the **internal sphincter;** its natural tone keeps the bladder from emptying until the pressure in the main part of the bladder rises above a critical threshold.

- *Beyond the posterior urethra, the urethra passes through the **urogenital diaphragm**, which contains a layer of muscle called the external sphincter of the bladder.*
- *This muscle is a voluntary skeletalmuscle and can be used consciously to prevent urination even when involuntary controls are attempting to empty the bladder.*
- *Beyond the posterior urethra, the urethra passes through the urogenital diaphragm, which contains a layer of muscle called the **external sphincter of the bladder.***
- *This muscle is a voluntary skeletalmuscle and can be used consciously to prevent urination even when involuntary controls are attempting to empty the bladder.*

Pelvic Nerves Provide the Principal Nervous

Coursing through the pelvic nerves, which connect with the spinal cord through the sacral plexus, are both sensory nerve fibers and motor nerve fibers. The sensory nerve fibers detect the stretch of the bladder wall and initiate reflexes that cause bladder emptying. The motor nerves transmitted to the pelvic nerves are parasympathetic fibers.

Micturition Reflex Is a Spinal Cord Reflex

The micturition reflex is a single complete cycle of *(1) a progressive and rapid increase in bladder pressure, (2) a period of sustained increase in bladder pressure, and (3) a return of the pressure to the basal tone of the bladder, as follows:*

• Sensory signals from the **bladder wall stretch** receptors are conducted to sacral segments of the spinal cord through the pelvic nerves and then **reflexively back** to the bladder through the parasympathetic nerves by way of the pelvic nerves.

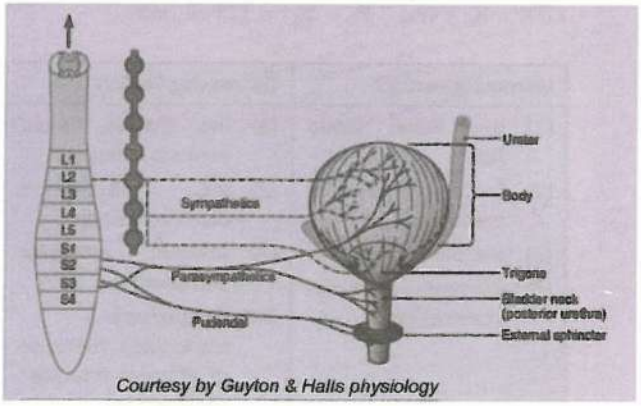
• Once the **micturition reflex is sufficiently powerful**, it causes another **reflex that passes through the pudendal nerves** to the external sphincter to inhibit it. If this inhibition is more potent than the voluntary constrictor signals to the external sphincter, urination occurs.

• The micturition reflex is an autonomic spinal cord reflex, but it can be **inhibited** or **facilitated by centers in the brain stem**, mainly the pons, and several centers in the cerebral cortex that are mainly excitatory.

Dynamics of Glomerular Filtration

Why Proteins Cannot Pass Through Glomerular Membrane

Although diameter of pores of glomerular membrane is 800A while diameter of plasma proteins is 600A, even then plasma proteins cannot pass thru glomerular membrane because -vely charged glomerular pores repel -vely charged plasma proteins, preventing them to appear in glomerular filtrate.



Courtesy by Guyton & Halls physiology

Glomerular Filtration Is the First Step in Urine Formation

Glomerular Membrane

Membrane of glomerular capillaries is called glomerular membrane.

Made up of

(1) Capillary endothelium having fenestra

(2) Basement membrane (negative charge Barrier) having large spaces

(3) Outer epithelial lining having slit-pores

Glomerular Filtrate

Fluid that filters through glomerulus into Bowman's space is called glomerular filtrate.

Composition

Glomerular filtrate is almost same as plasma but it has no RBC and 0.03% of proteins

Glomerular Pressure	Bowman's Capsule Pressure	Plasma Colloid Osmotic Pressure	Filtration Pressure
It promotes filtration of fluid thru glomerular mem. into Bowmans capsule.	It opposes filtration of fluid thru glomerular membrane into Bowman's capsule	It also opposes filtration of fluid thru glomerular membrane into Bowman's Capsule.	It is net pressure that forces fluid thru glomerular membrane into Bowman's capsule.
60 mm Hg.	18 mm Hg	32 mm Hg	It is equal to 60- (18+32) = 10 mm Hg

Glomerular Filtration Rate

Quantity of glomerular filtrate formed each min. in all nephrons of both kidneys is called glomerular filtration rate (GFR).

Formula

GFR = Filtration pressure x Filtration co- efficient.

Value (MCQs)

125m1/min or 180 lit/day (99% or 178.5 lit. reabsorbed)

The GFR can therefore be expressed as

$$\text{Net Filtration Pressure} = P_G - P_B - \pi_G = 10\,\text{mm Hg}$$

$$GFR = K_f \times (P_G - P_B - \pi_B) = 125\,\text{mL/min}$$

Increasing Factors	Decreasing Factors
(1) Inc. Renal Blood flow	(1) Inc. Plasma colloid osmotic pressure
(2) Inc. glomerular pressure	(2) Inc. Bowman's capsule pressure
(3) Inc. Blood pressure	(3) Afferent arteriolar constriction
(4) Efferent arteriolar constriction.	(4) Sympathetic stimulation (Because of afferent arteriolar constriction)

Hormones and Autacoids that Influence Glomerular Filtration Rate (GFR)

Homones and Autacoids that Influence Glomarular Flitration Rate (GFR)	
Hormone or Autacoid	Effect on GFR
Norepinephrine	↓
Epinephrine	↓
Endothelin	↓
Angiotensin II	↔ (prevents)
Endothelial-derived nitric oxide	↑
Prostaglandins	↑

Filtration Co-Efficient

GFR in both kidneys per mm Hg of filtration pressure is called filtration co-efficient.

Value

12.5 ml/min/mm Hg.

Glucose Filtered Through Glomerular Membrane Per Day

Value

180 gm/day (almost all is absorbed so that only traces of glucose appear in urine).

Juxta-Glomerular Complex

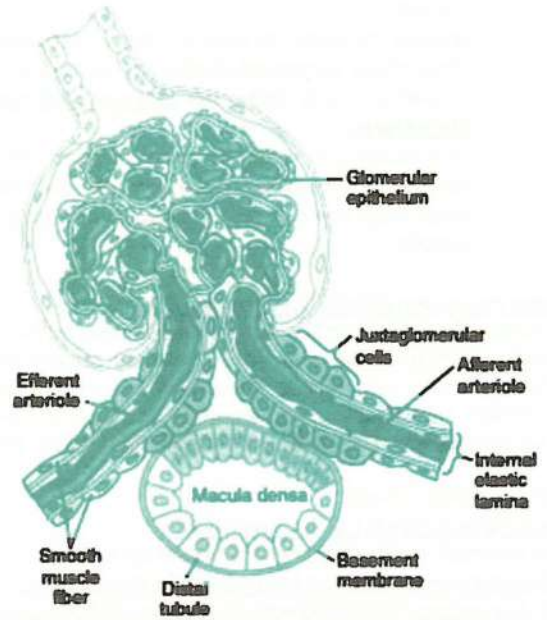
Its structure is as follows

(1) **Initial portion of distal tubule** passes in angle b/w afferent & efferent arterioles

(2) Epithelial cells of distal tubule that come in contact with afferent & efferent arterioles are more dense, called **"macula densa"**, & they secrete some substance into arterioles

(3) Smooth muscle cells of afferent & efferent arterioles that are in contact with macula densa are swollen & contain dark granules of inactive renin; these are called **"Juxta glomerular (JG) cells"**

(4) The whole complex of macula densa & JG cells is called juxta- glomerular complex



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Autoregulation of GFR

In normal kidneys, a fall in arterial pressure to as low as 75 mm Hg or a rise to as high as 160 mm Hg changes the GFR by only a few percentage points; this relative constancy of the GFR and renal blood flow is referred to as autoregulation

Why GFR is Autoregulated?

Because,

(1) If GRF is very slight → Fluid passes through tubule very slowly → all substances are reabsorbed → kidneys fail to eliminate essential waste products.

(2) If GRF is very high → fluid passes through tubule very rapidly → kidneys are unable to reabsorb substances of nutritional importance, e.g. glucose.

Mechanism of Autoregulation of GFR

GFR is autoregulated by "Tubuloglomerular feedback" which consists of two mechanisms, operating at the same time

Both of which depend on the special anatomic arrangement of the juxtaglomerular complex.

The juxtaglomerular complex consists of macula densa cells in the initial portion of the distal tubule and juxtaglomerular cells in the walls of the afferent and efferent arterioles. When blood pressure is decreased, delivery of sodium chloride is decreased to the macula densa cells, which are capable of sensing this change

(1) **Afferent Arteriolar Vasodilator Feedback Mechanism:**

(2) **Efferent Arteriolar Vasoconstrictor Feedback Mechanism:**

The decrease in sodium chloride concentration at the macula densa, in turn, causes two main effects:

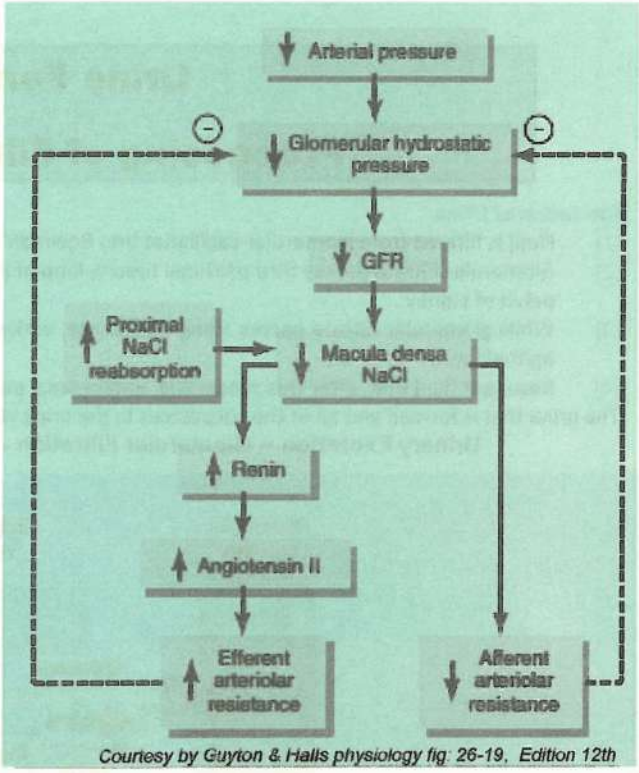
(1) a decrease in the resistance of the afferent arterioles, which increases glomerular hydrostatic pressure and the GFR toward normal levels, and

(2) an increase in renin release from the juxtaglomerular cells of the afferent and efferent arterioles, which causes increased angiotensin II formation.

Myogenic Mechanism Contributes to Autoregulation of Renal Blood Flow and the GFR.

This mechanism refers to the intrinsic capability of blood vessels to constrict when blood pressure is increased. The constriction prevents the vessel from being overstretched and, by increasing vascular resistance, helps prevent excessive increases in renal blood flow and the GFR when blood pressure rises. Conversely, with decreased blood pressure, the myogenic mechanism contributes to decreased vascular resistance.

Macula densa feedback mechanism for autoregulation of glomerular hydrostatic pressure and GFR during decreased renal arterial pressure



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Autoregulation of Renal Blood Flow

Renal blood flow is kept constant at 1100 ml/min despite wide variations in arterial pressure; this is called autoregulation of renal blood flow

Mechanism

Two,

(1) **Afferent Arteriolar Vasodilator Mechanism** When renal blood flow decrease → Feedback effect occurs at juxta-glomerular complex → Afferent arteriole dilates → Renal blood flow inc. to normal.

(2) **Myogenic Mechanism** When arterial pressure increase Walls of afferent arterioles are stretched → Secondary contraction of afferent arterioles → Renal blood flow decrease to normal.

Pressure Diuresis

Increase in urinary output due to increase in glomerular filtration caused by increased arterial pressure, is called pressure diuresis

Effect of Sympathetic Stimulation on Renal Blood Flow & GFR

(1) Stight-to-moderate sympathetic stimulation have only mild effect in decreasing renal blood flow & GFR.

(2) Strong acute sympathetic stimulation constricts renal arterioles & decreases renal blood flow, GFR & urine output.

(3) If sympathetic stimulation is continued, renal blood flow, GFR & urine output come to normal within 20-to-30 min

Urine Formation :
Processing of Filtrate in Tubules

Formation of Urine

(1) Fluid is filtered from glomerular capillaries into Bowman's capsule; this fluid is called "glomerular filtrate"

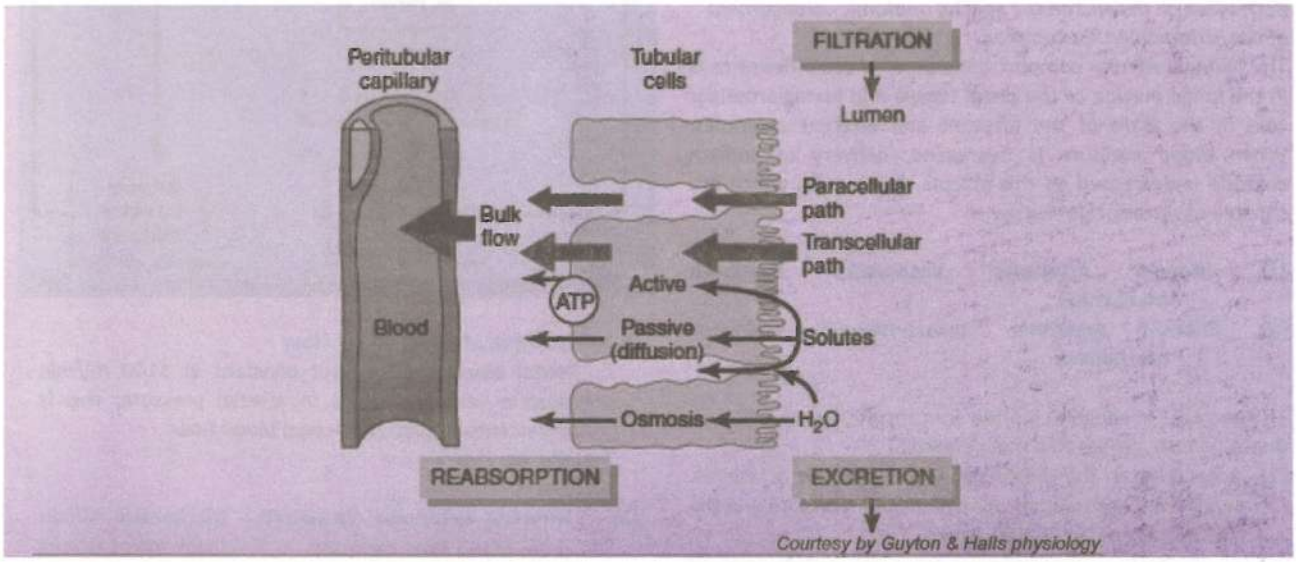
(2) Glomerular filtrate passes thru proximal tubule, loop of Henle, distal tubule, cortical collecting duct & collecting duct into pelvis of kidney

(3) While glomerular filtrate passes along this course, various substances are selectively reabsorbed or secreted by tubular epithelium

(4) Resultant fluid that, after this processing, enters renal pelvis, is called urine

The urine that is formed and all of the substances in the urine represent the sum of three basic renal processes.

Urinary Excretion = Glomerular Filtration - Tubular Reabsorption + Tubular Secretion



Filtration, Reabsorption, and Excretion Rates of Various Substances by the Kidneys

Substance	Amount Filtered	Amount Reabsorbed	Amount Excreted	% of Filtered Load Resorbed
Glucose (g/day)	180	180	0	100
Bicarbonate (mmol/day)	4320	4318	2	>99.9
Sodium (mmol/day)	25,560	25,410	150	99.4
Chloride (mmol/day)	19,440	19,260	180	99.1
Urea (g/day)	46.8	23.4	23.4	50
Creatinine (g/day)	1.8	0	1.8	0

Basic Mechanisms For Transport Through Tubular Mem.

(A) **Active Transport**

(1) Primary active absorption eg, Na^+, Ca^{++}

(2) Secondary active absorption eg, glucose, amino acid

(3) Secondary active urate ions

(B) **Passive Transport**

(1) Osmosis eg, water

(2) Diffusion eg, Cl^- ion & urea

Primary Active Transport of Na^+

Step-1

$Na,^+$ K^+ -ATPase system in basal & lateral surfaces of tubular epithelial cells of proximal tubule transports 3 Na^+ ions out of cell & 2 K^+ ions into cell (2 K^+ diffuse back out of cell into interstitium due to inc. permeability) ➔ Creates -70 mV inside epithelial cells

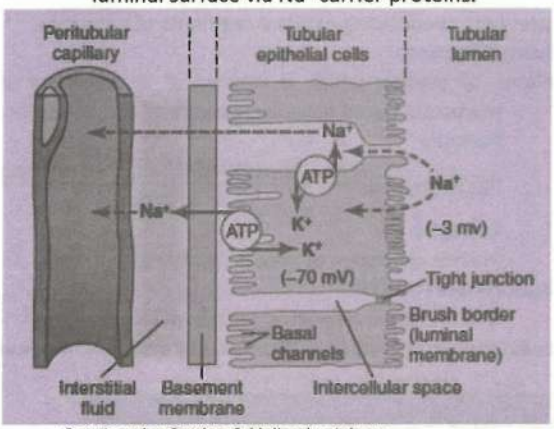
Step-2

Na^+ ions are passively transported through brushy borber of cell's luminal surface from tubular lumen into interior of cell due to

(1) Electrical gradient (ie, -70 mV inside the cell & -3 mV in tubular lumen)

(2) Conc. Gradient (ie, dec. Na^+ conc. inside the cell & increase Na^+ conc. in tubular lumen)

(3) Facilitated diffusion of Na^+ (along with other substances e.g. glucose & amino acids) on luminal surface via Na^+ carrier proteins.



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Mechanism For Absorption of Proteins

(1) Protein from tubular lumen is absorbed through brush border of proximal tubular epithelium by "pinocytosis".

(2) Inside proximal tubular epitheilal cells proteins is digested into its constituent amino acids

(3) Amino acids are absorbed into interstitial fluid by facilitated diffusion through basal & lateral surfaces

Mechanism For Absorption of Bicarbonate Ions

- H^+ ions are secreted into tubular lumen HCO_3 ions combine with H^+ in tubular lumen to form H_2CO_3
- H_2CO_3 dissociates into H_2O & CO_2
- CO_2, being lipid soluble diffuses thru tubular epithelium into interstitial fluid
- In interstitial fluid CO_2 combines with H_2O to form H_2CO_3 that dissociates into H^+ & HCO_3- ions

Substances Reabsorbed in Proximal Tubule

Note

65% of all reabsorption and secretion that occurs in tubullar system takes place in proximal tubule.

(1) Actively Reabsorbed Na^+, K^+, glucose, amino acids, uric acid, vit. C and lactic acid.

(2) Passively Reabsorbed Cl^-, H_2O, CO_2, urea and proteins.

Substances Secreted in Proximal Tubule

Actively secreted H^+, organic acids and bases.

Substances Transported in Loop of Henle

(1) Descending Portion of Thin Segment H_2O is passively reabsorbed

(2) Ascending Portion of Thin Segment Urea is passively secreted

(3) Thick Segment K^+ and Na+ are actively reabsorbed; Cl^- is reabsorbed due to potential difference.

Substances Reabsorbed in Diluting Segment

(1) Na^+ reabsorbed under influence of aldosterone

(2) Cl^- reabsorbed due to potential difference

(3) H_2O reabsorbed under influence of ADH.

Substances Secreted in Late Distal Tubule And Cortical Collecting Tubule

(1) NH_3

(2) K^+ and H^+ are secreted in exchange for Na+

Substances Transported in Collecting Duct

(1) H_2O reabsorbed under influence of ADH.

(2) Urea reabsorbed due to conccentration gradient caused by H_2O absorption.

(3) H^+ secreted against high concentration gradient for acid-base balance

Transport of Inulin and PAH

(1) Inulin (a polysaccharide = fructose polymer); neither reabsorbed nor secreted in tubule

(2) PAH (para amino hippuric acid); not reabsorbed, but secreted into lumen of tubule.

Obligatory Volume

Minimum volume of H_2O required by solid constituents of urine for their excretion, is called obligatory vol.

Obligatory Reabsorption of H_2O

65% reabsorption of H_2O that takes place in proximal tubule is called obligatory reabsorption of H_2O.

Facultative Reabsorption of H_2O

Reabsorption of H_2O that takes place in late distal tubule and cortical collecting tubule under influence of ADH, is called facultative reabsorption of H_2O.

Tubular Load

Total amount of a substance that filters through glomerular membrane into tubules each minute is called its tubular load.

Formula

TL= plasma clearance X GFR

Examples

Tubular loads of

(1) Glucose =125 mg/min

(2) Na = 18 mEq/min

(3) Urea = 33 mg/min

Tubular Transport Maximum (Tm)

Maximum rate of reabsorption of an actively reabsorbed substance, is called tubular transport maximum.

Examples

Tm for

(1) Glucose = 320 mg/min

(2) Phosphate = 0.1 mmole/min

Hormones that Regulate Tubular Reabsorption	
Hormone	Site of Action
Aldosterone	Collecting tubule
Angiotensin II	Proximal tubule, thick ascending loop of Henle/distal tubule
ADH	Distal tubule/collecting tubule & duct
ANT	Distal tubule/collecting tubule & duct
PTH	Proximal tubule, thick ascending loop of Henle/distal tubule

Threshold Concentration in Plasma

Every substance that has a tubular transport maximum has also a threshold concentration in plasma below which none of it appears in urine and above which progressively larger quantities appear in urine.

Example

Threshold concentration of glucose in plasma = 180 mg%

Gradient-Time Transport

It is a transport whose rate is determined by

(1) Concentration gradient of substance across mem.

(2) Time that the fluid containing substances remains within tubules

Examples

(1) Substances that are reabsorbed by diffusion

(2) Substances that are "rapidly" actively transported, eg Na+ absorption in proximal tubule

Note

In proximal tubule such substance do not have a transport maximum.

Glomerulotubular Balance in Proximal Tubule

It means that under normal conditions a constant percentage (65%) of Na. & H_2O is reabsorbed in proximal tubule regardless of GFR.

It prevents overloading of distal segments of nephrons.

Plasma Clearance

Volume of plasma which is cleared of a substance each minute, is called plasma clearance of that substance.

Formula

$$PC\ (ml/min) = \frac{urine.flow(ml/min)..\ x\ ..\ conc.\ inurine}{(conc.\ in\ plasma)}$$

Example

Plasma clearance of urea is 70 ml/min

Measurement of GFR

GFR = Plasma clearance per min of inulin;

because inulin is neither reabsorbed nor secreted in tubule.

Control of ECF Osmolality & Na^+ Concentration

Mechanism For Excreting Dilute Urine

When ECF osmolality decreases and ADH secretion by posterior pituitary gland decrease the Water reabsorption in late distal tubule, cortical collecting tubule and collecting duct, decrease ➔ More water excreted in urine (dilute urine)

ECF osmolality increase to normal.

Mechanism For Excreting Concentration Urine

Counter-Current Mechanism

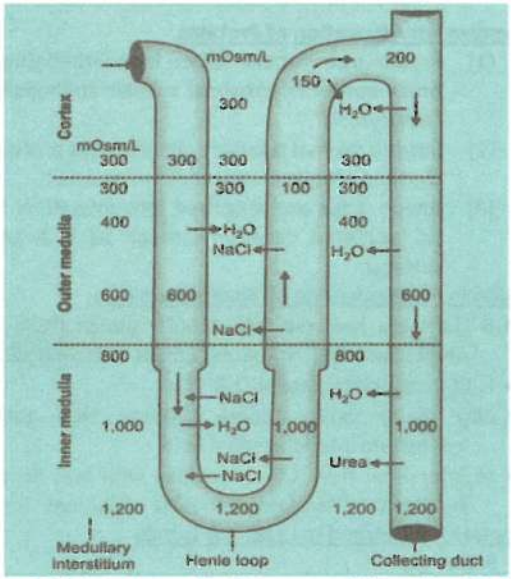
3 Steps

(1) Creating Hyperosmoiality in Medullary Interstitial Fluid By

(a) Active transport of Na^+ and Cl^- into medullary interstitium from thick portion of ascending limb of loop of Henle

(b) Active transport of Na^+ and Cl^- into medullary interstitium from collecting duct

(c) In presence of ADH water is reabsorbed from collecting duct, thereby increasing urea concentration in collecting duct. So, urea diffuses from collecting duct into medullary interstitium due to concentrated gradient.



(2) Maintenance of Hyperosmolality in Medullary Interstitium By

(a) Medullary blood flow is very slow; therefore, removal of solutes from medullary interstitium by blood is minimized.

(b) Vasa recta functions as counter-current exchange mechanism (***which is defined as a mechanism in which fluid flows through a U-tube so that fluid and solutes can exchange b/w two arms***). As blood flows down the descending limb of vasa recta, it takes

up solutes from medullary interstitium, but as blood flows up the ascending limb of vasa recta, it gives up solutes to medullary interstitium. Thus **counter-current exchange mechanism** of vasa recta maintains hyperosmolality in medullary interstitium.

(3) Enhancement of Medullary Hyperosmolality

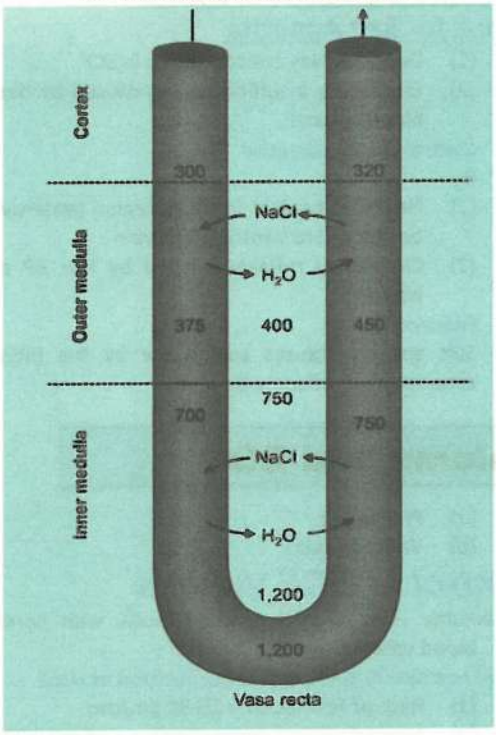
Medullary hyperosmolality is further enhanced by" countercurrent Multiplier" of loop of Henle

(a) Na, & Cl^- from thick ascending limb diffuses into medullary interstitium

(b) From medullary interstitium Na^+ & Cl diffuse into thin descending limb of loop of Henle & descending limb of vasa recta & are carried down to tip of papilla

(c) Much of Na+ & Cl^- from tips of loop of Henle & vasa recta diffuse into papillary interstitium, thereby enhancing its osmolality

(d) Remaining Na+ & Cl^- is carried again back up the ascending limb of loop of Henle, & above steps are repeated, thus "multiplying" conc. in medullary (papillary) interstitium.



(4) Formation of Concentrated Urine

In presence of ADH, late distal tubule, cortical collecting tubule and collecting duct become permeable to water. So, water is reabsorbed by osmosis from these tubules into medullary interstitium due to hyperosmolality (osmolality osmotic pressure sucking force). Thus urine contains less water and becomes concentrated.

Osmolar Clearance

Volume of plasma cleared per minute to osmoles of a substance is called osmolar clearance.

Free Water Clearance

Volume of plasma cleared per minute of free water is called free water clearance.

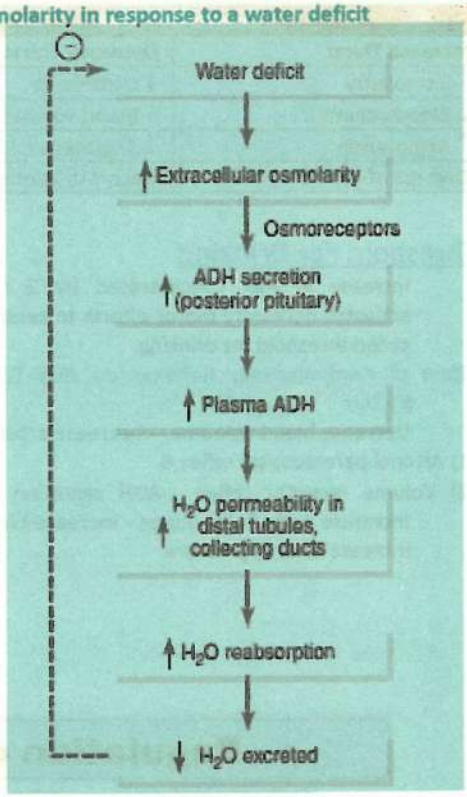
Normal ECF Na+ Concentrated & Osmolality

(1) Normal ECF Na+ Conc. = 142 mEq/Lit.

(2) Normal ECF Osmolality = 300 mOsm/Lit

Na+ determines over 90% of ECF osmolality. Therefore, they are regulated at the same time.

Osmoreceptor → Antidiuretic Hormone (ADH) Feedback Mechanism for Regulating Extracellular fluid Osmolarity in response to a water deficit



Courtesy by Guyton & Halls physiology

Regulation of ADH Secretion	
Increase ADH	**Decresae ADH**
↑ Plasma osmolarity	↓ Plasma osmolarity
↓ Blood volume	↑ Blood volume
↓ Blood pressure	↑ Blood prssure
Nausea Hypoxia	
Drugs: Morphone Nicotine Cyclophosphamide	Drugs: Clonidine (antihypertensive drug) Haloperidol (dopamine blocker)

Thirst

Conscious desire for water is called thirst.

Thirst Center

It is a small area located anteralaterally in the preoptic nucleus.

Stimuli for Thirst

(1) Increase ECF Na+
(2) Decreaes ICF K^+
(3) Angiotensin II
(4) Hemorrhage (ie, fluid loss)
(5) Decrease cardiac output
(6) Dry mouth

Control of Thirst	
Increase Thirst	**Decrease Thirst**
↑ Osmolarity	↓ Osmolarity
↓ Blood volume	↑ Blood volume
↑ Angiotensin	↓ Angiotensin II
Dryness of mouth	Gastric distention

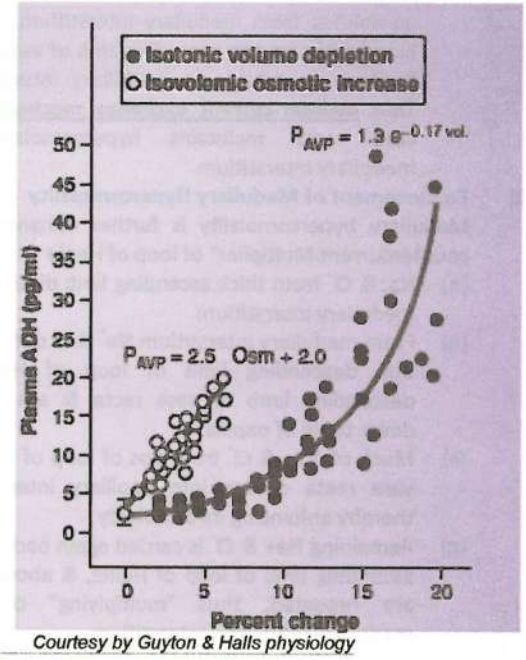
Threshold For Drinking

Increase in Na+ concentrated by 2 mEq/Lit that activates necessary motor efforts to cause drinking, is called threshold for drinking.

Effect of Cardiovascular Reflexes on ADH-Thirst Control System

Decrease blood voloume -- Decrease arterial pressure

(1) Arterial baroreceptor reflex &
(2) Volume receptor reflex - ADH secretion & thirst → Increrase body fluid volume - Increase blood volume - Increase arterial pressure



Courtesy by Guyton & Halls physiology

Stimuli for Salt Appetite

(1) Decrease Na+ concentration in ECF
(2) Circulatory insufficiency, eg caused by decrease blood volume

Control of Salt Appetite

By
(1) Neuronal centers in AV3V region (anteroventral border of 3rd ventricle) of brain
(2) Circulatory reflexes elicited by low BP or low blood vol.

Function

Salt appetite causes salt intake by the individual, especially in Addison's disease

Regulation of Blood Volume and ECF

Basic Mechanism For Blood Vol. Control (Renal -Body Fluid Feedback Mech.)

(1) When blood volume Increase ➔ Cardiac output increase ➔ Arterial pressure increase ➔ Increase loss of Na^+ & H_2O in urine (ie pressure natriuresis & pressure diuresis) - Increase salt & fluid loss from body Blood volume Decrease to normal.
(2) When blood volume Decrease ➔ All process in opposite direction ➔ Blood vol. increase to normal

Conditions in Which Blood Volume Increase.

(1) Heart diseases, eg
(a) Myocardial failure
(b) Valvular heart disease
(c) Congenital heart diseases
(2) Polycythemia
(3) Increased capacity of circulation, eg
(a) Pregnency
(b) Varicose veins

Control of ECF Volume

ECF volume is controlled simultaneously with control of blood volume

Rate of Formation & Plasma Concentration of Urea

(1) Rate of Formation = 25-30 gm/day
(2) Normal plasma concentration = 26 mg/100 ml.

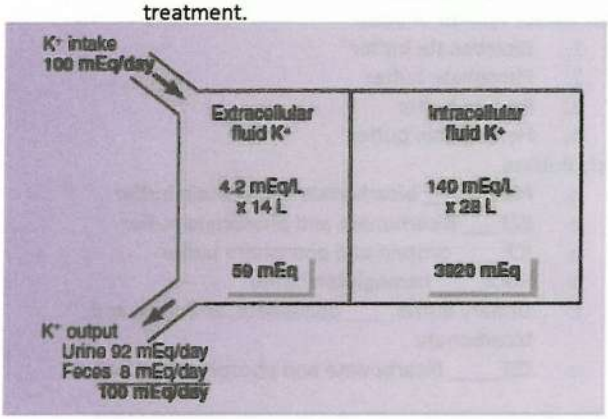
Regulation of urea excretion

By,
(1) Plasma urea conc. (directly prop.)
(2) GFR (directly prop.)

Factors that inc. K^+ excretion

(1) Increase ECF K^+ concentration
(2) Aldosterone
(3) Decrease H^+ concentration (H^+ competes with K^+ for secretion in exchange for Na+)

(4) Increase distal tubular flow rate, as occurs with vol. expansion, high Na+ intake, or diuretic treatment.



Normal Potassium intake distributaion of Potassium in the body fluids and Potassium output from the body

Factors that can Alter Potassium Distriubtion between the Intr-and Extracellular Fluid	
Factors that shift K^+ into Cells (decease Extracellular $[K^+]$	Factors that shift K^+ out of Cells (increase Extracellular $(K^+]$
• Insulin • Aldosterone • β-adrenergic stimulation • Alkalosis	• Insulin deficiency (diabetes mellitus) • Aldosterone deficiency (Addison's disease) • β-adrenergic blockade • Acidosis • Cell lysis • Strenuous exercise • Increased extracellular fluid osmolarity

Effects of Primary Aldosteronism & Addison's Disease on ECF K^+ Conc.

(A) Effect of Primary Aldosteronism

In primary aldosteronism, excess aldosterone is secreted by tumor of zona glomerulosa of adrenal gland Increase K^+ excretion Hyokalemia ➔ Paralysis due to failure of nerve transmission

(B) Effect of Addison's Disease In Addison's disease, aldosterone is not secreted due to destruction of adrenal glands ➔ Decrease K^+ excretion Hyperkalemia Cardiac arrest or fibrillation Death

Regulation of ECF Ca^{++} Conc

Ca^{++} concentration Decrease ➔ Parathyroid hormone secreted by parathyroid gland " Absorption of Ca^{++} from bones, kidneys and GIT increase ➔ ECF Ca^{++} concentration increase to normal.

Factors that Alter Renal Calcium Excretion	
↓ Calcium Excretion	↑ Calcium Excretion
↑ Psarathyroid hormone (PTH)	↓ PTH
↓ Extracellular fluid volume	↑ Extracellular fluid volume
↓ Blood pressure	↑ Blood pressure
↑ Plasma phosphate	↓ Plasma phosphate
Metabolic acidosis	Metabolic alkalosis
Vitamin D_3	

Acidosis

Inc. H^+ ion concentration or decrease pH is called acidosis (ie pH below 7.35)

Base

Proton acceptor or a substance that combines with H^+ ion to remove them from a solution, is called base

Alkali

Combination of alkaline metal (Na, K, etc.) with a highly basic ion (eg OR) is called alkali.

Alkalosis

Decrease H^+ ion concentration or inc. pH is called alkalosis (ie pH above 7.45)

pH

Negative log of H^+ ion conc. is called pH.

Formula

$pH = -\log (H^+)$

pH of Blood (7.4 ± 0.05)

(a) pH of arterial blood = 7.4

(b) pH of venous blood = 7.35 (due to CO_2 that forms H_2CO_3)

Intracellular pH is 7.0 due to

(a) Metabolism that causes formation of H_2CO_3

(b) Poor blood flow that causes acid accumulation

PH and H^+ Concentration of Body Fluids		
	H^+ Concentration (mEq/L	PH
Extracellular fluid Arterial blood Venous blood Interstitial fluid	 4.0×10^{-5} 4.5×10^{-5} 4.5×10^{-5}	 7.30 7.35 7.35
Intracellular fluid	1×10^{-3} to $\rightarrow \times 10^{-3}$	6.0 to 7.4
Urine	3×10^{-2} to 1×10^{-5}	4.5 to 8.0
Gastric HCl	160	0.8

Sytems for Regulation of Acid Base Balance

Three systems

(1) Acid-base buffer system

(2) Respiratory system

(3) Renal system

Acid-Base Buffer System For Regulation of Acid-Base Balance

An acid-base buffer system is a solution of weak acid and salt of weak acid or weak base and salt of weak base, which prevents marked changes in H^+ conc. (pH) when a strong acid or base is added to the solution

Henderson-Hasselbalch Equation

It is an equation to determine pH of a buffer system

pH = pK + Log Base/Acid

A buffer may be defined as a solution which **resists the change in pH** which might be expected to occur upon the addition of acid or base to the solution. Buffers consist of mixtures of weak acids and their corresponding salts, alternatively, weak bases and their salts.

Buffering Power

Ability of an add-base buffer system to prevent acidosis or alkalosis, is called buffering power.

Note

(1) Buffering power is greatest when pH is equal to pK

(2) Buffering power is directly proportional to conc. of buffer substance

Basic buffer system of body

1. Bicarbonate buffer
2. Phosphate buffer
3. Protein buffer
4. Hemoglobin buffer

Body Buffers

- Plasma ___ bicarbonate and protein buffer
- ECF___ Bicarbonate and phosphate buffer
- ICF____ protein and phosphate buffer
- RBCs____ hemoglobin buffer
- Urinary buffer____ phosphate, ammonia and bicarbonate
- CSF____ Bicarbonate and phosphate buffer

Regulation

	pH	H^+	PCO_2	HCO_3^-	
Normal	7.4	40mEq/L	40mm Hg	24 mEq/L	
Respiratory Acidosis	↓	↑	↑↑	↑	COPD, Airway obstruction, asthma, cardiac arrest
Respiratory Alkalosis	↑	↓	↓↓	↓	High altitude, hyperventilation
Metabolic Acidosis	↓	↑	↓	↓↓	Diabetic ketoacidosis, diarrhea, lactic acidosis, methanol poisoning
Metabolic Alkalosis	↑	↓	↑	↑↑	Vomiting, K deficiency, intake of diuretics and steroids

Compensation

Metabolic Acidosis

- Hyperventilation of lungs that **cause decrease in pCO_2**
- In respiratory acidosis pH will be low **cause fast and shallow breathing**
- In renal compensation pH will be low that will leads to increase H-ions excretion as H_2PO_4 and NH_4^+ that **cause HCO_3^- reabsorption**

Respiratory Acidosis

- HCO_3^- retained by kidney cause an increase in alkali reservoir
- In renal compensation, increase in excretion of H-ions (as that of H_2PO_4 and NH_4^+) **cause increase in reabsorption of HCO_3^-**

Acid	Conjugate Base	Base/Acid	Ratio	pKa	Organ
H_2CO_3 <=>	$H^+ + HCO_3^-$	$\frac{HCO_3^-}{H_2CO_3}$	$\frac{20}{1}$	6.1	lungs
HPr	H + Pr-			6.0—8.0	Blood
H_2PO_4 <=>	$H^+ + HPO_4^-$	$\frac{HPO_4^{2-}}{H_2PO_4}$	$\frac{4}{1}$	7.2	Kidney
NH4 <=>	$H^+ + NH_3$			9.3	Kidney
HHb <=>	$H^+ + Hb^-$			7.3	Lungs

Mechanism of action of bicarbonates

It consist of a solution of H_2CO_3 (weak acid) and NaHCO3 (salt of weak acid). Its pK is 6.1.

a) When strong acid like HCl is added, it combines with salt of weak acid and forms weak acid, thereby preventing rise in H^+ ions concentration(acidosis)

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

b) When strong base like NaOH is added, it combines with weak acid and forms weak base, thereby preventing fall in H^+ ions concentration(alkalosis)

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

Bicarbonate buffer system is most powerful system in the body.

Isohydric Principle

Whenever any condition causes H^+ ion conc. to change, it causes balance of all buffer systems to change at the same time, because all buffer systems work together. This phenomenon is called isohydric principle.

ACID—BASE BALANCE

- pH of blood 7.35 – 7.45
- pH of RBCs 7.2

Maintenance of pH

Chemical buffering system

a) **Bicarbonate buffering**

$H_2CO_3 \iff H^+ + HCO_3^-$

$\frac{HCO_3^-}{H_2CO_3} = \frac{20}{1}$ hence HCO_3^- is greater in body than carbonic acid, this is referred as alkali reservoir.its pK is 6.1

b) **Phosphate buffering**

it works as intracellular buffering for body e.g. NaH_2PO4. Its pK is 6.8

c) **Protein buffering**

it function only 2% of the total buffering. Its pK is 7.4. It consist of intracellular and plasma protein especially hemoglobin in RBCs.

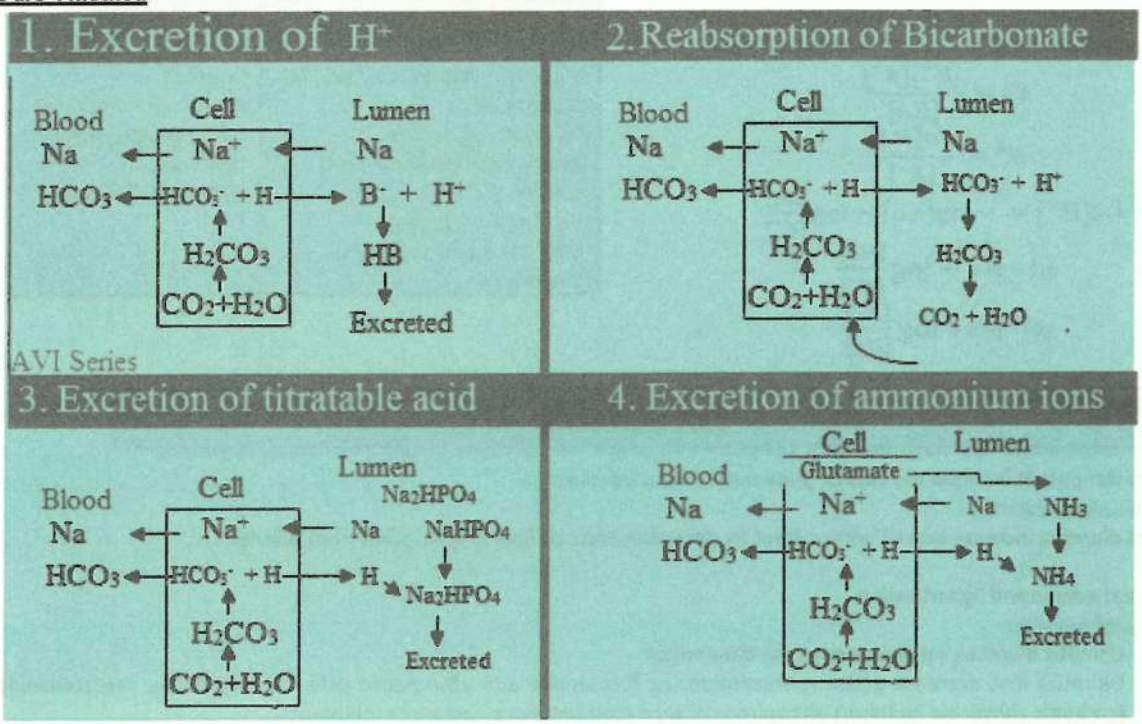
pH and pK

pH is -log of H+ concentration, Normal pH of blood plasma is 7.35 to 7.45

- Increase in H+ , pH will be below 7.35 cause acidosis
- Decrease in H+ , pH will be above 7.45 cause alkalosis

$$pH \propto log\frac{1}{H^+} = -\log[H^+]$$

There are 4 method



Measuring of pH

1. Litmus paper
2. Chemical indicators
3. pH meter

Sites	pH
Blood	7.4 – 7.2
Gastric juice	2.0
Pancreatic juice	8.0
Saliva	6.8
Urine	4.8

Respiratory Mechanism

Regulation of pH by respiratory mechanism is maintained by regulation of H_2CO_3 in blood

$$H_2CO_3 \xleftrightarrow{\text{Carbonic anhydrase}} H_2O + CO_2 \text{ (expired by lungs)}$$

Respiratory center is medulla oblongata and is very sensitive to in pH.

Renal Mechanism

Regulation of pH by renal mechanism is regulated by maintaining alkali reservoir beside excreting or reabsorbing acidic or basic substances.

pH Scale

Scale use to measure pH of a substance.

pH of solution whose H^+-concentration is 3.2x10-4 mol/L

PH = -log $[H^+]$

pH = -log (3.2×10^{-4})

pH = -log (3.2) – log (10^{-4})

pH = - 0.5 – (-4)

pH = 3.5

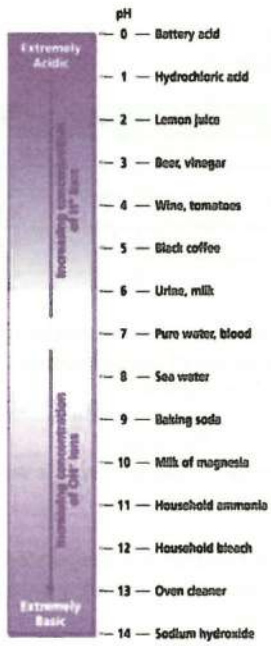
pH of 0.1M HCl

PH = -log $[H^+]$

pH = -log (10^{-1})

pH = - (-1)

pH = 1



$$HA \Leftrightarrow H + A^-$$

HA is weak acid and H is a proton form the conjugate Dissociation constant of acid (Ka) is a constant value also known as ionization constant.

$$Ka = \frac{[H^+][A^-]}{[HA]}$$

$$H^+ = \frac{Ka[HA]}{[A^-]}$$

$$-\log[H^+] = -\log[Ka] - \log\frac{[HA]}{[A^-]}$$

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

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

$$pH = pKa + \log\frac{Base}{Acid}$$

we obtain *Henderson – Hasselbach* equation

Isoelectric point

It is a pH at which an amino acid is electrically neutral, that is in which sum of positive charges is equal to negative charges.

Importance of equation ➔ calculate pH of buffer solution. Buffer solution of required pH can be prepared.

Anion Gap: difference between primary measured cations (Na, K) and primary measured anions (Cl^-, HCO_3^-). It respresents the concentration of all the unmeasured anions in plasma. Negatively charged proteins are calculated by anion gap, normal Anion gap is 8 to 16mmol/L If elevated, may be due to:

- Methanol
- Uremia (chronic renal failure)
- Diabetic ketoacidosis
- Paraldehyde or phenformin
- Iron tablets or INH (isoniazid)
- Lactic acidosis (CN-, CO, shock)
- Ethanol or Ethylene glycol
- Salicylates.

Metabolic Acidosis Associated with Normal or Increaesd Plasma Anion Gap	
Increaesd Anion Gap (Normochloremia)	**Normal Anion Gap (Hyperchloremia)**
Diabetic mellitus (ketoacidosis) Lactic acidosis Chronic renal failure Aspirin (acetylsalicylic acid) poisoning Methanol poisoning Ethylene glycol poisoning Starvation	Diarrhea Renal tubular acidosis Carbonic aphydrase inhibitors Addison's disease

Diuretics

A substance that increase the rate of urine output is called diuretic.

Mechanism of Action

Most diuretics increase rate of urine output by decreasing rate of fluid reabsorption from tubules.

Use

to treat edema and hypertension

Types of diuretics

(1) Osmotic diuretics, eg urea, sucrose and mannitol

(2) Diuretics that decrease active reabsorption, eg furosemide and ethacryanic acid, chlorothiazide, acetazolamide (carbonic anhydrase inhibitor) and spironolactone (competitive aldosterone inhibitor)

Classes of Diuretics, Their Mechansims of Action, and Tubular Sites of Action		
Class of Diuretic	Mechanism of Action	Tubular Site of Action
Osmotic diuretics (mannitol)	Inhibit water and solute reabsorption by increasing osmolarity of tubular fluid	Mainly proximal tubules
Loop diuretics (furosemide, bumetanide)	Inhibit Na+-K+-Cl- co-transport in luminal membrane	Thick ascending loop of Henle

Thiazide diuretics (hydrochlorothiazide, chlorthalidone)	Inhibit Na+-Cl- co-transport in luminal membrane	Early distal tubules
Carbonic anhydrase inhibitors (acetazolamide)	Inhibit H+ secretion and HCO3- reabsorption, which reduces Na+ reabsorption	Proximal tubules
Aldosterone antagonists (spironolactone, eplerenone)	Inhibit action of aldosterone on tubular receptor, decrease Na+ reabsorption, and decrease K+ secretion	Collecting tubules ti
Sodium channel blockers (triameterene, amiloride)	Block entry of Na+ into Na+ channels of luminal membrane decrease Na+ reabsorption, and decrease K+ secretion	Collecting tubules

Renal Pathology

Nephritis

Inflammation of kidney (either glomerulus, tubule or interstitial renal tissue) is called nephritis.

Nephrosis

Purely degenerative lesion of renal tubules, is called nephrosis.

Acute Renal Failure or Shutdown

In this kidneys suddenly stop working entirely.

Causes

(1) Acute glomerulonephritis
(2) Tubular necrosis
(3) Transfusion reaction

Some Causes of Prerenal Acute Renal Failure
Intravascular volume depletion
Hemorrhage (trauma, surgery, postpartum, gastrointestinal)
Diarrhea or vomiting
Burns
Cardiac Failure
Myocardial infarction
Valvular damage
Peripheral vasodilation and resultant hypotension
Anaphylactic shock
Anesthesia
Sepsis, severe infections
Primary renal hemodynamic abnormalities
Renal artery stenosis, embolism, or thrombosis of renal artery or vein

Some Causes of Intrarenal Acute Renal Failure
Small vessel and/or glomerular injury
Vasculitis (polyarteritis nodosa)
Cholesterol emboli
Malignant hypertension
Acute glomerulonephritis
Tubular epithelial injury (tubular necrosis)
Acute tubular necrosis due to ischemia
Acute tubular necrosis due to toxins (heavy metals ethylene glycol, insecticides, poison mushrooms carbon tetrachloride)
Renal interstitial injury
Acute pyelonephritis
Acute allergic interstitial nephritis

Glomerulonephritis

Acute Glomerulonephritis	Chronic Glomerulonephritis
It means acute inflammation of glomerulus.	It means acute inflammation of glomerulus lastingfor months
Streptococcal sore throat or tonsillitis → Antibodies against streptococcal antigen → Antigen-antibody reaction Insoluble immune complex Entrapped in glomeruli → Cells of glomeruli proliferate and WBCs entrapped in glomeruli → Inflammation of glomeruli Glomeruli blocked or become excessively permeable and RBCs leak into glomerular filtrate → cute renal failure	In chronic glomerulonephritis insoluble antigen antibody complex plugs glomeruli → Inflammation of glomeruli Glomerular membrane becomes progressively thickened and invaded by fibrous tissue Glomeruli replaced by fibrous tissue and lose their function for ever → Chronic renal failure

Tubular Necrosis

It means destruction of epithelial cells of renal tubule.

Causes

(1) Renal poisons (eg CCl_4, → Nephrotoxic effects on tubular epithelial cells Epithelial cells die and slough away from basement membrane and plug renal tubules - Acute renal failure.

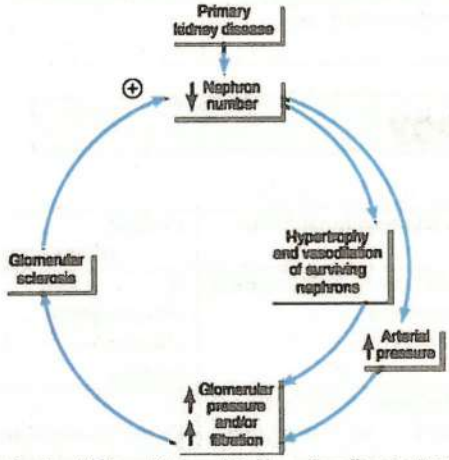
(2) Severe acute renal ischemia due to circulatory shock Lack of adequate nutrition → Tubular epithelial cells die and slough away from basement membrane and plug renal tubules Acute renal failure.

Transfusion Reaction

- Hemolysis of RBCs
- Release of Hb into plasma
- Hb passes out into glomerular filtrate
- tubular load of Hb becomes greater than can be reabsorbed by proximal tubules
- Excess Hb precipitates in tubules thereby blocking them Acute renal failure.

Renal Failure

Effects of Acute Renal Failure	Chronic Renal Failure
(1) Salt and water retention (2) Hypertension (3) Edema (4) Uremia (5) Acidosis	In this progressively more nephrons are destroyed until kidneys stop working



Vicious Cycle of Chronic Renal Failure Leading to End-Stage Renal Disease

Some Causes of Chronic Renal Failure
Metabolic disorders
Diabetes mellitus
Obesity
Amyloidosis
Hypertension
Renal vascular disorders
Atherosclerosis
Nephrosclerosis-hypertension
Immunologic disorders
Glomerulonephritis
Polyarteritis nodosa
Lupus erythematosus
Infections
Pyelonephritis
Tuberculosis
Primary tubular disorders
Nephrotoxins (analgesics, heavy metals)
Urinary tract obstruction
Renal calculi
Hypertrophy of prostate
Urethral constriction
Congenital disorders
Polycystic disease
Congenital absence of kidney tissue (renal hypoplasia)

Most common Causes of End Stage Renal Disease (ESRD)	
Cause	Percentage of Total ESRD patients
Dabetes mellitus	44
Hypertension	26
Glomerulonephritis	8
Polycystic kidney disease	2
Other unknown	20

Pyelonephritis

It means inflammation of renal pelvis, extending into glomeruli and tubules.

Cause

Colon bacilli due to fecal contamination of urinary tract

Renal Ischemia

It means dec. blood supply to kidneys.

Causes

(1) Atherosclerosis of large renal arteries
(2) Fibromuscular hyperplasia of large renal arteries
(3) Benign nephrosclerosis (Benign = not malignant)

Isothenuria

Excretion of urine with same osmolality as that of plasma is called isothenuria

Occurs

In renal failure due to rapid flushing of glomerular filtrate thru tubules.

Hemodialysis

Removal of certain waste products from blood due to difference of their rates of diffusion thru a semipermeable membrane, is called hemodialysis.

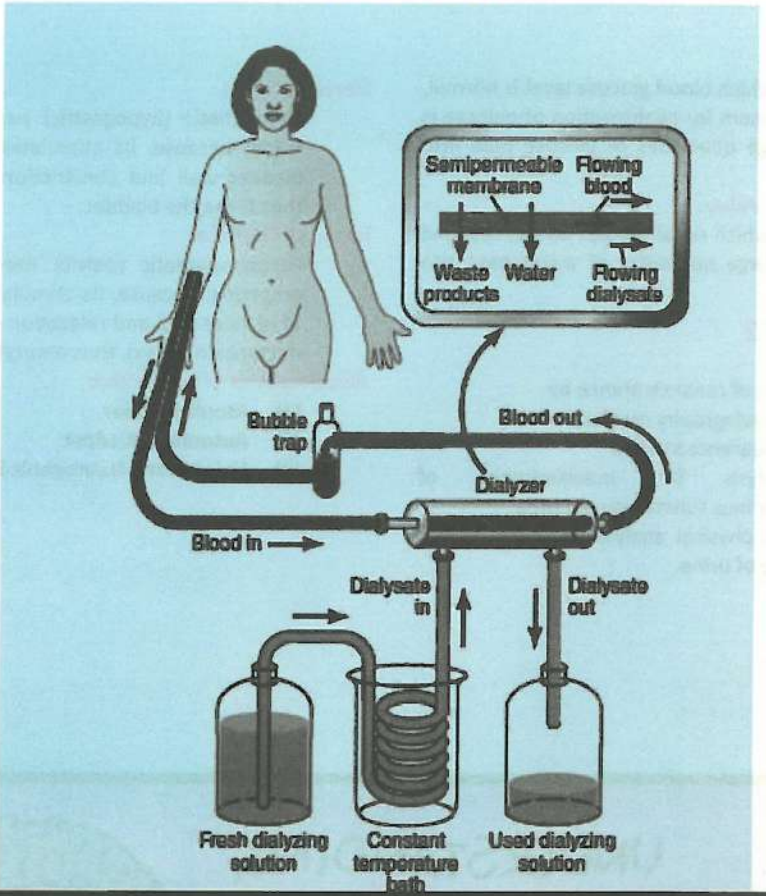
Dialyzing Fluid

It is a fluid identical to plasma but having no urea, urate, creatinine, sulfate, phosphate or any other urinary excretory product.

Basic Principle of Artificial Kidney

Blood is passed thru minute blood channels bounded by a thin semi-permeable membrane (eg, cellophane). On other side of membrane is a dialyzing fluid into which unwanted substances in uremic blood pass by diffusion due to concentration difference.

Courtesy by Guyton & Halls Physiology



Comparison of Dialyzing Fluid with Normal and Uremic Plasma

Constituent	Normal	Dialyzing Fluid	Uremic Plasma
Electrolytes (mEq/L			
Na^+	142	133	142
K^+	5	1.0	7
Ca^{++}	3	3.0	2
Mg^{++}	1.5	1.5	1.5
Cl^-	107	105	107
HCO_3^-	24	35.7	14
Lactate	1.2	1.2	1.2
HPO_4^-	3	0	9
Urate	0.3	0	2
$Sulfate^=$	0.5	0	3
Nonelectrolytes			
Glucose	100	125	100
Urea	26	0	200
Creatinie	1	0	6

Nephrotic Syndrome

It is a disease characterized by loss of large quantities of plasma proteins into urine.

Cause

Increase permeability of glomerular membrane.

Found in:

(1) Chronic glomerulonephritis

(2) Amyloidosis due to damage of basement membrane of glomerulus caused by deposition of proteinoid substance

(3) "Minimal Change" Nephrotic Syndrome In this, negative electrical charge normally exhibited by glomerular mem. is reduced or lacking.

Symptom

Edema due to decrease plasma colloid osmotic pressure

Renal Glycosuria

It is a condition in which blood glucose level is normal, but transport maximum for reabsorption of glucose is dec., therefore large quantities of glucose pass into urine each day.

Nephrogenic Diabetes Insipidus

It is a condition in which renal tubules do not respond well to ADH and large quantities of water pass into urine each day.

Renal Function Tests

Three categories

(1) Determination of renal clearance by

(a) Intravenous pyelography method

(b) Radioactive clearance studies

(2) Blood analysis for measurement of concentration of various substances, eg urea

(3) Chemical and physical analysis of urine, eg vol. And specific gravity of urine.

Nerve of Filling

Sympathetic (hypogastric) nerve is called nerve of filling; because, its stimulation causes relaxation of bladder wall and constriction of internal sphincter, thus filling the bladder.

Nerve of Emptying

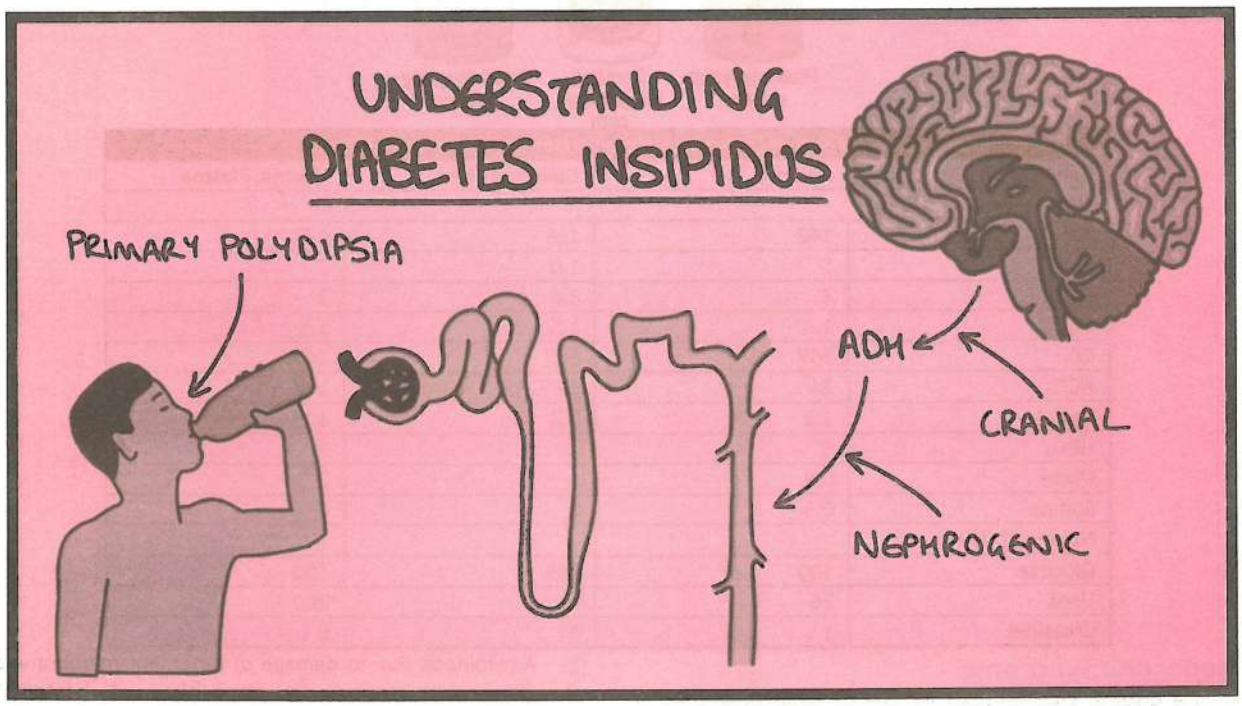
Parasympathetic (pelvic) nerve is called nerve of emptying; because, its stimulation causes contraction of bladder wall and relaxation of internal sphincter (ie micturition reflex), thus emptying the bladder.

Abnormalities of Micturition

(1) Atonic Bladder

(2) Automatic Bladder

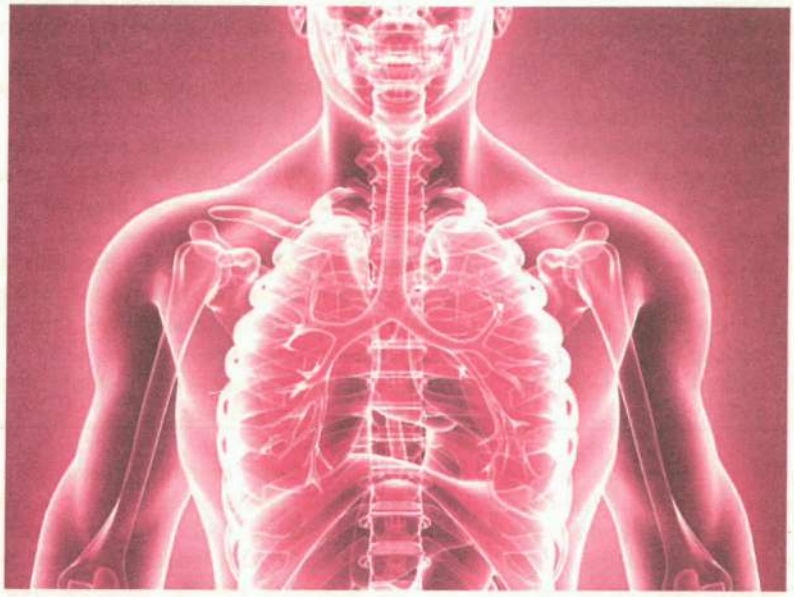
(3) Uninhibited Neurogenic Bladder



Chapter # 8

Respiratory System

Contents



Pulmonary Ventilation

Respiration

Exchange of O_2 & CO_2 b/w atmosphere & body cells is called respiration.

The major functional events of respiration include

(1) pulmonary ventilation, which is the movement of air in and out of the alveoli;

(2) diffusion of oxygen and carbon dioxide between the blood and alveoli;

(3) transport of oxygen and carbon dioxide to and from the peripheral tissues; and

(4) regulation of respiration.

Functions of Respiration

(1) Exchange of O_2 & CO_2 b/w alveolar air & blood.

(2) Excretion of volatile substances, eg NH3, ketone bodies essential oils, alcohol, water vapours, etc.

(3) Maintenance of acid-base balance by adjusting CO_2 elimination

(4) Maintenance of temp. balance by losing heat in expired air.

(5) Helps venous return by- decrease intra-thoracic pressure & increase intra-abdominal pressure during inspiration

Mechanism of Respiration

Mechanism of Inspiration	Mechanism of Expiration
• Inspiration is induced by the contraction of the diaphragm (main muscle of inspiration), along with some accessory muscles that expand the chest wall. (Active process). • Net effect of contracting these muscles is to decrease (make more negative) intrapleural pressure. • The expansion of lung causes the gases in the alveoli to expand, creating a slightly negative alveolar pressure. This causes air to flow into the lungs. • Other muscles of inspiration are used primarily during exercise or in diseases that increases airway resistance (e.g. asthma) • Vertical diameter of chest cavity is inc. by downward movement of diaphragm • Antero-posterior diameter of chest cavity is inc. by elevation of ribs	• Expiration under resting conditions is produced simply by the relaxation of the muscles of inspiration. (Passive process). • The relaxation of the diaphragm & accessory muscles of inspiration increases (makes more positive) intrapleural pressure. • Lung deflation begins, equal to intrapleural pressure. • Deflation of lung compresses the gases in the alveoli, creating a slightly positive alveolar pressure. This causes air to flow out of the lungs. • Muscles of expiration are used during exercise or increased airway resistance (e.g. asthma). • Vertical diameter of chest cavity is dec. by upward movement of diaphragm • Antero-posterior diameter of chest cavity is dec. by depression of ribs.
Muscles of Inspiration 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 ribs to rise and thus increases the anterior -posterior dimensions of the chest. (1) Diaphragm (primary muscle of inspiration) (2) Sternocleidomastoid(elevates sternum) (3) Serratus arterior (4) Scaleni (elevates first two ribs) (5) External intercostals.(moves ribs upward & outward)	**Muscles of Expiration** 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. (1) Elastic recoil of lungs (it is not a muscle, but it is the main factor) (2) Rectus abdorninis (main muscle) (3) Internal intercostals.(pull ribs downward & inward)

Forces Acting on the Lung System

Units of Pressure

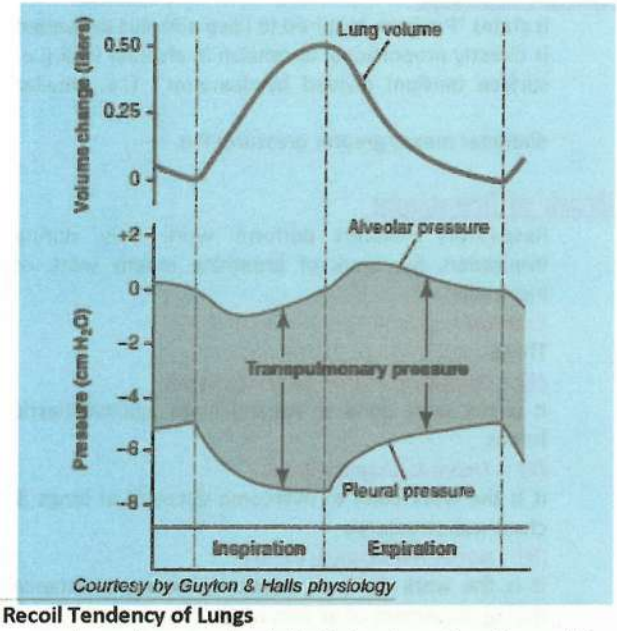
In respiratory physiology, they are usually given as cm H_2O.

1 cm H_2O = 0.74 mm Hg (1 mm Hg = 1. 36 cm H_2O)

Transpulmonary pressure

'The difference between the alveolar pressure and the pleural pressure. This is called the transpulmonary pressure."

It is a measure of the elastic forces in the lungs that tend to collapse the lungs at each instant of respiration, called the ***recoil pressure***.



Courtesy by Guyton & Halls physiology

Recoil Tendency of Lungs

Lungs have a natural elastic tendency to collapse; this is called recoil tendency of lungs.

Causes

(1) Elastic and collagen fibers of the lungs which try to shorten

(2) Surface tension elastic force of fluid lining inside wall of alveoli, that tries to make alveoli smaller

Intra pleural pressure

The pressure between the two layers of the lungs (vaccum)."

The fluid present between two layers is the 'Only Fluid' (no water at all).

Intra pleural pressure unit = -cm of H_2O

(;. Not in mmHg because it is a unit of air)

Value

(1) -5 cm H_2O at beginning of inspiration

(2) -7.5 cm H_2O at height of inspiration

Intra alveolar pressure

"The pressure of air in the lungs is called intra alveolar pressure(in +ve)."

Intra alveolar pressure at rest = 0 mmHg

(1) During Inspiration

Alveolar pressure becomes slightly negative with respect to atmospheric pressure, ie -1 cm H_2O → atmospheric air (rich in O_2) flows inward thru respiratory passages.

(2) During Expiration

Alveolar pressure becomes slightly positive with respect to atmospheric pressure, ie + 1 cm H_2O → alveolar air (rich in CO_2) flows outward thru respiratory passages

Compliance of Lungs

The ease with which the lungs can expand known as compliance.

$$\text{Compliance} \propto \text{Inspiration} \propto \frac{1}{\text{Expiration}}$$

- Compliance increases in Obstructiive diseases.
- Compliance decreases in the restrictive diseases

FACTORS

➢ *SUFACTANT*

It reduce the surface tension (is the ability of the surface molecules to attract the other molecules of the water toward them).

In alveolus there present the thin lining that increase the surfactant.

Compliance $\propto$ Inspiration $\propto$ Compliance

➢ *ELASTIC TISSUE*

More the elastic tissue in lungs less will be the compliance.

$$\text{Surfactant} \propto \frac{1}{\text{Elastic Tissue}}$$

Value

(1) For Both Lungs = 200 ml/cm H_2O

(2) For Lung-Thorax System = 110 ml/cm H2O

Surface Tension Elastic Force

It is the force that is exerted by surface tension of fluid lining inside wall of alveoli.

Function

It causes lungs to collapse,

Surfactant

It is a complex mixture of phospholipids dipalmitoyl lecithin, surfactant apoproteins & calcium ions, secreted by type II alveolar epithelial cells.

Functions

(1) It decrease surface tension of fluid lining alveoli, thereby preventing elastic tendency of lungs to collapse & promoting alveolar stability.

(2) It prevents accumulation of edema fluid in alveoli.

(3) Lack of surfactant leads to respiratory distress syndrome.

(4) Smoking decreases lung surfactant.

Hyaline Membrane Disease or Respiratory Distress Syndrome of Newborn (RDS)

It is a disease of new-born & especially of premature babies, who do not secrete adequate quantities of surfactant. Therefore, alveoli of these babies collapse which makes lung expansion difficult. Without immediate treatment, these babies die due to inadequate ventilation.

Premature birth & 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.

Symptoms include

1- Increased lung recoil & 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 lung.

2- Atelectasis

There is a greater tendency for small alveoli to collapse. Once collapse occurs, it is difficult to reinflate these 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 represents a large force prompting capillary filtration.

Law of Laplace

It states "Pressure required to keep alveolus expanded is directly proportional to tension in alveolar wall (i.e. surface tension) divided by diameter". (i.e. smaller diameter means greater pressure) $P \alpha \frac{T}{r}$

Work of Breathing

Respiratory muscles perform work only during inspiration. So, work of breathing means work of inspiration.

Division

Three,

(1) Compliance Work or Elastic Work

It is the work done to expand lungs against elastic forces.

(2) Tissue Resistance Work

It is the work done to overcome viscosity of lungs & chest wall structures

(3) Airway Resistance Work

It is the work done to overcome airway resistance during movement of air into lungs.

Spirometry & Spirogram

Spirometry

Process of recording of volume movements of air into & out of lungs, is called spirometry

Spirogram

Graphical recording of changes in lung volume under different conditions of breathing is called spirogram.

Pulmonary volumes

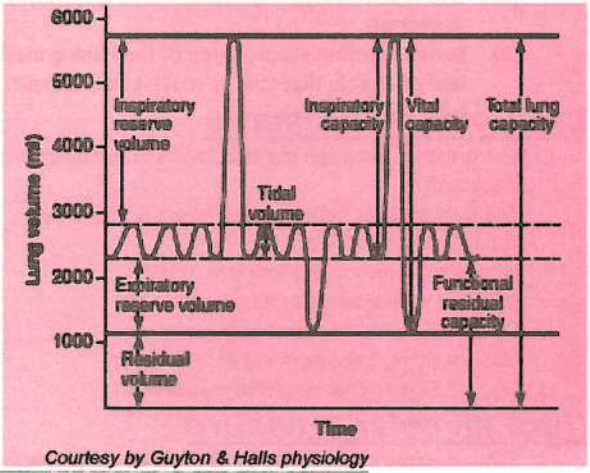
There are the 4 volumes, first three can be calculated by spirometry and the last by the Helium Dilution method

1. **The tidal volume** is the volume of air inspired or expired with each normal breath; it amounts to about **500** milliliters in the adult male.

2. **The inspiratory reserve volume** is the extra volume of air that can be inspired over and above the normal tidal volume when the person inspires with full force; it is usually equal to about **3000** milliliters.

3. **The expiratory reserve volume** is the maximum extra volume of air that can be expired by forceful expiration after the end of a normal tidal expiration; this normally amounts to about **1100** milliliters.

4. **The residual volume** is the volume of air remaining in the lungs after the most forceful expiration; this volume averages about **1200** milliliters.



Courtesy by Guyton & Halls physiology

Lungs capacities

It Is the combination of two or more pulmonary volumes

1. The inspiratory capacity

equals to the tidal volume plus the inspiratory reserve volume. This is the amount of air (about **3500** milliliters) a person can breathe in, beginning at the normal expiratory level and distending the lungs to the maximum amount.

2. The vital capacity

equals the inspiratory reserve volume plus the tidal volume plus the expiratory reserve volume. This is

the maximum amount of air a person can expel from the lungs after first filling the lungs to their maximum extent and then expiring to the maximum extent (about **4600** milliliters).

3. The functional residual capacity

equals the expiratory reserve volume plus the residual volume. This is the amount of air that remains in the lungs at the end of normal expiration (about **2300** milliliters).

4. The total lung capacity

is the maximum volume to which the lungs can be expanded with the greatest possible effort (about **5800** milliliters); it is equal to the vital capacity plus the residual volume.

$IC = IRV + V_T$

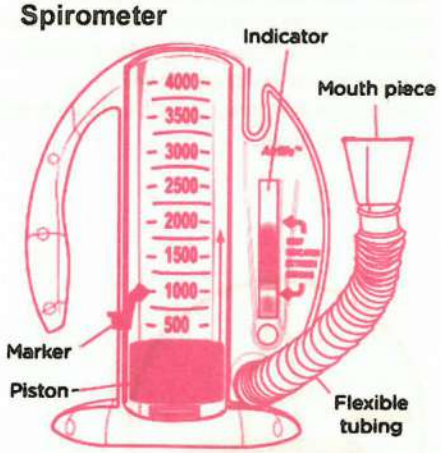
$VC = IRV + V_T + ERV$ OR $VC = IC + ERV$

$FLC = ERV + RV$

$TLC = IC + FRC$ OR $TLC = VC + RV$

1 and 2 can be calculated by spirometry but 3 and 4 by helium dilution method due to residual volume.

Spirometer



Muscle bulk of male is lager than a female that's why they consume more air. Bulk is more due to the testosterone hormone present in the males.

Factors That Decrease Vital Capacity

(1) Laying down position
(2) Paralysis of respiratory musdes
(3) Decrease pulmonary compliance
(4) Pulmonary congestion

Resting Expiratory Level

When all inspiratory muscles are completely relaxed, lungs return to a relaxed state called resting expiratory level. Volume of air in lungs at this level is equal to functional residual capacity (=2300 ml).

Measurement of Functional Residual Capacity

Functional residual capacity is measured by "Helium Dilution Method"

FRC = $(C_iHe / C_fHe - 1)\ V_i$-Spir.

Where;

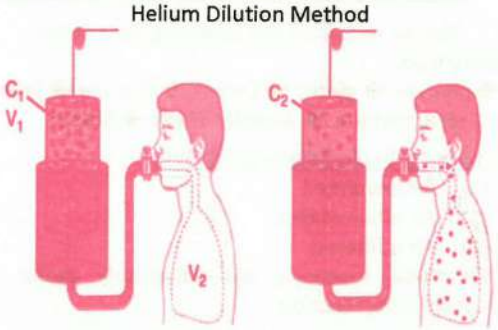
FRC = Functional residual capacity

CiHe = Initial conc. of He in spirometer

CfHe = Final conc. of He in spirometer

Vi-spir = Initial vol. of spirometer

Helium Dilution Method



$C_1 \times V_1 = C_2 \times (V_1 + V_2)$

Minute Respiratory Volume

Total amount of new air moved into respiratory passages each minute is called minute respiratory volume

Formula

MRV = Tidal volume x Respiration rate

Value

MRV = 500 x 12 = 6 lit/min.

Rate of Alveolar Ventilation

Rate at which new air reaches gas exchange areas of lungs (ie, alveoli, alveolar sacs, alveolar ducts & respiratory bronchioles) each min., is called alveolar ventilation rate.

Formulation

RAV = Tidal vol. - Dead space vol. X Resp. rate

Value

RAV = (500 -150) x 12 = 4200 ml/min

Dead Space Air

Volume of breathed air that never reaches gas exchange areas but simply fill respiratory passage, is called dead space air.

Value

150 ml

Dead Space

The air present in the conductive airway called the ***dead space*** (no gas exchange).

There are 2 types of dead space

1. ***Anatomical dead space*** "The air from nose to terminal bronchiols called the anatomical dead space."	2. ***Physiological dead space*** "It is the addition of Respiratory Bronchiols + Alveolar trunk+ Alveoli in the anatomical dead space called the physiological dead space."

Air Passage

The air pass from the following parts in the respiratory track,
Nose ➔ pharynx ➔ glottis ➔ Larynx ➔ Trachea ➔ Bronchi (3 types) ➔ Bronchiols ➔ Alveolar Trunk ➔ Alveoli

Respiratory Functions of Nose

(1) Air is warmed
(2) Air is humidified
(3) Air is filtered

All these functions are collectively called "Air-conditioning function"

Vocalization

Production of voice is called vocalization or speech.

Composition

(1) Phonation by vibration of vocal cords in larynx
(2) Articulation by lips, tongue & soft palate.
(3) Resonance by mouth., nose & associated nasal sinuses & pharynx

Tracheobronchial tree

Trachea and bronchi are together called tracheobronchial tree. It forms a part of air passage.

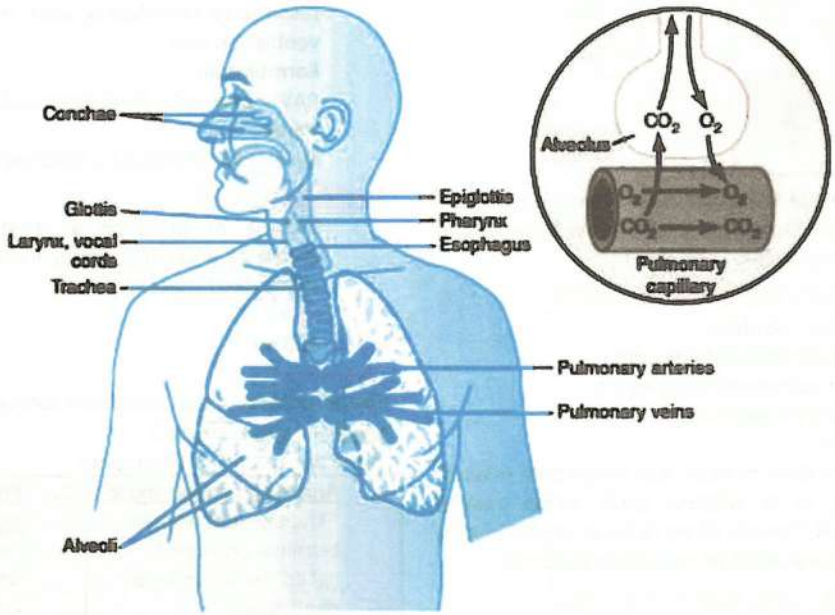
Components of tracheobronchial tree

1. **Trachea** bifurcates into two main or **primary bronchi** called right and left bronchi
2. Each primary bronchus enters the lungs and divides into **secondary bronchi**
3. Secondary bronchi divide into **tertiary bronchi.** In right lung, there are 10 tertiary bronchi and in left lung, there are eight tertiary bronchi
4. Tertiary bronchi divide several times with reduction in length and diameter into many generations of **bronchioles**
5. When the diameter of bronchiole becomes 1 mm or less, it is called **terminal bronchiole**
6. Terminal bronchiole continues or divides into **respiratory bronchioles,** which have a diameter of 0.5 mm.

Upper and Lower Respiratory Tracts

Generally, respiratory tract is divided into two parts:

1. Upper respiratory tract that includes all the structures from nose up to vocal cords; vocal cords are the folds of mucous membrane within larynx that vibrates to produce the voice
2. Lower respiratory tract, which includes trachea, bronchi and lungs.



Courtesy by Guyton & Halls physiology

Pleura

Each lung is enclosed by a bilayered serous membrane called pleura or **pleural sac.** Pleura has two layers namely inner **visceral** and outer **parietal** layers. Visceral layer is attached firmly to the surface of the lungs. At hilum, it is continuous with parietal layer, which is attached to the wall of thoracic cavity.

Intrapleural Space or Pleural Cavity

Intrapleural space or pleural cavity is the narrow space in between the two layers of pleura.

Intrapleural Fluid

Intrapleural space contains a thin film of serous fluid called intrapleural fluid, which is secreted by the visceral layer of the pleura

Pleural Effusion

It is the collection of large amounts of free fluid in pleural space.

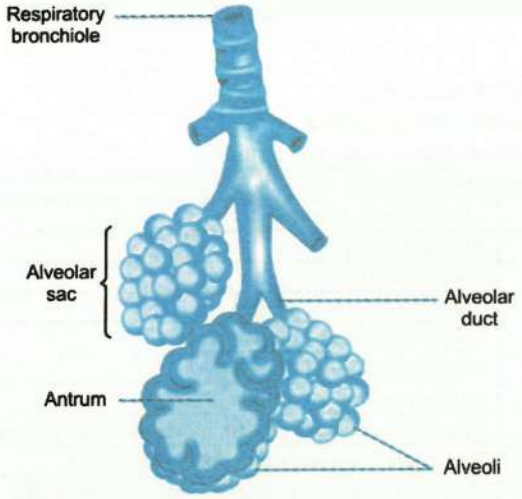
Caused by

(1) Blockage of lymphatic drainage from pleural cavity

(2) Cardiac failure

(3) Decrease plasma colloid osmotic pressure

(4) Breakdown of capillary membrane of pleural cavity due to infection or inflammation



Respiratory Unit

Respiratory unit includes:

1. Respiratory bronchioles
2. Alveolar ducts
3. Alveolar sacs
4. Antrum
5. Alveoli.

Function of Mucous Coat & Cilia of Respiratory Passages

All respiratory passages (from nose to terminal bronchioles) are kept moist by a mucous coat that entraps small particles out of inspired air. Cilia of lining ciliated epithelium beat towards pharynx that causes mucous coat & entrapped particles to move towards pharynx whence they are either swallowed or coughed to exterior.

Protective Mechanisms of Respiration

Two,

(1) Cough Reflex

Cough is a sudden noisy expulsion of air thru mouth from lungs, produced to clear resp. passageways of foreign particles.

Mechanism

- Cough begins with deep inspiration followed by forced expiration with closed glottis. This increases the intrapleural pressure above 100 mm Hg. Then, glottis opens suddenly with explosive outflow of air at a high velocity.
- Velocity of the airflow may reach 960 km/hour. It causes expulsion of irritant substances out of the respiratory tract.

Reflex Pathway

- Receptors that initiate the cough are situated in several locations such as nose, paranasal sinuses, larynx, pharynx, trachea, bronchi, pleura, diaphragm, pericardium, stomach, external auditory canal and tympanic membrane.
- Afferent nerve fibers pass via vagus, trigeminal, glossopharyngeal and phrenic nerves. The center for cough reflex is in the medulla oblongata.
- Efferent nerve fibers arising from the medullary center pass through the vagus, phrenic and spinal motor nerves. These nerve fibers activate the primary and accessory respiratory muscles.

(2) Sneez Reflex

Sneeze is an involuntary, sudden, violent & audible expulsion of air thru nose.

Mechanism

Sneezing starts with deep inspiration, followed by forceful expiratory effort with opened glottis resulting in expulsion of irritant agents out of respiratory tract.

Reflex Pathway

- Sneezing is initiated by the irritation of nasal mucous membrane, the olfactory receptors and trigeminal nerve endings present in the nasal mucosa.
- Afferent nerve fibers pass through the trigeminal and olfactory nerves. Sneezing center is in medulla oblongata. It is located diffusely in spinal nucleus of trigeminal nerve, nucleus solitarius and the reticular formation of medulla.
- Efferent nerve fibers from the medullary center pass via trigeminal, facial, glossopharyngeal, vagus and intercostal nerves. These nerve fibers activate the pharyngeal, tracheal and respiratory muscles.

Maximum Expiratory Flow

When a person expires with great force, expiratory air flow reaches a max. flow beyond which flow cannot be inc.; it is called max, expiratory flow. Its value is greater when lungs are filled with large vol.of air.

(1) Constricted lung diseases, eg tuberculosis, silicosis, kyphosis, scoliosis & fibrotic pleurisy

(2) Airway obstruction disease, eg asthma & emphysema.

Diorder of Respiratory Tract

- ⇨ Obstructive
- ⇨ Restrictive

Obstructive	Restrictive
It cause due to expiratory problem.	It cause due to inspiratory problem.
FEV_1 is reduced more than FVC. The FEV_1 & FVC ratio will be less than 80%.	The FEV_1 & FVC ratio will remain normal.
Example • Asthma • Chronic obstructive pulmonary disease (COPD), types 1. Chronic Bronchitis 2. Emphysema	Example • Any cancer of the lungs • Pneumonia • Metal Lungs disease (cause by the inhaling the metal and accumulation of metal) , that may be the 1. Cilicosis (glass factory) 2. Asbestosis (textile/garment) 3. Coal worker pneumoconiosis
Here, decrease VC	Decrease VC
Increase TLC, RV, FRV	Decrease TLC, RV, FRC
FEV_1/VC is less than 80%	So , FEV_1/VC remain normal

Obstructive Versus Restrictive Pattern

- FEV_1= Forced expired volume during the first second, usually measured in liters.
- Forced vital capacity always decreases when pulmonary function is compromised.
- A decrease in FEV1 /FVC ratio is evidence of an obstructive rather than a restrictive pattern.

Abbreviations and Symbols for Pumonary Function			
VT	Tidal volume	Pa	Atmospheric pressure
FRC	Functional residual capacitx	Palv	Alvolar pressure
ERV	Expiratory reserve volume	Ppl	Pleural pressure
RV	Residual volume	PO_2	Partial pressure of oxygen
IC	Inspiratory capacity	PCO_2	Partial pressure of carbon dioxide
IRV	Inspiratory reserve volume	PN_2	Partial pressure of nitrogen
TLC	Total lung capacity	PaO_2	Partial pressure of oxygen in arterial blood
VC	Vital capacity	$PaCO_2$	Ppartial pressure of carbon dioxide in arterial blood
Raw	Resistance of the airways to flow of air into the lung	PAO_2	Partial pressure of oxygen in alveolar gas
C	Compliance	$PACO_2$	Partial pressure of carbon dioxide in alveolar gas
VD	Volume of dead space gas	PAH_2O	Partial pressure of water in alveolar gas
VA	Volume of alveolar gas	R	Respiratory exchange ratio
V1	Inspired volume of ventilation per minute	Q	Cardiac output
VE	Expired volume of ventilation per minute		
VS	shunt flow,		
VA	Alveolar ventilation per minute	CaO_2	Concentration of oxygen in arterial blood
V_{O2}	Rate of oxygen uptake per minute	CV_{O2}	Concentration of oxygen in mixed venous blood
V_{CO2}	Amount of carbon dioxide eliminated per minute	S_{O2}	Percentage saturation of hemoglobin with oxygen
V_{CO}	Rate of carbon monoxide uptake per minute	SaO_2	Percentage saturationo f hemoglobin with oxygen in arterial blood
D_{LO2}	Diffusing capacity of the lungs for oxygen		
D_{LCO}	Diffusing capacity of the lungs for carbon monoxide		

Pulmonary Circulation

The Lung Has Three Circulations: Pulmonary, Bronchial, and Lymphatic

Pulmonary Vessels

(1) Pulmonary Arteries

Carry deoxygenated blood from right ventricle to lungs for gaseous exchange.

(2) Pulmonary Veins

Carry oxygenated blood from lungs to left artrium.

Bronchial Arteries

Arise

From descending thoracic aorta

Function

Carry oxygenated blood to supply connective tissue, septa and bronchi of lungs

Pressures in Pulmonary System

(1) Systolic pulmonary arterial pressure = 25 mm Hg

Diastolic pulmonary arterial pressure = 8 mm Hg

(3) Mean pulmonary arterial pressure = 15 mm Hg
(4) Pulse pressure in pulmonary arteries = 17 mm Hg
(5) Pulmonary capillary pressure = 7 mm Hg
(6) Left atrial and pulmonary venous pressure = 2 mm Hg

Blood Volume in Lungs

Value = 450 ml

Lung as Blood Reservoir

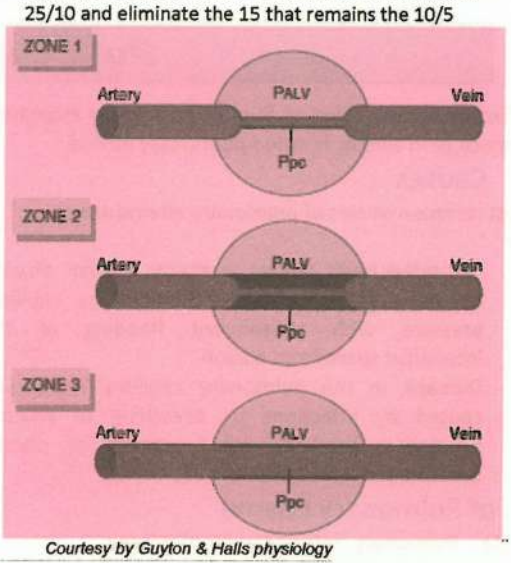
Lungs act as blood reservoir and can contribute 250 ml blood to systemic circulation when blood is needed, eg after hemorrhage.

Zones of Lung

There present the 3 zones in the lungs Zone 1 is not present in normal lungs.

- Due to the heart the lungs are divided into the 2 zones
- At the level of the heart is the **Base.**
- At the upper level of the heart is the **Apex.**
- The pressure in the vena cava is 5/0 and in right atrium is the 5/0 and in the right ventricle is the 25/0 and in pulmonary artery is the 25/10 (why the pressure increase from 5 to 25 mmHg? Because the right ventricle have more muscles that cause an increase the pressure. Vein is double layered and artery is triple layered cause an increase in the elasticity and increase diastole.)
- **Pulmonary Artery divide to the Pulmonary capillaries**

The pressure in the pulmonary capillaries at the base is the 25/10 and at the apex is 25/10 and eliminate the 15 that remains the 10/5



Courtesy by Guyton & Halls physiology

ZONE 2
Gaseous exchange will take place only during the systole.
In diasystole capiliary is collapsed and there is ***no gas exchange***.

ZONE 3
Gaseous exchange will take place both in systole and diasystole. $\frac{25\ systole}{10\ diasystole}$

- It present in the normal lungs
- The different zone in the lungs are due to in the difference of blood pressure in the pulmonary at the apex and base.

ZONE 1
No gaseous exchange will take place both in systole and diasystole.
It present in the abnormal lungs.
Pulmonary capillaries are permanently damaged due to the

1. **Hemorrhage** of pulmonary capillary
2. **CAWP** (continuous positive airway pressure)
   'alveolus expands extensively that capillary get collapse.'
3. **Astronauts**
   Use over gravity cause the capillaries permanently collapsed.

In exercise the_____ zone is present?
zone 3 where pressure is $\frac{50-15}{25} = \frac{35}{10}$
and in lying position is the zone 3 (apex finished and all become base)

Alveoli Remain Dry

Negative interstitial pressure pulls fluid from alveoli through alveolar membrane into interstitial space, thereby keeping alveoli dry.

Pressures Acting on Pulmonary Capillary Mem

(1) Pulmonary Capillary Pressure
It is pressure tending to push fluid out of capillaries.
Value =7 mm Hg

(2) Plasma Colloid Osmotic pressure
It is pressure tending to pull fluid from intertitial space into capillaries.
Value = 28 mm Hg

(3) Negative Interstitial Fluid Pressure
It is pressure tending to pull fluid from capillaries into interstitial space.
Value = -8 mm Hg

(4) Interstitial Fluid Colloid Osmotic Pressure It is the pressure tending to pull fluid from capillaries into interstitial space.

Pulmonary Edema

Excess accumulation of fluid in pulmonary interstitial space or in alveoli, is called pulmonary edema.

Causes

The most common causes of pulmonary edema are as follows:

- Left-sided heart failure or mitral valvular disease causes a great increase in pulmonary capillary pressure with subsequent flooding of the interstitial spaces and alveoli.
- Damage to the pulmonary capillary membrane caused by infections or breathing of noxious substances produces rapid leakage of plasma proteins and fluid out of the capillaries

Types of Pulmonary Edema

(1) Pulmonary "interstitial fluid" edema
It is the accumulation of fluid in pulmonary interstitial spaces

(2) Pulmonary "alveolar" edema
It is the accumulation of fluid in alveoli

Pulmonary Edema Safety Factor

It is combination of all factors that tend to prevent edema in lungs. These are

All the following factors must be overcome before edema can occur:

(1) normal negativity of the interstitial fluid pressure,
(2) lymphatic pumping of fluid out of the interstitial spaces, and
(3) decreased colloid osmotic pressure of the interstitial fluid caused by "washout" resulting from increased loss of fluid from the pulmonary capillaries

Diffusion of Gases

Factors Affecting Rate of Gas Diffusion in a Fluid

$$D \propto \frac{\Delta P \times A \times S}{d \times \sqrt{MW}}$$

Where,

D	=	Diffusion rate
ΔP	=	Pressure gradient for diffusion
A	=	Cross-sectional area of pathway
S	=	Solubility co-efficient of gas
T	=	Temperature
D	=	Distance
MW	=	Molecular weight of gas.

Diffusion Co-Efficient

Ratio of solubility co-efficient of a gass to under-root of its molecular weight (S/ √MW) is called diffusion coefficient.

Why Composition of Alveolar Air is Different From That of Atomospheric Air

Dependence of Rate of Diffusion

Rate of diffusion of a gas is directly proportional to partial pressure of that gas.

Henry's Law

It states "Concentration of a dissolved gas in fluid = partial pressure of that gas x solubility co-efficient."

Solubility Co-Efficient

Ratio of conc. of a gas dissolved in a fluid to its partial pressure, is called solubility co-efficient of that gas.

Example

Solubility co-efficient of CO_2 is 20 times greater than that of O_2

Pressure Gradient For Diffusion

Pressure in high pressure area minus pressure in low pressure area divided by distance of diffusion is called pressure gradient for diffusion or diffusion gradient.

Reasons

(1) Alveolar air is only partially replaced by atmospheric air with each breath.
(2) O_2 is constantly absorbed from alveolar air
(3) CO_2 is constantly diffusing from pulmonary blood into alveoli
(4) Atmospheric air entering respiratory passage is humidified.

Rate at Which Alveolar Air is Renewed By Atmospheric Air

Alveolar air is renewed by atmospheric air at a slow rate of 350 ml per breath. So, half of alveolar air is renewed in 17 sec.

Importance of Slow Renewal

(1) Prevents sudden changes in gas conc. of blood
(2) Prevents excessive inc. or dec. in tissue O_2 conc. tissue CO_2 concentration & tissue pH.
(3) Makes respiratory control mechanism more stable.

Factors Affecting Gas Diffusion Through Respiratory Membrane

(1) Thickness of respiratory mem. (inversely)
(2) Surface area of respiratory mem. (directly)
(3) Diffusion co-efficient of gas (directly)
(4) Pressure difference (directly)

Diffusing Capacity of Respiratory Membrane

Vol. of a gas that diffuses thru respiratory mem. each minute for a pressure difference of 1 mm Hg, is called diffusing capacity of respiratory membrane.

Diffusing Capacities For

(1) O_2 = 21 ml/mm Hg
(2) CO_2 = 420 ml/min/mm Hg

Ventilation-Perfusion Ratio

Ratio of alveolar ventilation (Va) to blood flow (Q) is called ventilation - perfusion ratio.

Formula

VPR = Va/Q

PHYSIOLOGICAL SHUNT

Definition

Physiological shunt is defined as a diversion through which the venous blood is mixed with arterial blood.

Components

Physiological shunt has two components:

1. Flow of deoxygenated blood from **bronchial circulation** into pulmonary veins without being oxygenated makes up part of normal physiological shunt
2. Flow of deoxygenated blood from **thebesian veins** into cardiac chambers directly

Partial Pressures of Respiratory Gases as They Enter and Leave the Lungs (at sea Level)								
	Atmospheric Air (mm Hg)		Humidified Air (mm Hg)		Alveolar Ai (mm Hg)		Exired Air (mm Hg)	
N_2	597.0	(78.62&)	563.4	(74.09%)	569.0	(74.9%)	566.0	(74.5%)
O_2	159.0	(20.84%)	149.3	(19.67%)	104.0	(13.6%)	120.0	(15.7%)
CO_2	0.3	(0.04%)	0.3	(0.04)	40.0	(5.3%)	27.0	(3.6%)
H_2O	3.7	(0.50%)	47.0	(6.20%)	47.0	(6.2)	47.0	(6.2)
Total	760.0	(100.0)	760.0	(100.0)	760.0	(100.0%)	760.0	(100.0%)

Transport of O_2 & CO_2

Transport of Oxygen

Oxygen is transported from alveoli to the tissue by blood in two forms:

1. As simple physical solution
2. In combination with hemoglobin.

Partial pressure and content of oxygen in arterial blood and venous blood

Gases		blood	Blood
Oxygen	Partial pressure (mm Hg)	95	40
	Content (mL%)	19	14
Carbon Dioxide	Partial pressure (mm Hg)	40	46
	Content (mL%)	48	52

AS SIMPLE SOLUTION

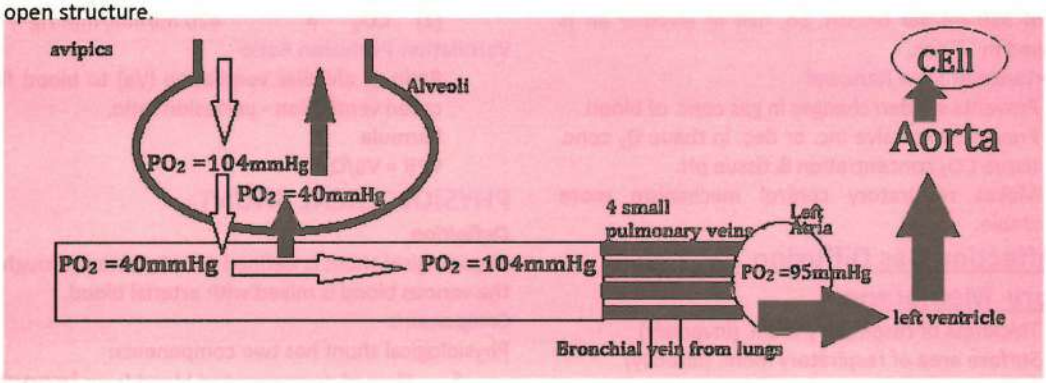
- Oxygen dissolves in water of plasma and is transported in this **physical form.** Amount of oxygen transported in this way is very negligible.
- It is only 0.3 mL/100 mL of plasma.
- It forms only about 3% of total oxygen in blood. It is because of poor solubility of oxygen in water content of plasma.
- Still, transport of oxygen in this form becomes important during the conditions like muscular exercise to meet the excess demand of oxygen by the tissues.

IN COMBINATION WITH HEMOGLOBIN

Oxygen combines with hemoglobin in blood and is transported as **oxyhemoglobin.** Transport of oxygen in this form is important because, maximum amount (97%) of oxygen is transported by this method

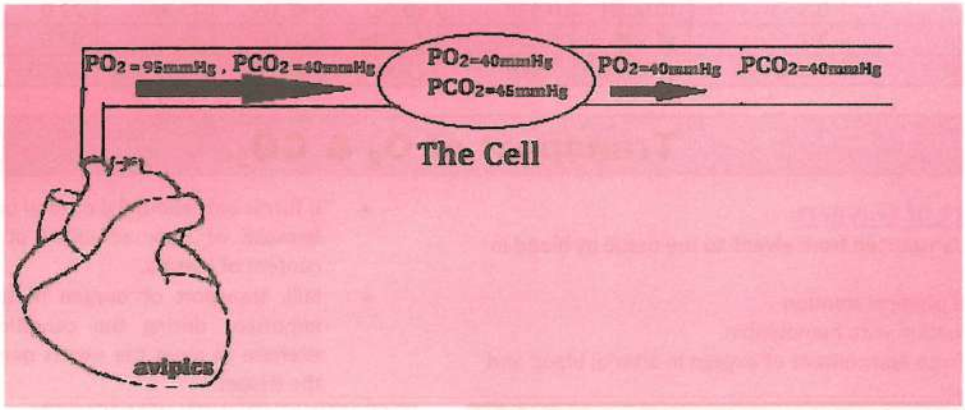
- The presence of the deoxygenated blood gives the blue color and oxygenated blood gives the red color.
- Two things catch the oxygen 1. Heamoglobin 2.Plasma
- 97% oxygen directly bind the heamoglobin and 3% get dissolved in plasma.
- Reasons that oxygen binds the heamoglobin
  1. 4 oxygen molecules bind single heamoglobin
  2. Tight bonding between them that is covalent

- It is easy to calculate the pressure of the oxygen in plasma because there is no membrane as in RBCs but it is an open structure.
- Pressure of the gases always calculated that present in the plasma.



Positive co-perativity

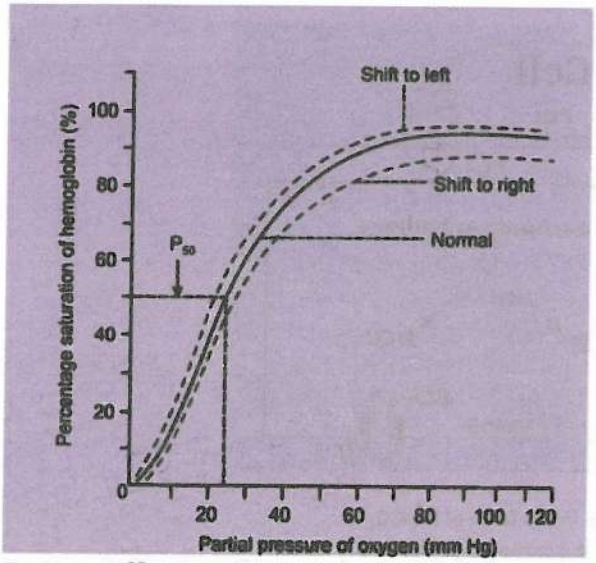
- Hb- attach with the 4 oxygen molecules
- Hb- contain the 4 iron molecules (ferrus normally and abnormally may be the ferric)
- Hb moves in all the direction to occupy the more oxygen
- Hb- get more and more oxygen than plasma.
- The PO_2 in the capillary is 40mmHg and in the alveoli before exchange is 104mmHg.
- AFTER exchange the PO_2 in the capillary becomes 104mmHg and in the alveoli after exchange would become 40mmHg.
- As the figure show that the pulmonary vein divide into the 4 parts and enter the left atria individually.
- The PO_2 in the left atria would become 95mmHg because the bronchial vein also empty into the pulmonary vein.
- The arterial blood moves from the left atria to the left ventricle and after that to the aorta (PCO_2=40mmHg) that supplies the cells(PCO_2 =45mmHg).
- The PO_2 in the aorta is 95mmHg and the PO_2 in the cell is 40mmHg the gas move in the pressure gradient and PO_2 move out of the cell is the 40mmHg.
- High concentration of the CO_2 in the cell trigger the heamoglobin and plasma to detach the O_2.
- Cell membrane is permeable to all the gases that are lipid soluble.



Oxygen-Hb Dissociation Curve

It is a curve that denotes relationship b/w percent 02 saturation of Hb & partial pressure of O_2.

Shift of O_2-Hb Dissociation Curve



Factors Affecting Oxygen-hemoglobin Dissociation Curve

Oxygen-hemoglobin dissociation curve is shifted to left or right by various factors:

1. Shift to left indicates acceptance **(association)** of oxygen by hemoglobin
2. Shift to right indicates **dissociation** of oxygen from hemoglobin.

1. Shift to right

Oxygen-hemoglobin dissociation curve is shifted to right in the following conditions:

i. Decrease in partial pressure of oxygen
ii. Increase in partial pressure of carbon dioxide (Bohr effect)
iii. Increase in hydrogen ion concentration and decrease in pH (acidity)
iv. Increased body temperature
v. Excess of 2,3-diphosphoglycerate (DPG) in RBC.

2. Shift to left

Oxygen-hemoglobin dissociation curve is shifted to left in the following conditions:

i. In fetal blood because, fetal hemoglobin has got more affinity for oxygen than the adult hemoglobin
ii. Decrease in hydrogen ion concentration and increase in pH (alkalinity).

Right Deviation	Left Deviation
CO_2 increases	CO_2 decreases
H^+ increases	H^+ decreases
Temperature increases	Temperature decreases
2,3 Bis phosphoglycerate (BPG-intermediate of the glycolysis) increases	2,3 Bis phosphoglycerate (BPG-intermediate of the glycolysis) decreases

Bohr Effect

Shift of O_2-Hb dissociation curve by changes in blood CO_2 & H^+ concentration, is called Bohr effect.

Importance

It casues

(1) Binding of O_2 to Hb in lungs (because CO_2 is less in alveoli leftward shift of the curve)
(2) Release of O_2 from Hb in tissues (because CO_2 is more in tissues rightward shift of the curve)

Factors influencing Bohr effect

All the factors, which shift the oxygen-dissociation curve to right (mentioned above) enhance the Bohr effect.

Poisoning

Oxygen Poisoning

If a person breaths O_2 at high pressure of O_2, amount of O_2 transported in dissolved state becomes tremendous, resulting in toxic effects; this is called O_2 poisoning.

Symptoms

(1) Increase O_2 → Inc. oxidation of cellular enzymes → Decrease cellular metabolism.
(2) Increase O_2 → Constriction of arterial walls → Decrease blood flow Cellular death.

Carbon Monoxide Poisoning

CO combines 230 times more rapidly at same point on H^+ molecule as does O_2; so, CO prevents binding of O_2 with Hb, resulting in toxic effects; this is called CO poisoning.

Treatment

(1) Pure O_2 at high pressure that displace CO
(2) 5% CO_2 that stimulates respiratory center.

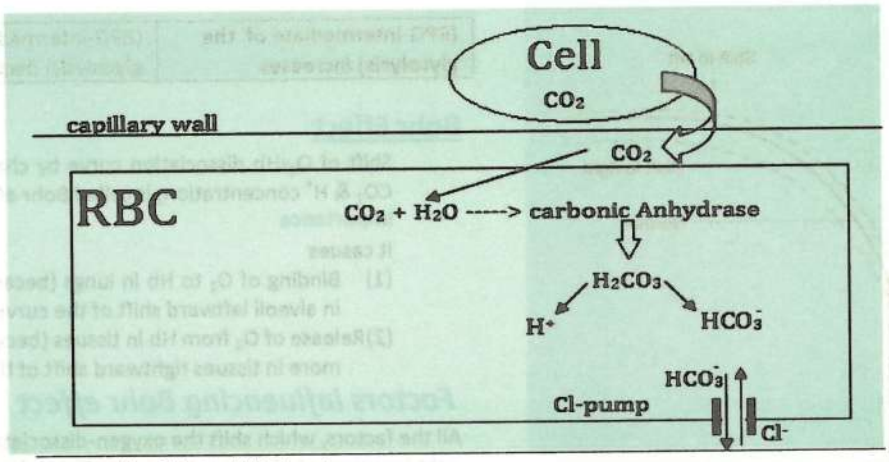
Transport of CO_2 in Blood

Carbon dioxide is transported by the blood from cells to the alveoli. Carbon dioxide is transported in the blood in four ways:

1. As dissolved form (7%)
2. As carbonic acid (negligible)
3. As bicarbonate (63%)
4. As carbamino compounds (30%).

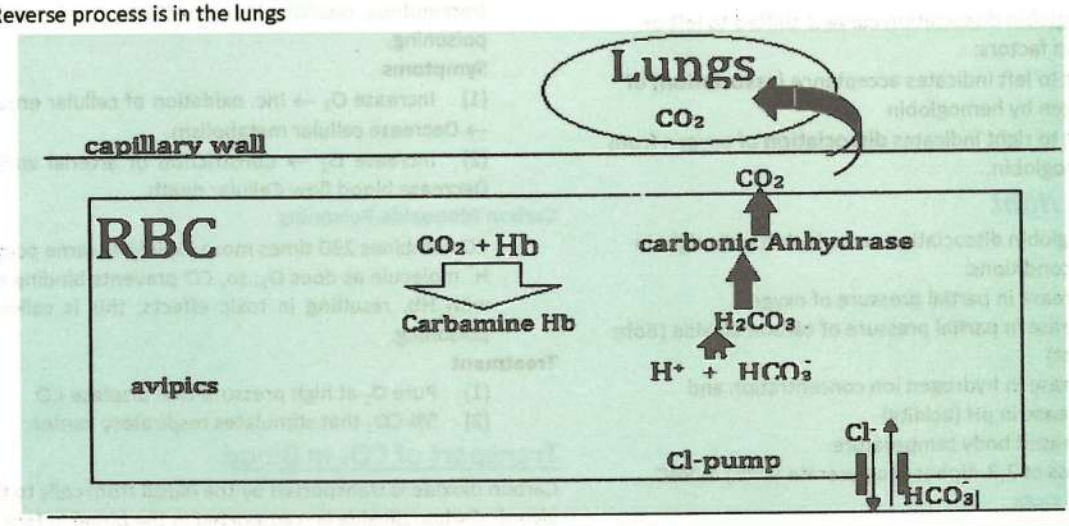
The CO_2 in the cell get pass to the capillary wall and after that to the RBC because it is permeable to the gases.

- In the RBC the CO_2 combine with the water in the presence of the enzyme carbonic anhydrase to form the H_2CO_3 that futher form the H^+ and HCO_3



- Chloride pump moves the Cl in and HCO_3 out.
- PCO_2 ; 70% CO_2 move in the plasma in the form of HCO_3 and 30% in the form of Hb-CO_2.
- Hb prefer the CO to attach first after that the oxygen and in last the carbon dioxide.
- Hb-CO is the carboxy heamoglobin, CO and oxygen compete for the same site on the Hb.
- PCO_2 moves in the blood in the form of bicarbonate HCO_3.

Reverse process is in the lungs

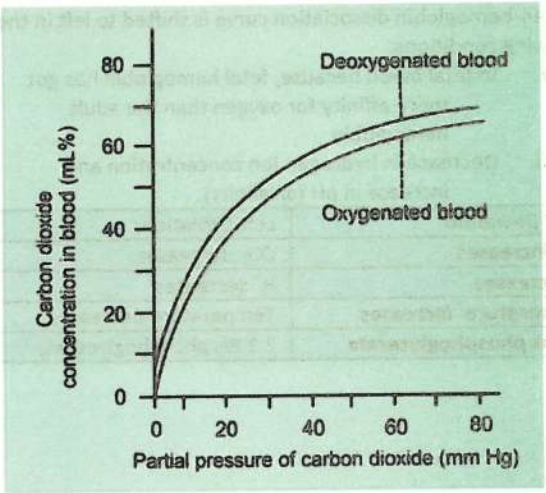


Chloride Shift

While HCO_3^- diffuses out of RBC, Cl^- diffuses in to RBC to maintain electrical potential balance of RBC, this is carried out by bicarbonate-chloride carrier protein. This phenomenon is called chloride shift.

CO_2 Dissociation Curve

A curve denoting relationship b/w quantity of CO_2 combined with blood in all forms & partial pressure of CO_2, is called CO_2 dissociation curve.



Haldane Effect

Increase in CO_2 in blood will cause O_2 to be displaced from Hb & binding of O_2 with Hb displaces CO_2 from blood; this is called Haldane effect.

Blood pH During CO_2 Transport

During CO_2 transport blood pH dec. to 7.3 due to H2CO3 formation.

Respiratory Exchange Ratio

Ratio of CO_2 output to O_2 uptake is called respiratory exchange ratio.

Regulation of Respiration

(A) Nervous control
- Respiratory center

(B) Chemical control
- Chemosensitive area in brain
- Peripheral chemoreceptors (carotid & aortic bodies)

(C) Others
- Exercise
- Voluntary
- Irritants in air passages
- J receptors
- Brain edema

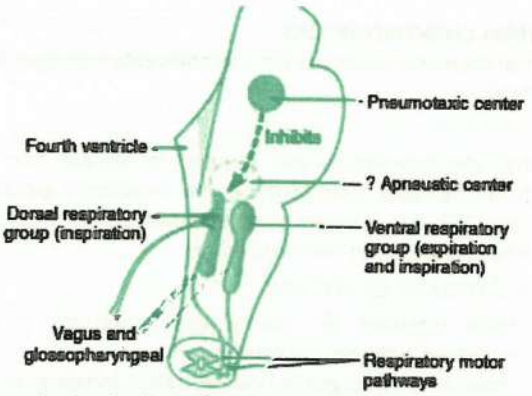
Respiratory Center

Group of neurons located bilaterally in medulla: pons which control all aspects of respiration, are collectively called respiratory center.

Divisions

Four,
(1) Dorsal respiratory group (Medulla)
(2) Ventral respiratory group (Medulla)
(3) Pneumotaxic center (Pons)
(4) Apneustic center (Pons)

For spontaneous breathing , an intact medulla must be connected to the diaphragm (via the phrenic nerve). Thus a complete C_1 or C_2 lesion will prevent diaphragmatic breathing but not complete C^{++} or lower lesion



Courtesy by Guyton & Halls physiology

1. Dorsal group of neuron
- Most important center for normal person.
- During the normal inspiration
- Dorsal group of neuron send message to diaphragm cause contraction and inspiration.
- Inspiratory Ramp signal
- Signal send from dorsal group of neuron to diaphragm for normal inspiration. Sudden shut off signal (just like the switching off the button of light)

2. Ventral group of neuron
- 2nd important
- During exercise
- During exercise ventral group of neuron has no function (both during inspiration and expiration)
- In exercise both ventral and dorsal group of neuron (diaphragm) work.

3. Pneumotaxic Center

Location

Dorsally in nucleus para-brachialis of upper pons
- Transmits signals to dorsal inspiratory area to cause switch-off of inspiratory ramp signal
- Thus limits period of inspiration
- Hence increases rate of respiration

Apneustic Center

Location

Lower pons
- Sends signals to dorsal inspiratory area prevent switch-off of inspiratory ramp signal.
- Thus prolongs period of inspiration
- Hence decreases rate of respiration

Chemical Control of Respiration

Chemical mechanism of regulation of respiration is operated through the chemoreceptors. Chemoreceptors are the sensory nerve endings, which give response to changes in chemical constituents of blood.

Changes in Chemical Constituents of Blood which Stimulate Chemoreceptors

1. Hypoxia (decreased pO_2)
2. Hypercapnea (increased pCO_2)
3. Increased hydrogen ion concentration.

Types of Chemoreceptors

Chemoreceptors are classified into two groups:
1. Central chemoreceptors
2. Peripheral chemoreceptors.

CENTRAL CHEMORECEPTORS

Central chemoreceptors are the chemoreceptors present in the brain.

Situation

Central chemoreceptors are situated in deeper part of medulla oblongata, close to the dorsal respiratory group of neurons. This area is known as **chemosensitive area** and the neurons are called chemoreceptors.

Mechanism of Action

- Main stimulant for central chemoreceptors is the increased hydrogen ion concentration.
- However, if hydrogen ion concentration increases in the blood, it cannot stimulate the central chemoreceptors because, the hydrogen ions from blood cannot cross the **bloodbrain barrier** and **blood-cerebrospinal fluid barrier.**
- On the other hand, if carbon dioxide increases in the blood, it can easily cross the blood-brain barrier and bloodcerebrospinal fluid barrier and enter the interstitial fluid of brain or the cerebrospinal fluid.
- Hydrogen ions stimulate the central chemoreceptors. From chemoreceptors, the excitatory impulses are sent to dorsal respiratory group of neurons, resulting in increased ventilation

Other Factors that Affect Respiration

1. Impulses from Higher Centers

Higher centers alter the respiration by sending impulses directly to dorsal group of neurons. Impulses from anterior cingulate gyrus, genu of corpus callosum, olfactory tubercle and posterior orbital gyrus of cerebral cortex inhibit respiration. Impulses from motor area and Sylvian area of cerebral cortex cause **forced breathing.**

2. Impulses from Stretch Receptors of Lungs:

Hering-Breuer Reflex

- HeringBreuer reflex is a **protective reflex** that restricts inspiration and prevents overstretching of lung tissues. It is initiated by the stimulation of stretch receptors of air passage.
- Stretch receptors are the receptors which give response to stretch of the tissues. These receptors are situated on the wall of the bronchi and bronchioles.

3. Impulses from 'J' Receptors of Lungs

'J' receptors are **juxtacapillary receptors** which are present on the wall of the alveoli and have close contact with the pulmonary capillaries.

Conditions when 'J' receptors are stimulated

i. Pulmonary congestion
ii. Pulmonary edema
iii. Pneumonia
iv. Over inflation of lungs
v. Microembolism in pulmonary capillaries
vi. Stimulation by exogenous and endogenous chemical substances such as histamine,

4. Impulses from Irritant Receptors of Lungs

Besides stretch receptors, there is another type of receptors in the bronchi and bronchioles of lungs, called irritant receptors.

Stimulation of irritant receptors produces **re flex hyperventilation** along with **bronchospasm.** Hyperventilation along with bronchospasm prevents further entry of harmful agents into the alveoli

5.Anesthesia

This also causes resp. depression.

Causes of Respiratory Center Depression

(1) Cerebro-vascular diseases
(2) Acute brain edema
(3) Anesthesia

Patho-Physiology

Pulmonary Emphysema

Emphysema is one of the obstructive respiratory diseases in which lung tissues are extensively damaged. Damage of lung tissues results in loss of alveolar walls.

Because of this, the elastic recoil of lungs is also lost.

Emphysema is caused by:

1. Cigarette smoking
2. Exposure to oxidant gases
3. Untreated bronchitis.

Development

1. Smoke or oxidant gases irritate the bronchi and bron chioles, leading to chronic infection
2. It increases the mucus secretion from the respiratory epithelial cells causing obstruction of air passage
3. Cilia of respiratory epithelial cells are partially paralyzed and the movement is very much reduced. Because of this, the mucus cannot be removed from the respiratory passage.
4. Destruction of alveolar mucus membrane
5. Destruction of elastic tissues occur

Effects

(1) Increase airway resistance
(2) Decrease diffusing capacity of lungs
(3) Abnormal ventilation-perfusion ratio
(4) Pulmonary hypertension

Pneumonia

Pneumonia is the **inflammation** of lung tissues, followed by the accumulation of blood cells, fibrin and exudates in the alveoli. Affected part of the lungs becomes **consolidated.**

Causes

Inflammation of lung is caused by:
1. Bacterial or viral infection
2. Inhaling noxious chemical substance.

Types

Pneumonia is of two types, namely **lobar pneumonia** and **lobular pneumonia.** When it is lobular and associated with inflammation of bronchi, it is known as **bronchopneumonia.**

Effects

Following are the effects of pneumonia:
1. Fever
2. Compression of chest and chest pain
3. Shallow breathing
4. Cyanosis
5. Sleeplessness (insomnia)
6. Delirium.

Atelectasis

Atelectasis refers to partial or complete **collapse of lungs.** When a large portion of lung is collapsed, the partial pressure of oxygen is reduced in blood, leading to respiratory disturbances.

Causes

1. Deficiency or inactivation of surfactant. It causes collapse of lungs due to increased surface tension, which leads to respiratory distress syndrome.
2. Obstruction of a bronchus or a bronchiole. In this condition, the alveoli attached to the bronchus or bronchiole are collapsed.
3. Presence of air **(pneumothorax),** fluid **(hydrothorax),** blood **(hemothorax)** or pus **(pyothorax)** in the pleural space.

Effects

Effects of atelectasis are decreased partial pressure of oxygen, leading to dyspnea.

Asthma

Bronchial asthma is the respiratory disease characterized by difficult breathing with **wheezing.** Wheezing refers to **whistling type** of respiration. It is due to bronchiolar constriction, caused by spastic contraction of smooth muscles in bronchioles, leading to obstruction of air passage.

Causes

1. *Inflammation of air passage:*
2. *Hypersensitivity of afferent glossopharyngeal*
3. *Pulmonary edema and congestion of lungs caused by left ventricular failure:*

Tuberculosis

Tuberculosis is the disease caused by **tubercle bacilli.** This disease can affect any organ in the body. However, the lungs are affected more commonly. Infected tissue is invaded by macrophages and later it becomes fibrous. Affected tissue is called **tubercle**

Feature

- Initially, alveoli in the affected part become nonfunctioning, due to thickness of respiratory membrane.
- If a large part of lungs is involved, the diffusing capacity is very much reduced. In severe conditions, the destruction of the lung tissue is followed by formation of large **abscess cavities.**

PNEUMOTHORAX

Pneumothorax is the presence of air in pleural space. Intrapleural pressure, which is always negative, becomes positive in pneumothorax and it causes collapse of lungs.

Causes

Air enters the pleural cavity because of damage of chest wall or lungs during accidents, bullet injury or stab injury.

Types

Pneumothorax is of three types:
1. Open pneumothorax
2. Closed pneumothorax
3. Tension pneumothorax.

Hypoxia

Decrease PO_2 in the blood **OR** decrease oxygen supply to the tissue

Types

1. Atmospheric hypoxia
   It is the low O_2 in the atmosphere e.g. hilly area.
2. **Lungs hypoxia / Ventilation hypoxia / Hypoxic hypoxia**
   Due to lungs problem and mostly expiratory problem.
   Rx **Give 100% pure Oxygen in 1 and 2**

Causes

Local causes	Central causes
Restrictive lungs disease	1. Mysthemia Gravis → In Neuromuscular junction , automotors → Fatigue (chest muscles) 2. Quardiplegia → Paralysis of all the body except face .

3. Anemic hypoxia
   low hemoglobin that cause the low oxygen transport.
4. Stagnant hypoxia
   Tissue problem due to having the CN poisoning that inhibit the ETC (use O_2 at the end step and there is no Oxygen usage after that).
   Treatment
   Normally Fe^{++} present in the Hb but Fe^{+3} Hb (met Hb), met Hb give that have more tendency to join the CN.

Rx 100% pure Oxygen is useless because O_2 can't bind the hemoglobin and ETC is inhibited

CYANOSIS

Whenever deoxygenated Hb raises more than 5gm/dl in blood

Hb = in normal is 15g/dl

Causes

Local causes	Central
Peripheral cyanosis At the tip of the fingers and hand side	Congenitial heart problem

Determining Factors

(1) Quantity of deoxy-Hb in arterial blood
(2) Rate of blood flow
(3) Skin thickness

Neurogenic or Emotional Dyspnea

It means difficulty in breathing due to abnormal state of mind, although respiratory system is normal.

Hypercapnia

Increase CO_2 in the body fluids.

Cause

Associated with hypoxia only in hypoventilation & circulatory deficiency.

Methods of Artificial Respiration

(1) Mouth-to-mouth breathing
(2) Resuscitator
(3) Tank respirator

Mountain Sickness

It is a disease caused by exposure to high altitude due to hypoxia.

Symptoms of Chronic Mountain Sickness

(1) Increase red cell mass & hematocrit
(2) Increase pulmonary arterial pressure
(3) Enlarged right heart
(4) Decrease peripheral arterial pressure
(5) Congestive heart failure
(6) Death

Symptoms of Acute Mountain Sickness

(1) Acute cerebral edema
(2) Acute pulmonary edema

Caisson Disease

If a diver remains beneath sea for a long time, large amounts of N2 becomes dissolved in his body fluids. When the diver suddenly comes back to sea surface, N_2 bubbles develop in his ICF or ECF that damage different areas of body, esp. brain. This is called Caisson disease.

Symptoms

(1) Local pain in legs or arms
(2) Dizziness
(3) Paralysis
(4) Chokes or shortness of breath
(5) Extreme fatigue & pain
(6) Collapse with unconsciousness

Prevention

Caission disease can be prevented by bringing the diver to sea surface slowly, so that lungs can eliminate N_2.

Cheyne-Stokes Breathing

It is a periodic breathing characterised by rhythmic waxing & warming of deep respiration.

Mechanism

Increase respiration → Increase CO_2 blown off → Decrease blood CO_2 → Does not excite respiratory center Decrease respiration Decrease CO_2 blown off → Increase blood CO_2 Excities respiratory center → Increase respiration So on.

Causes

(1) Cardiac Failure
(2) Damage to brain stem
(3) Hypoxia

Terms to know

Eupnea = Normal breathing
Tachypnea = Rapid breathing
Bradypnea = Slow breathing
Hyperpnea = Increase rate of alveolar ventilation to cause over-respiration
Hypopnea = Decrease rate of alveolar ventilation to cause under-respiration
Apnea = Stoppage of breathing
Dyspnea = Difficult or labored breathing
Dysphonia = Difficulty in speaking
Asphyxia = Interruption of gas exchange in lungs resulting in cessation of life.
Anoxia = Total lack of O_2
Hypoxia = Decrease O_2
Anoxemia = Lack of O_2 in blood Hypoxemia = Decrease O_2 in blood Hypercapnia = Increase CO_2 in blood Hypocapnia = Decrease CO_2 in blood Acapnia = No CO_2 in body fluids.

Body Plethysmograph

It is an air-tight tank into which a person is placed & is used to measure different aspects of pulmonary function.

Chapter # 13

Endocrinology

Contents

Study of hormones secreted by ductless (endocrine) glands, is called endocrinology.

Hormone

Neurohormone

Neurohormone is a chemical substance that is released by the nerve cell directly into the blood and transported to the distant target cells.

Examples are oxytocin, antidiuretic hormone and hypothalamic releasing hormones.

Difference B/W Factor and Hormone

(1) Factor

A substance that has actions of a hormone but that has not been purified and identified as a distinct chemical compound, is called factor.

(2) Hormone

When a factor has been purified and identified as a distinct chemical compound, it is called hormone.

Types (2)

(1) Local Hormones

These have specific local effects, eg

(a) Acetylcholine
(b) Secretin
(c) Cholecystolcinin

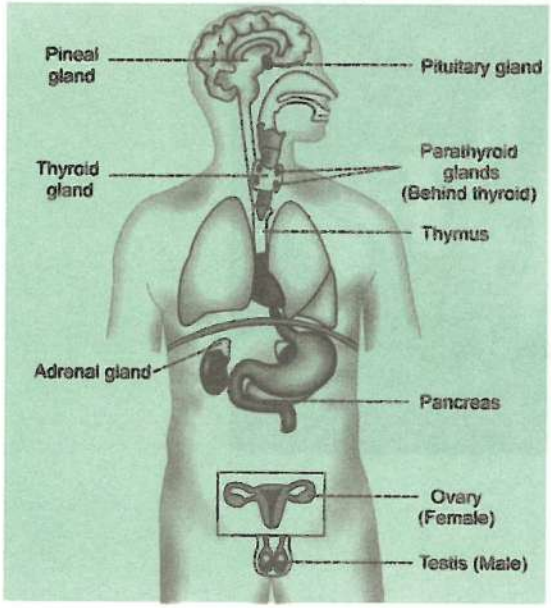
(2) General Hormones

They affect body cells far away from their point of secretions.

Sub-Types

Two,

(a) General hormones that affect all cells of body, eg growth hormone and thyroid hormone
(b) General hormones that affect only target-cells because they have specific receptors for hormones, eg ACTH, ovarian hormones, etc.



Target Organ/cell

It is defined as having a particular type of receptors for a particular type of hormone, with which the hormone can bind.

Endocrine Glands

Endocrine glands are the glands which synthesize and release the classical hormones into the blood. Endocrine glands are also called **ductless glands** because the hormones secreted by them are released directly into blood without any duct. Endocrine glands are distinct from exocrine glands which release their secretions through ducts.

Some Glands and their functions

Anterior pituitary	1. Growth hormone (GH) 2. Thyroid-stimulating hormone (TSH) 3. Adrenocorticotropic hormone (ACTH) 4. Follicle stimulating hormone (FSH) 5. Luteinizing hormone (LH) 6. Prolactin
Posterior pituitary	1. Antidiuretic hormone (ADH) 2. Oxytocin
Thyroid gland	1. Thyroxine (T_4) 2. Triiodothyronine (T_3) 3. Calcitonin
Parathyroid gland	Parathormone
Pancreas – Islets of Langerhans	1. Insulin 2. Glucagon 3. Somatostatin 4. Pancreatic polypeptide
Adrenal cortex	*Mineralocorticoids* 1. Aldosterone 2. 11-deoxycorticosterone
	Glucocorticoids 1. Cortisol 2. Corticosterone
	Sex hormones 1. Androgens 2. Estrogen 3. Progesterone
Adrenal medulla	1. Catecholamines 2. Adrenaline (Epinephrine) 3. Noradrenaline (Norepinephrine) 4. Dopamine
Testis	1. Testosterone 2. Dihydrotestosterone 3. Androstenedion
Ovary	1. Estrogen 2. Progesterone

Hormones secreted by other organs

Pineal gland	Melatonin
Thymus	1. Thymosin 2. Thymin
Kidney	1. Erythropoietin 2. Thrombopoietin 3. Renin 4. 1,25-dihydroxycholecalcifero (calcitriol) 5. Prostaglandins
Heart	1. Atrial natriuretic peptide 2. Brain natriuretic peptide 3. C-type natriuretic peptide
Placenta	1. Human chorionic gonadotropin (HCG) 2. Human chorionic somatomammotropin 3. Estrogen 4. Progesterone

Classification of Hormones

Types	Hormones
Peptide,	• Ant. Pituitary hormones - GH, ACTH, prolactin • Post. Pituitary hormones - ADH and oxytocin • Pars intermedia of pituitary gland - alpha and beta MSH • Islets of Langerhans - insulin, glucagon and somatostatin. • Parathyroid hormone • Thyroid gland - calcitonin • GU hormones • Releasing and inhibitory hormones and factors of hypothalamus. • Ovary – relaxin
Amines	• Acetylcholine • Catecholamines, epinephrine and norepinephrine • Melatonin (by pineal body)
Steroids	• Adrenal cortex - cortisol, aldosterone and adrenal androgens • Ovary - estrogen and progesterone • Testis – testosterone
Amino acids	• Thyroxine (T4) • Tri-iodothyronine (T3
Glycoproteins	• TSH and LH • Human chorionic gonadotropin

Storage of Hormones

(1) Protein Hormones

Typically, the initial protein formed by the endoplasmic reticulum is larger than the active hormone and is called a preprohormone.

The signal sequence of this large protein is cleaved in the endoplasmic reticulum to form a **prohormone** → Subsequently, in the Golgi apparatus the prohormone is packaged in secretion granules along with proteolytic enzymes that cleave the **prohormone into active hormone** and other fragments → When the endocrine cell is stimulated, the secretion granules migrate from the cytoplasm to the cell membrane → Free hormone and co-peptides are then released into the extracellular fluid by exocytosis.

(2) Steroid Hormones

- Once the steroid hormone appears in the cytoplasm, storage does not take place, and the hormone diffuses through the cell membrane into the extracellular fluid.
- Much of the cholesterol in steroid-producing cells is removed from the plasma, but there is also de novo synthesis of cholesterol from acetate.

(3) Amino Acid Hormones

- As with steroid hormones, there is no storage of thyroid hormones in discrete granules, and once thyroid hormones appear in the cytoplasm of the cell they leave the cell via diffusion through the cell membrane.
- In contrast to steroid hormones, there are large stores of thyroxine and triiodothyronine as part of a large iodinated protein (**thyroglobulin**) that is stored in the lumens of thyroid follicles.
- In comparison, the other group of hormones derived from tyrosine, the adrenal medullary hormones epinephrine and norepinephrine, are taken up into preformed vesicles and stored until secreted. As with protein hormones stored in secretion granules, catecholamines are released from adrenal medullary cells through exocytosis.

Transport of Hormones in the Blood

- Water soluble hormones: (peptides & catecholamines) Dissolved in plasma.
- teroid & thyroid hormones: Circulate in blood mainly bound to plasma proteins.

Difference between two Major Classes of Hormones		
	LIPID – SOLUBLE HORMONES (STERODIS, 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: thyroid homones	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 Exception: adrenal androgens	Dissolved in plasma (free, unbound)
Half – life	Long (hours, days) □ to affinity for protein carrier	Short (minutes) □ to Molecular weight

"Clearance" of Hormones from the Blood

Two factors can increase or decrease the concentration of a hormone in the blood. One of these is the rate of hormone secretion into the blood. The second is the rate of removal of the hormone from the blood, which is called the *metabolic clearance rate*

Metabolic clearance rate = Rate of disappearance of hormone from the plasma /

Concentration of hormone

Methods

In four ways

(1) Metabolic destruction by tissues
(2) Binding with tissues
(3) Excretion by liver into bile
(4) Excretion by kidneys into urine

Metabolic Clearance Rate of Hormone

Vol. (ml) of plasma cleared of hormone per minute, is called metabolic clearance rate of hormone.

Hormone Receptors

These are specific binding sites in cell

Nature

They are mostly proteins and are specific for a single hormone.

Location

(1) In cell membrane for protein, peptides and catecholamines
(2) In cytoplasm, for steroid hormones
(3) In nucleus, for thyroid hormones (T4 and T3)

Properties of Receptors Hormone Specificity

Hormone Specificity

A hormone affects only cells that possess receptors specific to that particular hormone e.g.adrenocorticotropic hormone (ACTH) and luteinizing hormone (LH) both increase the secretion of steroid hormones. However, ACTH does so only in the adrenal hormones. However, ACTH does so only in the adrenal cortex and LH only in gonadal tissue.

Permissive action

A phenomenon in which one type of hormone must be present before another hormone can act; e.g., to prevent hypoglycemia, cortisol must be present for glucagon to carry out glycogenolysis.

Regulation of Hormone Receptors

Receptor proteins are not static components of the cell. Their number increases or decreases in various conditions. Generally, when a hormone is secreted in excess, the number of receptors of that hormone decreases due to binding of hormone with receptors. This process is called **down regulation.** During the deficiency of the hormone, the number of receptor increases, which is called **upregulation.**

Mechanism of Hormonal Action

Three,

(1) Membrane Permeability Mechanism

Hormones (eg neurotransmitters) combine with receptor on cell mem. -7 Conformational change in receptor molealle - Mem. Permeability change for ions - Excitation or inhibition of cell depending on nature of ions.

(2) Activating intracellular enzymes

First Messenger

The hormone which acts on a target cell, is called first messenger or **chemical mediator.** It combines with the receptor and forms hormone-receptor complex.

Second Messenger

Hormone-receptor complex activates the enzymes of the cell and causes the formation of another substance called the second messenger or **intracellular hormonal mediator**

(a) Cyclic AMP MAchanism

- Cyclic AMP, cAMP or cyclic adenosine 3'5'-monophosphate acts as a second messenger for protein hormones and catecholamines.
- Hormone (1st messengers) combines with receptor on cell membrane → Activates adenyl cyclase - Converts cytoplasmic ATP to cyclic AMP (2nd messenger)

- Following effects
  - (i) Alters cell mem. permeability.
  - (ii) Activates enzymes
  - (iii) Causes muscle contraction or relaxation
  - (iv) Causes protein synthesis
  - (v) Causes secretion

(b) Ca^{++} Calmodulin Mechanism

- Many hormones act by increasing the calcium ion, which fucntions as second messenger along with another protein called calmodulin or troponin C.
- Hormone (1st messenger) combines with receptor on cell membrane - Ca^{++} enters cytoplasm → Ca^{++} binds with 3 or → sites of a protein calmodulin → Calmodulin (2nd messenger) activated

Following effects

(i) Activates enzymes other than activated by cAMP.
(ii) Activates myosin kinase that causes smooth muscle contraction.

(c) Other 2nd messengers

Include

(i) Cyclic GMP
(ii) Inositol triphosphate
(iii) Prostaglandins

(3) Acting on Gene / protein formation

Sequence of Events during Activation of Genes

i. Hormone enters the interior of cell and binds with receptor in cytoplasm (steroid hormone) or in nucleus (thyroid hormone) and forms hormonereceptor complex
ii. Hormone-receptor complex moves towards the DNA and binds with DNA
iii. This increases transcription of mRNA
iv. The mRNA moves out of nucleus and reaches ribosomes and activates them
v. Activated ribosomes produce large quantities of proteins
vi. These proteins produce physiological responses in the target cells.

Measurement of Hormone Concentration in Blood

- By Radio-immuno-assay method.
- **Enzyme-Linked Immunosorbent Assay**

Endorine Glands, Hormones, and Their Functions and Structure

Gland/ tissues	Hormones	Major Functoins	Chemical Strucutre
Hypothalamus	Thyrotropin-releasing hormone (TRH)	Stimulates secretion of TSH and prolactin	Peptide
	Corticotropin-releasing hormone (CRH)	Causes release of ACTH	Peptide
	Growth hormone-releasing hormone (GHRH)	Causes release of growth hormone	Peptide
	Growth hormone inhibitory hormone (GHIH) (somatostatin)	Inhibits release of growth hormone	Peptide
	Gonadotropin-releasinghormone (GnRH)	Cause release of LH and FSH	
	Dopamine or prolactin-inhibiting factor (PIF)	Inhibits release of prolactin	
Anterior pituitary	Growth hormone	Stimulates protein synthesis and overall growth of most cells and tissues	Peptide
	Thyroid-stimulating hormone (TSH)	Stimulates synthesis and secretion of thyroid hormones (thyroxine and triiodothyronine)	Peptide
	Adrenocorticotropic hormone (ACTH)	Stimulates synthesis and secretion of adrenocortical hormones (cortisol, adrogens, and aldosterone)	Peptide
	Prolactin	Promotes development of the female breasts and secretion of milk	Peptide
	Follicle-stimulating hormone (FSH0	Causes growth of follicles in the ovaries and maturation in Sertoli cells of testes	Peptide
	Luteinizing hormone (LH)	Stimulates testosterone synthesis in Leydig cells of testes; stimulates ovulation, formation of corpus luteum, and estrogen and progesterone s thesis in ovaries	Peptide
Posterior pituitary	Antidiuretic hormone (ADH0 (also called vasopressin)	Increases water reabsorption by the kidneys and causes vasoconstriction and increased blood pressure	Peptide
	Oxytocin	Stimulates milk ejection from breasts and uterine contractions	Peptide

Thyroid	Thyroxine (T_4) and triiodothyronine (T_3)	Increases the rates of chemical reactions in most cells, thus increasing body metabolic rate	Amine
	Calcitonin	Promotes deposition of calcium in the bones and decreases extracelhdar fluid calcium ion concentration	Peptide
Adrenal cortex	Cortisol	Has multiple metabolic functions for controlling metabolism of proteins, carbohydrates, and fats; also has anti-inflammatory effects	Steroid
	Aldosterone	Increases renal sodium reabsorption" potassium secretion, and hydrogen ion secretion	Steroid
Adrenal medulla	Norepinephrine, epinephrine	Same effects as sympathetic stimulation	Amine
Pancreas	Insulin (β cells)	Promotes glucose entry in many cells, and in this way controls carbohydrate metabolism	Peptide
	Glucagons (α cells)	Increases synthesis and release of glucose from the liver into the body fluids	Peptide
Parathyroid	Parathroid hormone (PTH)	Controls serum calcium ion concentration by increasing calcium absorption by the gut and kidneys and releasing calcium from bones	Peptide
Testes	Testosterone	Promotes development of male reproductive system and male secondary sexual characteristics	Steroid
Ovaries	Estrongs	Promotes growth and development of female reproductive system, female breasts, and female secondary sexual characteristics	Steroid
Placenta	Human chorionic gondotropin (HCG)	Promotes growth of corpus luteum and secretion of estrogens and progesterone by corpus luteum	Peptide
	Human somatomammotropin	Probably helps promote development of some fetal tissues as well as the mother's breasts	Peptide
	Estrogens	See actions of estrogens from ovaries	Steroid
	Progesterone	See actions of progesterone from ovaries	Steroid
Kidney	Renin	Catalyzes conversion of angiotensinogen to angiotensin I (acts as an enzyme)	Peptide
	1,25-Dihydroxycholecalciferol	Increases intestinal absorption of calcium and bone mineralization	Steroid
	Erythropoietin	Increases erythrocyte production	Peptide
Heart	Atrial natriuretic peptide (ANP)	Increases sodium excretion by kidneys, reduces blood pressure	Peptide
Stomach	Gastrin	Stimulates HCl secretion by parietal cells	Peptide
Small intestine	Secretin	Stimulates pancreatic acinar cells to release bicarbonate and water	Peptide
	Cholecystokinin (CCK)	Stimulates gallbladder contraction and release of pancreatic enzymes	Peptide
Adipocytes	Leptin	Inhibits appetite, stimulates thermogenesis	Peptide

Neurotransmitters and Hormones that influence Feeding and Satiety Centers in the Hypothalamus	
Decrease Feeding (Anorexigenic)	Increase Feeding (Orexigenic)
α-Melanocyte-stimulating hormone (α-MSH)	Neuropeptide Y (NPY)
Leptin	Agouti-related protein (AGRP)
Serotonin	Melanin-concentrating hormone (MCH)
Norepinephrine	Orexins A and B

Corticotropin-releasing hormone	Endorphins
Insulin Cholecystokinin (CCK)	Galanin (GAL) Amino acids (glutamate and γ-aminobutyric acid)
Glucagon-like peptide (GLP)	
Cocaine- and amphetamine-regulated transcript (CART)	Ghrelin
Peptide YY (PYY)	

Pituitary Gland

Pituitary Gland (Hypophysis)

- Pituitary gland or **hypophysis** is a small endocrine gland with a diameter of 1 cm and weight of 0.5 to 1 g.
- It is situated in a depression called '**sella turcica**', present in the sphenoid bone at the base of skull.
- It is connected with the hypothalamus by the **pituitary stalk** or **hypophyseal stalk.**

Divided into

(1) Anterior pituitary (Adenohypophysis) originates from Rathke's pouch.

(2) Posterior pituitary (neurohypophysis) originates from hypothalamus.

(3) Pars intermedia in b/w (1) and (2)

Cell Types in Anterior Pituitary Gland

Anterior pituitary has two types of cells, which have different staining properties:

1. Chromophobe cells
2. Chromophil cells

Chromophil Cells

Chromophil cells contain large number of granules and are darkly stained.

Types of chromophil cells

Chromophil cells are classified by two methods.

1. Classification on the basis of staining property: Chromophil cells are divided into two types:

i. **Acidophilic cells** or **alpha cells,** which form 35%

ii. **Basophilic cells** or **beta cells,** which form 15%.

2. Classification on the basis of secretory nature: Chromophil cells are classified into five types:

i. **Somatotropes (50%),** which secrete growth hormone

ii. **Corticotropes (20%),** which secrete adrenocorticotropic hormone

iii. **Thyrotropes (5%),** which secrete thyroid-stimulating hormone (TSH)

iv. **Gonadotropes(5%) ,** which secrete follicle-stimulating hormone (FSH) and luteinizing hormone (LH)

v. **Lactotropes (20%),** which secrete prolactin (SMC, TG)

Cells and Hormones of the Anterior Pituitary Gland and Their Physiological Functions

Cell	Hormone	Chemistry	Physiological Actions
Somatotropes	Growth hormone (GH; somatotropin)	Single chiain of 191 amino acids	Stimulates body growth; stimulates secretion of IGF-I; stimulates lipolysis; inhibits actions of insulin on carbohydrate and lipid metabolism
Corticotropes	Adrenocorticotropic hormone (ACTH: corticotropin)	Single chain of 39 amino acids	Stimulates production of glucocorticoids and androgens by the adrenal cortex; maintains size of zona fasciculata and zona reticularis of cortex
Thyrotropes	Thyroid-stimulating hormone (TSH; thyrotropin)	Glycoprotein of two subunits, a (89 amino acids) and p (112 amino acids	Stimulates production of thyroid hormones by thyroid follicular cells; maintains size of follicular cells
Gonadotropes	Follicle-stimulating hormone (FSH)	Glycoprotein of two subunits, a (89 amino acids) and 3 (112 amino acids	Stimulates development of ovarian follicles; regulates spermatogenesis in the testis

	Luteinizing hormone (LH)	Glycoprotein of two subunits, a (89 amino acids) and p (115 amino acids_	Causes ovulation and formation of the corpus luteum in the ovary; stimulates production of estrogen and progesterone by the ovary; stimulates testosterone production by the testis
Lactotropes, Mammotropes IGF insulin-like growth factor	Prolactin (PRL)	Single cahin of 198 amino acids	Stimulates milk secretion and production

Courtesy by Guyton & Halls Physiology

Cell Types in Posterior Pituitary Gland

Posterior pituitary gland is composed of glial-like cells called pituicytes which do not secrete hormones. They support terminal nerve fibers and endings that originate in supraoptic and paraventricular nuclei of hypothalamus.

Sites of Formation and Transport of Posterior Pituitary Hormones

Sites of Formation

(1) Supraoptic nuclei Form ADH.
(2) Paraventricular nuclei Form oxytocin

Transport

ADH and oxytocin combine with carrier protein, called neurophysins, and are transported from supraoptic and paraventricular nuclei to terminal nerve endings in posterior pituitary gland.

Hypothalamic-Hypophyseal Portal System

- Capillaries in median eminence (lowermost portion of hypothalamus) form hypothalamic-hypophyseal portal vessels
- Enter anterior Pituitary sinuses. This is called hypothalamic-hypophyseal portal system.

Function

This portal system carries hypothalamic releasing and inhibitory hormones

Hypothalamic Releasing and Inhibitory Hormones or Factors

(1) Growth hormone releasing hormone (GHRH)
(2) Growth hormone inhibitory hormone (GHIFI)
(3) Thyrotropin releasing hormone (TRH)
(4) Prolactin inhibitory hormone (PIH)
(5) Corticotropin releasing hormone (CRH)
(6) Luteinizing hormone releasing hormone (LHRH) Causes release of both LH and FSH

Hypothalamic Releasing and inhibitory Hormones That Control Secretion of the Anterior Pituitary Gland

Hormone	Structure	Primary Action on Anterior Pituitary
Thyrotropin-releasing hormone (TRH)	Peptide of 3 amino acids	Stimulates secretion of TSH by thyrotropes
Gonadotropin-releasing hormone (GnRH)	Single chain of 10 amino acids	Stimulates secretion of FSH and LH by gonadotropes
Corticotropin-releasing hormone (CRH)	Single chain of 41 amino acids	Stimulates secretion of ACTH byCorticotropes
Growth hormone-releasing hormone (GHRH)	Single chain of 44 amino acids	Stimulates secretion of growth hormone by somatotropes
Growth hormone inhibitory hormone (somatostatin)	Single chain of 14 amino acids	Inhibits secretion of growth hormone by somatotropes
Prolactin-inhibiting hormone (PIH)	Dopamine (a catecholamine)	Inhibits secretion of prolactin by lactotropes

Damage to the Pituitary Stalk

When the connection between the hypothalamus and the anterior pituitary is severed (e.g. damage to the pituitary stalk), 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 the growth hormone decreases demonstrate that the main factor regulating the release of growth hormone is the releasing factor GHRH.

Sheehan Syndrome

The pituitary in pregnany 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% women with severe post partum hemorrhage. Symptoms vary,

depending on the extent and location of pituitary damage.

Gonadotroph Downregulation

In the hypothalamic - anterior pituitary system, hormonal release is mainly pulsatile. A possible exception is the thyroid system. The pulsatile release of GnRH prevents downregulation of its receptors on the gonadotrophs of the anterior pituitary. A constant infusion of GnRH will cause a decrease in the release of both LH & FSH.

Hyperprolactinema

May result from medications (dopamine antagonists) or disease 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 feed back effects of estrogen & subsequent LH surge and sometimes galactorrhea (inappropriate production of milk). Serum levels of estradiol are usually decreased.

In Men, may produce galactorrhea, decreased libido, impotence & hypogonadism. Serum levels of testosterone are usually decreased.

Treatment includes surgical removal of tumor or medical treatment with bromocriptine (dopamine agonist)

GROWTH HORMONE

Somatotropin or somatotropic hormone

Nature		Protein
Site of Secretion		Somatotropes (acidophilic cells) of ant. pituitary gland.
Mechanism of Action		
Carbohydrates	Cellular Glucose	Decrease
	Blood Glucose	Increase
Protein		Synthesis • Increase amino acid entry into cells, like insulin • Increase protein synthesis by ribosomes due to direct effect on ribosomes • Increase transcription of DNA to form mRNA - Increase protein synthesis • Decrease protein catabolism; because GH mobilizes free fatty acids to supply energy
Lipids		Lipolysis • Mobilizes free fatty acids from adipose tissue • Increase free fatty acid concentration In body fluid
Other actions		• Act on cartilage and bone to stimulate their growth. • It deposit the connective tissue & Thicken the skin • Increase growth of viscera, eg liver, kidney, etc. • Increase milk secretion due to prolactin-like action. • GH promotes growth of all tissues due to (a) increase size of cell and (b) increase mitosis.
Regulation	Stimulate	• Acute hypoglycemia • Chronic hypoproteinemia • Decrease plasma free fatty acid level • Stress, trauma, emotion, exercise • Starvation • Deep sleep (stage II & IV)
	Inhibit	• GHIH • Glucagon • Hyperglycemia • Hyperlipidemia • Growth hormone (exogenous) • Somatomedins (insulin-like growth factors)

Disorders	
Hyper secretion	Inc. activity of pituitary gland is called hyperpituitarism. **Types** Two **(1) Gigantism** Increase GH secretion before adolescence, so that person becomes a giant with height of 8-9 feet, is called gigantism. **Characteristics** (a) Height increase upto 8-9 feet (b) Hyperglycemia Beta-cells burn out due to over-stimulation Diabetes mellitus **Causes** (a) Acidophilic (GH-secreting) tumors of ant. pituitary gland. (b) Increase somatomedin formation **(2) Acromegaly** Increase GH secretion after adolescence, is called acromegaly. **Characteristics** (a) Soft tissue enlarge and bones inc. in thickness (b) Forehead slants forward (c) Nose and lips inc. in size (d) Jaw protrudes forward (prognathism) (e) Coarse facial features (acronegalic facies) (f) Finger and hand inc. in size (g) Foot increase in size (h) Kyphosis or hunched back
Hypo secretion	**Panhypopituitarism** Decrease secretion of all ant. pituitary hormones is called pan-hypopituitarism. (Pan = all) **Types** Two **(1) Dwarfism** Panhypopituitarism in children is called dwarfism. **Characteristics** (a) Features of body develop in appropriate proportion to each other, but rate of growth is dec. (b) No thyroid deficiency (c) No adrenocortical deficiency (d) No mental retardation (e) Sexually retarded due to deficiency and LH (f) 1 /3 dwarfs have only GH deficiency and they secrete FSH and LH; so, they are not sexually retarded. **Causes** (a) Congenital (b) Inflammation of ant. pituitary gland (c) Trauma to anterior pituitary gland **Treatment** By human growth hormone synthesized by Escherichia coli by recombinant DNA technology. **Lorin Dwarf** It is due to hereditary inability to form somatomedin(IGF-1) in response to GH (although GH secretion is normal). **(2) Simmond's Disease** Panhypopituitarism in adults is called simmond's disease. **Characteristics** (a) Hypothyroidism (b) Decrease FSH & LH secretion Sexual functions are lost

	(c) Lethargy (d) Weight gain **Causes** (a) Craniopharyngeomas and chromophobe tumors that compress and destroy pituitary gland (b) thrombosis of pituitary blood vessels

Diabetogenic Effect of GH

GH → Hyperglycemia -*Beta cells stimulated by (1) hyperglycemia and (2) direct effect of GH → Beta cells secrete extra insulin → Beta cells burn out due to over-stimulation → Diabetes mellitus.

Pituitary Diabetes

Specific increase in GH or generalized inc. in all ant. pituitary hormones cause elevated blood glucose conc.; this is called pituitary diabetes.

Difference b/w Pituitary Diabetes and Diabetes Mellitus

(1) In PD glucose utilization is moderately depressed; while in DM there is no glucose utilization.

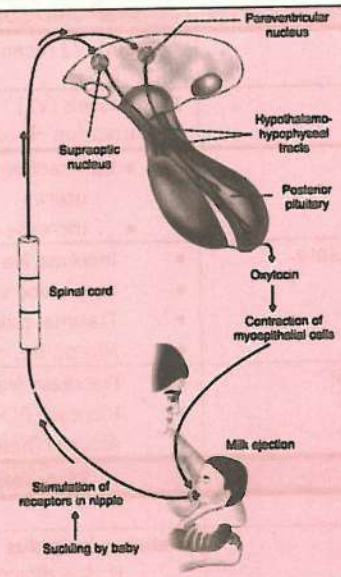
(2) In PD blood glucose is refractory to insulin injection, because insulin is already present; while in DM blood glucose dec. by insulin injection as DM is caused by insulin lack.

(3) Side effects of DM are absent in PD.

ADH (VASOPRESSIN)

Nature		Protein (polypeptide)
Site of Secretion		Supra-optic nuclei of hypothalamus.
Mechanism of Action		
On Kidney		Act on th V2 receptors of Kidney and retain the water from excess loss
On vessels		1. Vessels (V1) Vasopression ➔ constrict arterioles ➔ increase arterial pressure
Other actions		• Contraction of any smooth muscle in body, eg G1T, bile duct and uterus • Increase urinary retention
Regulation	Stimulate	• Increase Na+ conc. Or inc. osmolality of ECF • Low blood volume And low BP • Trauma, pain, anxiety • Morphine, nicotine, tranqulizers and anesthetics
	Inhibit	• Decrease Na+ Concentrationor decrease osmolality of ECF • Increase Blood vol. and increase Blood Pressure • Alcohol (hence causes diuresis)
Disorders		
Hyper secretion		
Hypo secretion		**Diabetes Insipidus** It is a disease characterized by passage of excess water (but no abnormal constituent) in urine due to absence of ADH. **Causes** (1) Destruction of supraoptic nuclei (2) Tumor of hypothalamus or hypophysis that destroys supraoptic nuclei. **Types** (a) **Central Neurogenic Diabetes Insipidus**: Sufficient ADH is not available to affect the renal collecting ducts. (b) **Nephrogenic Diabetes Insipidus**: Due to the inability of the kidneys to respond to ADH. **Characteristics** (1) Polyuria = 4-6 lit. urine/day (2) Polydipsia = Inc. water intake **Treatment** By injecting ADH suspended in oil (for slow release)

Effects of Primary Polydipsia, Diabetes Indsipidus and SIADH			
	Primary Polydipsia	Central Neurogenic Diabetes Insipidus	SIADH
1. Permeability of collecting ducts to H_2O	↓	↓	↓
2. Urine flow	↑	↑	↓
3. Urine osmolarity	↓	↓	↑
4. EFC volume	↑	↓	↑
5. ECF osmolarity (Na concentration)	↓	↑	↓
6. ICF volume	↑	↓	↓
7. ICF osmolarity	↓	↑	↓

OXYTOCIN	
Nature	Poly peptide
Site of Secretion	Paraventricular nuclei of hypothalamus
Mechanism of Action	
On uterus	Powerfully stimulates (constrict) pregnant uterus toward end of gestation ➔ Helps parturition
On Milk ejection	 Mechanism➔ Baby suckles nipple ➔ Afferent impulses to paraventricular nuclei of hypothalamus ➔ Oxytocin released ➔ Oxytocin carried by blood to breast Causes contraction of myoepithelial cells that surround alveoli ➔ Milk ejection or milk letdown.
Other actions	• Increase fertilization • Cause vasodilation and lower BP • Cause prolectin secretions
Regulation	Release just before and after delivery
Disorders	
Hypo/ Hyper secretion	No disease

Thyroid Gland

- Thyroid gland is composed of large number of closed **follicles.** These follicles are lined with cuboidal epithelial cells, which are called the **follicular cells.**
- Follicular cavity is filled with a colloidal substance known as **thyroglobulin,** which is secreted by the follicular cells.
- Follicular cells also secrete tetraiodothyronine (T4 or thyroxine) and tri-iodothyronine (T3). In

between the follicles, the **parafollicular cells** are present

Hormones of thyroid

Thyroid gland secretes three hormones:

1. Tetraiodothyronine or T_4 (thyroxine)
2. Tri-iodothyronine or T_3
3. Calcitonin

Daily Rates of T3 & 14 Secretion

(1) T4 90µg/day
(2) T3 35 µg/day
(3) Reverse T3 Another 35 µg/day T3 is formed in tissues from T4; this is called reverse T3.

Formation of T3 And T4

a. steps

1.Iodide Trapping (Iodide Pump)

Active transport of iodide from ECF into thyroid follicular cells and then into follicle, is called iodide trapping (iodide pump)

I⁻ Requirements

1mg/week or 50 mg per year.

I⁻ Absorption from GIT

I⁻ is absorbed from GIT into blood in same manner as Cl".

2. Formation and secretion of Thyroglobulin

ER and Golgi apparatus of thyroid follicular cells synthesize and secrete into follicles a glycoprotein, called thyroglobulin, containing 70 tyrosine amino acid residues. Thyroid hormones T3 and T4 are formed as a part of thyroglobulin.

T Latent Period of T3 & T4

Period in which T3 & T4 show no activity inspite of remaining in blood, is called latent period of T3 & T4.

Value

(1) T3 = 6-12 hrs
(2) T4 = 2-3 days

Causes of Latent Period

(1) Strong binding T3 & T4 with plasma proteins and intracellular proteins
(2) Slow release of T3 & T4
(3) Also because their actions are mediated by protein-formation mechanism

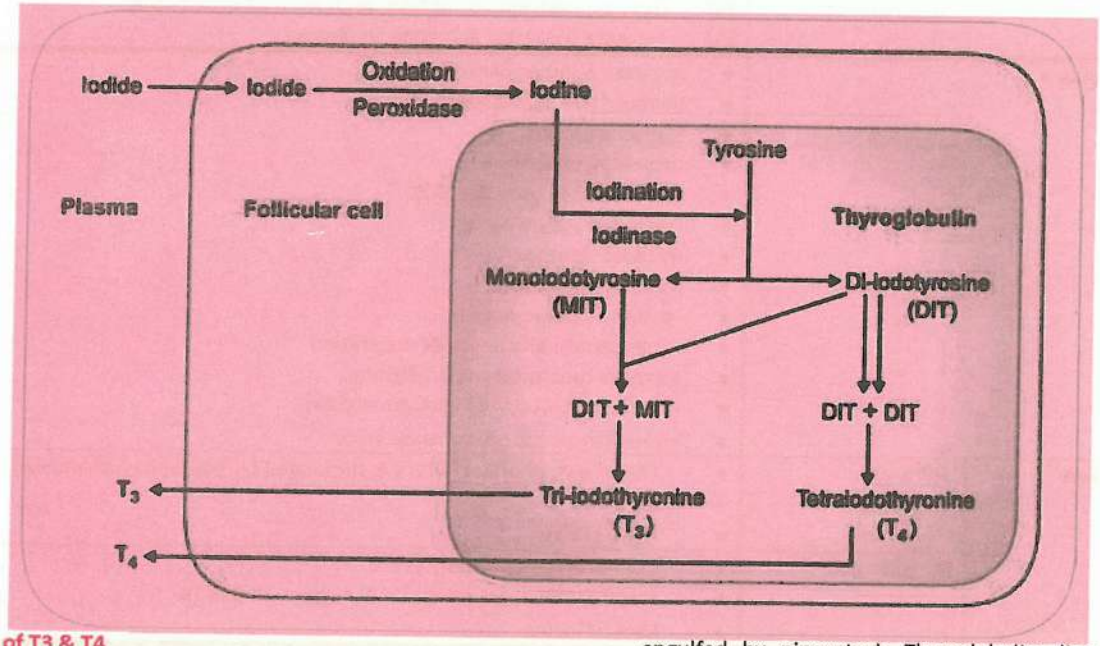
3.Oxidation of Iodide

[Oxidation = removal of electron. Iodide (I-) is oxidized into iodine (12) in thyroid follicle. This process is accelerated by peroxidase and hydrogen peroxide.

4.Iodination of Tyrosine (Organification of thyroglobulin)

In this process, iodine (12) combines with tyrosine of thyroglobulin and forms thyroid metabolic hormones, T3 and T4. This is accelerated by iodinase.

(1) Tyrosine + 12 Mono-iodo tyrosine
(2) MIT + 12 7 Di-iodo tyrosine
(3) MIT + DIT Tri-iodo thyronine (T3)
(4) DIT + DIT Tetra-iodo-thyronine (thyroxine or T4)



Storage of T3 & T4

Thyroid hormones (T3 & T4) are stored in thyroid follicles as part of thyroglobulin. There is 1 T3 molecule for every 10 molecules of T4.

Release of T3 & 14

Apical surface of thyroid follicular cells send out pseudopodal extensions Portions of thyroglobulin engulfed by pinocytosis Thyroglobulin digested by lysosomal enzymes, eg proteinases T3 & T4 released.

Recycling of 12

MET & DIT in thyroglobulin are released during digestion , MET & DIT acted upon by deiodinase Iodine released from MIT & DIT 12 used for additional

thyroid hormone formation This process is called recycling of 12.

Transport of T3 & 14

T3 & T4 are transported in blood by combining with plasma proteins

(1) 2/3 with thyroxine-binding globulin (its affinity is 10 times more for T4 than T3).

(2) 1/4 with thyroxine-binding prealbumin

(3) 1/10 with albumin

Plasma Times of T3 & 14

Time required for 1/2 of T3 or T4 to be released from blood into tissue cells is called plasma half time of T3 or T4.

Values

(1) 1/2 time of T3 = 1.3 days

(2) 1/2 time of T4 = 6 days

Difference B/W T3 &

(1) T4 is 90% & T3 is 10%

(2) T4 binds 10 times more rapidly to thyroxine-binding globulin than T3.

(3) T4 also binds more rapidly to intracellular proteins than T3

(4) Duration of action of T4 is → times more than that of T3

(5) T3 acts → times more rapidly than T4.

(6) In target cell T4 is deiodinated to T3, so, true intracellular hormone is T3 rather than T4.

THYROID HORMONE

Nature		AMINES
Site of Secretion		Discussed earlier
Mechanism of Action		
Carbohydrates	**Cellular Glucose**	Increase
	Blood Glucose	Decrease
Protein		Synthesis (a) By increasing translation process in ribosomes (b) By increasing transcription process in nucleus (c) increase intracellular enzymes
Lipids		Lipolysis (a) Increase mobilization of fatty acids from adipose tissue (b) Increase free fatty acid conc. in plasma
Other actions		• Increase number of mitochondria • Incraese ATP formation • Promote growth • Increase metabolism • Incraese BMR upto 60-100% • Decrease body weight • Incraese apetite • Incraese Blood flow • Incraese cardiac output • Increase rate and depth of respiration • Increase muscle strength (slightly) • Increase secretions of endocrine gland • Hypsethyroidism → decrease libido
Regulation	Stimulate	• TSH of ant. pituitary (which is stimulated by TRH of hypothalamus) • Cold • Low BMR
	Inhibit	• Excitement and anxiety • Negative feedback inhibition by excess 13 and T4 • Lack of iodine
Disorders		
Hyper secretion		Toxic goiter, thyrotoxicosis or Graves' disease. **Causes** a. Autoimmunity Long-acting thyroid stimulator (LATS), an antibody Binds at same receptors on thyroid cell mem., that bind with TSH → Inc. T3 & 14 secretion.

	b. Localized adenoma in thyroid gland Increase T3 & T4 secretion. Symptoms • Damage vision • Inability to sleep • Nervousness • Tachycardia • Increase respiration • Increase apetite • Decrease body weight • Hair loss (hirtuism)
Hypo secretion	Autoimmunity Antibodies destroy thyroid gland Decrease secretions T3 & T4 Two diseases **1. Cretinism** Hypothyroidism in children is called cretinism. **Caused by** (a) Congenital lack of thyroid gland (congenital cretinism) (b) Iodine lack (endemic cretinism) Sypmtoms Symptoms do not appear till six months because enough thyroid hormone is present in mother's milk • Stunted growth • Short club like fingers • Deformed bones, teeth, disproportionate growth, rough & dry skin, scanty hairs • Sex characters retarded • Decrease apetite • Low blood sugar • Immunity lowered **2. Myxedema** Hypothyroidism in adults is called myxedema Sypmtoms • Non-pitting edematous appearance. Bagginess under eyes. Swelling of face. Decrease hair growth • Impotency in males • Loss of memory • Decrease apetite • Low heart rate • Somnolence (extreme) • Arteriosclerosis **Treatment of Hypothyroidism** • Daily oral ingestion of tablet of thyroid extract or pure thyroxine **Goiter** Enlargement of thyroid gland, causing a swelling in front of neck is called goiter. **Types** (1) **Endemic Colloid Goiter** Due to iodine deficiency (2) **Idiopathic Nontoxic Colloid Goiter** Due to mild thyroiditis (inflammation of thyroid gland). (3) **Toxic Goiter** It occurs in hyperthyroidism due to LATS.

Pathologic Changes in Thyroid Hormone Secretion			
	T_4	THS	TRH
1. Primary hypothyroidism	↓	↑	↑
2. Pituitary hypothyroidism (secondary)	↓	↓	↑
3. Hypothalamic hypothyroidism (tertiary)	↓	↓	↓
4. Pituitary hyperthyroidism	↑	↑	↓
5. Grave's disease (autoimmune)	↑	↓	↓

Parathyroid Hormone and Calcitonin

Parathyroid Glands

Number

Four in human beings

Location

Each parathyroid gland is located behinds each of upper and lower poles of thyroid gland.

Color

Dark-brown fat like apperance

Size

6mm long, 3mm wide, 2mm thick.

Types of Cells

(1) Chief cells: Secrete parathyroid hormone
(2) Oxyphil cells: Secrete little parathyroid hormone

PARATHYROID HORMONE		
Nature		Protein
Mechanism of Action		
cAMP		
Other actions		Blood • Increase Blood Calcium ➔increase absorption from bone • Decrease Calcium excretion by kidney • Decrease PO_4 Concentration Bone • Increases absorption of Ca^{++} and PO_4 from bone Kidney • Increase calcium absorption in DCT and collecting duts • Increase PO_4 excretion GIT Parathyroid hormone converts 25-hydroxycholecaliferol into 1,25-dihydroxycholecalciferol which causes (a) Increase Ca^{++} absorption from intestine (b) Increase PO_4 absorption from intestine
Regulation	Stimulate	• Decrease Ca^{++} concentration in ECF. • Rickets • Pregnancy • Lactation • Increase PO_4 concentartion in ECF
	Inhibit	• Increase Ca^{++} concentration in ECF • Excess Ca^{++} in diet • Excess vit. D3 in diet • Decrease PO4 concentration in ECF.
Disorders		
Hyper secretion		**Hyperparathyroidism** **Primary Hyperparathyroidsim** May due to tumor parathyroid **Symptoms** BONE STONE GRONS ⇨ Multiple fractures ⇨ Kidney stone ⇨ GIT (calbindin)

	Secondary Hyperparathyroidism It is secondary to defects outside the parathyroid gland. **Caused by** Hyperplasia of parathyroid gland due to low level of Ca++ ions , as in (1) Low Ca in diet (2) Pregnancy (3) Lactation (4) Rickets (5) Osteomalacia **Symptoms** Same as primary hyperparathyroidism. But not so severe
Hypo secretion	**Hypoparathyroidism** • Removal or destruction of parathyroid gland during thyroidectomy • Malformation of parathyroid gland • Autoimmunity against parathyroid gland • Infection of parathyroid gland **Symptoms** (1) Hypocalcemia Tetany (2) Hyperphosphatemia (3) Obstruction of respiration due to spasm of laryngeal muscles **Treatment** (1) Vit. D3 with Calcium (2) Parathyroid hormone

CALCITONIN

Nature		Ppolypeptide
Site of Secretion		**Secreted by** Parafollicular cells (C cells) of thyroid gland
Mechanism of Action		
cAMP		
Other actions		Blood • Decrease Ca^{++} concentration Bones • Decrease formation of osteoblasts • Decrease rate of remodeling GIT • Decrease Ca^{++} absorption Kidney • Decrease Ca^{++} absorption
Regulation	Stimulate	Increase in plasma Ca^{++} concentration causes inc. secretion of calcitonin
	Inhibit	Decrease in plasma Ca^{++} concentration causes decrease secretion of calcitonin.
Disorders		
Hyper secretion		
Hypo secretion		

Adrenal gland

There are two types of the adrenal gland

1. Adrenal cortex — These are steroids
2. Adrenal Medulla — These are amines and derivatives .

Types of cortex

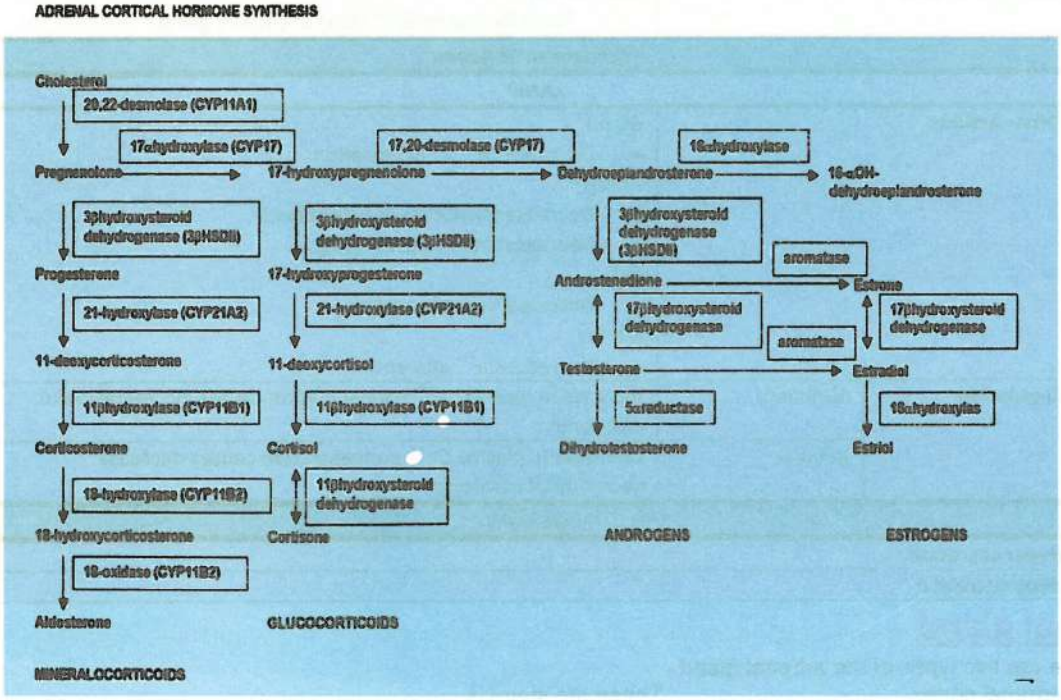
There are three types of adrenal cortex

Outer to inner

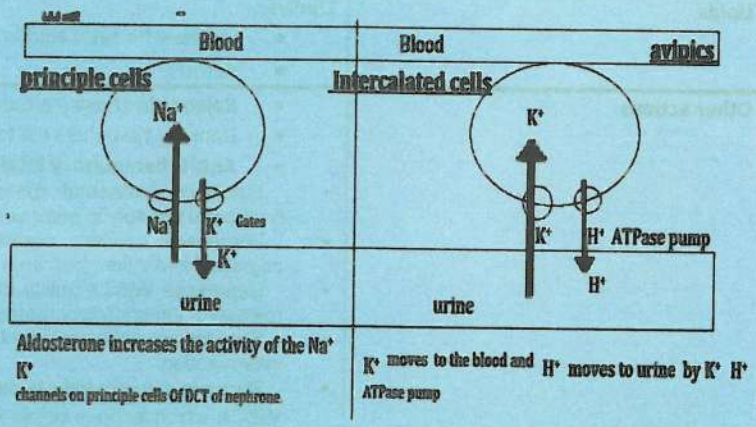
Zona Glomerulosa	Zona fasiculata	Zona Reticularis
Mineralocorticoids • Aldosterone • Cortisol • Cortisone	Glucocorticoids & Androgens • Cortisol • Prednisone • Corticosterone	Glucocorticoids & Androgens • Action like testosterone

Adrenal Steroid Hormones in Adults; Syhnthetic Steroids Their Relative and Glucocorticoid and Mineralocorticoid Activities				
Steroid	Average plasma Concentration (free and bound, µg/100 ml)	Average Amount Secreted (mg/24 hr)	Glucocorticoid Activity	Mineralocorticoid Activity
Adrenal Steroids				
Cortisol	12	15	1	1
Corticosterone	0.4	3	0.3	15.0
Aldosteroine	0.006	0.15"	0.3	3000
Doxycorticoster-one	0.003	0.2	0.2	100
Dehydroepiandrosterone	175	20	-	-
Synthetic Steroids				
Cortisone	-	-	1.0	1.0
Prednisolone	-	-	4	0.8
Methylprednisone	-	-	5	-
Dexamethasone	-	-	30	-
9α-fluorocortisol	-	-	10	125

Steps of Formation of Adrenocortical Hormones



ALDOSTERONE

Nature	Steriods
Site of Secretion	Distal Convulated tubules
Mechanism of Action	
Protein	Synthesis
On renal tubules	• Aldosterone causes inc. Na^+ absorption in exchange for K^+ and H^+ by late distal tubule, collecting tubule and collecting duct. • Causes H_2O absorption due to conc. gradient created by Na+ absorption - Increase ECF vol.  Aldosterone increases the activity of the Na^+ K^+ channels on principle cells Of DCT of nephrone K^+ moves to the blood and H^+ moves to urine by K^+ H^+ ATPase pump
On circulation	• Causes increase blood volume • Causes increase cardiac output • Increase blood pressure
Other actions	• Cause increase sodium and Chloride reabsorption from sweat • Cause increase sodium and Chloride reabsorption from GIT
Regulation — Stimulate	• Increase K^+ concentration • Increase activity of rennin-angiotensin system. • Decrease Na^+ concentration • Undefine pituitary factor (but not ACTH) • ACTH • Hypovolemia and hypotension
Disorders	
Hyper secretion	Cohn' s Disease
Hypo secretion	Addison disease Effects • Disturb mineralocorticoids (aldosterone) ➔ hyponatremia, shock , cardiac toxicity , acidosis • Disturb Glucocorticoids (cortisol) ➔ decrease glucose, Depress body metabolism, • No cortisol → No negative feedback inhibition of ACTH and MSH secretion → Increase ACTH and MSH → Melanin pigmentation in thin skin areas, eg lips and nipples

Aldosterone Escape (IMP)

- When excess aldosterone is administered ➔ Excess Na^+ and H_2O absorption ➔ Increase ECF volume ➔ Increase blood volume ➔ Increase cardiac output ➔ Increase BP
- Pressure diuresis and pressure natriuresis
- This ***secondary loss*** of Na+ and H_2O is called aldosterone escape.

CORTISOL

True Stress Hormone

Nature		Steriod
Site of Secretion		Zona fasciculata and zona retricularis of adrenal cortex.
Mechanism of Action		
Carbohydrates	**Cellular Glucose**	Decrease
	Blood Glucose	Increase (increase gluconeogenesis)
Protein		Proteolysis (use for gluconeogensis) • Cause increase AA in Blood
Lipids		Lipolysis • Increase fre fatty acid in blood • Ketosis
Other actions		• ***Release in stress*** (release AA and fatty acid) • Damage tissue use AA to form new proteins • **Anti-Inflammatory Effect** ▪ Stabilizes lysosomal mem. Prevents release of inflammation-causing lysosomal proteolytic enzymes ▪ Decreases capillary permeability , Prevents plasma loss and WBC migration into inflammed area ▪ Depresses WBC's ability to digest phagocytized tissue - Prevents further release of inflammatory materials. ▪ Suppresses antibodies and T-cells Prevents immune reactions that cause inflammation. ▪ Reduces fever mainly because it reduces the release of interleukin-I from WBCs, which is the principle excitement to hypothalamic temp. control sys. • Cause eosinopenia • Supress immunity
Regulation	Stimulate	• (+) Adrenal corticotropic hormone • (+) Corticotropic releasing factor Moring time +++ Evening ---
	Inhibit	Cortisol Negative feedback inhibition of CRF and ACTH secretion - Cortisol secretion inhibited.
Disorders		
Hyper secretion		Cushing disease • Increase gluconeogensis and decrease glucose utilization ➔ increase blood glucose level • Muscle weakness due to protein metabolism • Osteoporosis • Buffalo torso • Acne and hirsutism • Moon face appearance **Difference between Cushing Syndrome and Cushing Disease** (1) **Cushing Syndrome** It is caused by excessive cortisol secretion by adrenal cortex tumor (2) **Cushing Disease** It is caused by excessive ACTH secretion by tumor of anterior pituitary gland. **Adrenal Diabetes** Cortisol causes elevated blood glucose level due to increase gluconeogenesis and decrease glucose utilization; this is called adrenal diabetes. (1) Pituitary diabetes is weakly insulin sensitive (2) Adrenal diabetes is moderately insulin sensitive (3) Pancreatic diabetes (ie diabetes mellitus) ie strongly insulin sensitive.

ANDROGENS	
Nature	Steriods
Site of Secretion	Zona fasciculata and zona reticularis of adrenal cortex
Other actions	• Their secretion during childhood cause part of early development of male sex organs • Cause much of growth of pubic and axillary hairs in female • Some adrenal androgens in males are converted to testosterone in extraadrenal tissues.
Disorders	
Hyper secretion	**Adrenogenital Syndrome** ○ **In Female** ▪ Masculine hair distribution on body and pubis ▪ Deeper voice ▪ Enlargement of clitoris - Resembles penis ▪ Thick skin ▪ Inc. muscle protein ○ **In Males Before Puberty** ▪ Rapid development of male secondary sex characteristics ▪ Inc. sex desire ○ **In Males After Puberty** Virilizing characteristics of adrenal androgens are obscured by testosterone secreted by testis.

Adrenal Medulla

There are three types of adrenal medulla that all are amines and derivatives

Epinephrine	Nor-epinephrine	Dopamine
• 80%	• 20%	
• Vasodilation	• Vasoconstriction	

Catecholamines

Phenylalanine → tyrosine → DOPA → Dopamine → nor epinephrene → Epinephrene

EPINEPHRENE & NOR-EPINEPHRENE *Adrenaline and nor-adrenaline*		
Nature		Amines
Site of Secretion		By adrenal medulla as a result of sympathetic stimulation
Mechanism of Action		
Carbohydrates	**Cellular Glucose**	Decrease
	Blood Glucose	Increase
Protein		Proteolysis (Glycogenolysis is prefer over gluconeogenesis here.)
Lipids		Liposlysis (Glycogenolysis is prefer over gluconeogenesis here.)
Other actions		**Epinephrene** Dilates the blood vessels of Skeleton muscles , brain and heart (all contain β-cells) **Nor-Epinephrene** Constrict the blood vessels of whole body except these three. • Sympthatic NS (constrict the blood vessels during emergency and excess blood moves to sk. Muscles , brain and heart)

Regulation	Stimulate	• α-receptors Nor-epinephrine loves these receptors (vasoconstrictions) • B-receptors Epinephrine loves/prefer these receptors (vasodilation)
	Inhibit	---
Disorders		
Tumor		Pheochromocytoma is a tumor of the adrenal medulla • Increase of epinephrine and nor-epinephrine • Pulsatile and episodic hypertension ***Sign and symptoms '*** Neck muscles pain headache tachycardia skin pale color eye red

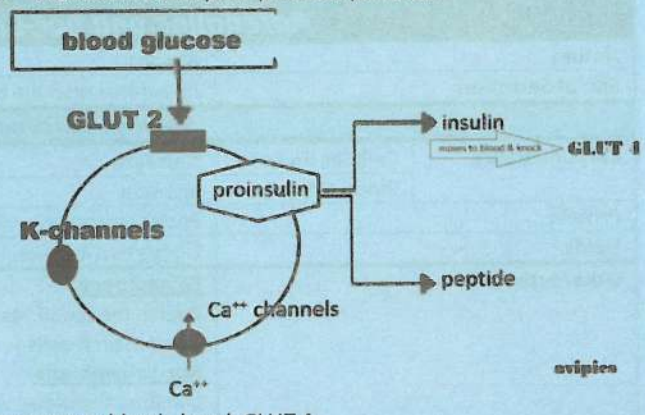
Hormones of Islets of Langerhans

Pancreas

Consists of

(1) Acini Secrete digestive juice
(2) Islets of Langerhans Consists of
(a) Alpha Cells Secrete glucagon
(b) Beta Cells Secrete insulin
(c) Delta Cells Secrete somatostatin
(d) PP cells Secrete pancreatic polypeptide

INSULIN

Nature		Protein
Site of Secretion		On high Glucose tissues
Mechanism of Action		
Carbohydrates	**Cellular Glucose**	Highly increase (in skeleton and adipose tissue) ***HOW CELLULAR UPTAKE INCREASE INSULIN RELEASE?*** 1. Glucose enter the GLUT 2 , close the potassium channels 2. Ca++ channels open (depolarization) Trigger the β cells of pancreas 3. Proinsulin is always in β cells of pancreas  Insulin moves to blood , knock GLUT 4 • Inhibits glycogen breakdown by inhibiting phosphorylase • Promotes glucose utilization • Insulin causes glucose storage after meal and this glucose is released b/w meals when there is no insulin

	Blood Glucose	Highly decrease
Protein		Synthesis • Inhibit gluconeogensis • Inhibit catabolism of protein
Lipids		Lipogensis
Other actions		Insulin functions synergistically with growth hormone to promote growth by protein formation.
Regulation	Stimulate	• Hyperglycemia / increased Fructose, mannose • Amino acids • Ketones • Hormones Glucagon, GH, cortisol, progesterone, estrogen, and GIT hormones • Increased blood FFA • Parasympathetic stimulation; Ach • Beta-adrenergic stimulation. • Insulin resistance; obesity • Sulfonylurea drugs (glyburide,
	Inhibit	• Hypoglycemia • Starvation • Exercise • Stress
Disorders		
Hyper secretion		Hypoglycemia
Hypo secretion		Diabetes Mellitus

Glucose Utilization By Brain

(1) Brain utilise only glucose for energy

(2) Brain cells need not insulin for glucose entry into them

DIABETES Mellitus

Increase in the blood glucose level

⇨ Treatment / tests

Before meal	After meal
Fasting blood glucose level	Random blood glucose level
Normal value 65 -- 92mg/dl Diabetes 110mg/dl	Normal value 126mg/dl Diabetes 126mg/dl

Sign and symptoms

1. Glucose in the urine
2. Polyurea
3. Polydipsia
4. Polyphagia
5. Increased glucose level
6. Acidosis
7. Dehydration
8. Coma
9. Shock
10. Muscle weakness
11. Fatty liver
12. Lipolysis
13. Skin infection
14. Weight loss
15. Eye problems

Stages of diabetes

1st stage	1-2yrs	Diet control and life style change ,no smoking , no alcohol, no sweats .
2nd stages	2-5yrs	Tablets
3rd stage	Life time	Insulin injection

Types of diabetes There are two types of diabetes

Types I Juvenile DM (Insulin Dependent DM)	Type II Maturity-Onset DM
Insulin dependent diabetes mellitus	Non Insulin dependent diabetes mellitus
Destruction of beta cells of pancreas	Receptors insensitivity
Plasma glucose is increased	Plasma glucose increased
Insulin is injected from the first day	1st , 2nd , 3rd stages
Autoimmune disease (β-cell receptors make antibodies)	Fats cover the GLUT 4 receptors
Non genetic	Genetic
Before 30 years	After 30 years
C-peptide not present	C-peptide present

Plasma usually low or absent	Plasma usually normal or high
Body mass usually low (wasted)	Obese

GLYCOGEN

Nature		Protein
Site of Secretion		Low Glucose level tissues
Mechanism of Action		
Carbohydrates	**Cellular Glucose**	Decrease
	Blood Glucose	Increase (gluconeogensis)
Protein		Proteolysis
Lipids		Lipolysis
Other actions		Increase strength of heart Increase bile secretion Inhibits gastric acid secretion
Regulation	Stimulate	• Hypoglycemia • Increase amino acid conc. • Exercise and stress • Starvation and malnutrition
	Inhibit	• Hyperglycemia • Hyperlipidemia • Ketonemia • Somatostatin
Disorders		
Hyper secretion		Diabetes Mellitus
Hypo secretion		Hypoglycemia

SOMATOSTATIN

Nature		Same as GHIH of hypothalamus
Site of Secretion		**Secreted by** Delta cells of islets of Langerhans
Mechanism of Action		
Other actions		• Inhibits secretion of insulin and Glucagon • Decreases motility of stomach, duodenum and gall bladder • Decreases secretion and absorption in GIT
Regulation	Stimulate	• Increase blood glucose • Increase amino acids • Increase fatty acids • GIT hormones

Courtesy by Guyton & Halls Physiology

Androgens

Any steroid hormone that has masculinizing effects, is called androgen.

Include

(1) Testosterone (principle androgen)
(2) Dihydrotestosterone
(3) Androstanedione

Note

Testosterone is converted in target tissues into more active form, dihydrotestosterone.

TESTOSTERONE

Nature		Steriod
Site of Secretion		**(1) In Fetus** (a) By genital ridges under influence of male chromosome "Y" (7th week) (b) Later by fetal testis under influence of HCGTH from placenta **(2) Leydig Cells** Which are (a) Non-existent in childhood (b) Abundant in newborn male infant and in adult male after puberty
Mechanism of Action Protein formation Mechanism		
Other actions		**In fetus** • Develop of penis, scrotum, prostate, seminal vesicle and male genital duct • Suppresses formation of female genital organs • Causes descent of testes through inguinal canal into scrotum during last two months of gestation ***Secondary Sexual Characters*** **In male they include** • Body Hairs: Testosterone causes inc. hair growth: Over pubis, male pattern is convex, Upward along linea alba, On chest , On face and On back • Baldness: Testosterone causes dec. hair growth on top of head, producing baldness • Voice: Testosterone causes hypertrophy of laryngeal mucosa and enlargement of larynx, which first causes "cracking voice", and then causes typical masculine bass voice • Skin: Testosterone increases skin thickness, secretion of sebaceous gland and acne. ***On Testes*** Increases spermatogenesis in seminiferous tubules. ***On Protein Metabolism*** Increases protein synthesis ***On Muscles*** Increases muscle development due to increase protein synthesis ***On Bones*** Increases bone thickness ***On Male Pelvis*** Narrows pelvic outlet ***On Body Length*** Decreases body length due to early fusion of epiphysis with shafts.
Regulation	Stimulate	Human choroinic gonadotropin from placenta Causes Leydig cell formation in testis Testosterone secreted.
	Inhibit	Excess testosterone secreted by Leydig cells Negative feedback inhibition of LHRH secretion by hypothalamus Inhibits LH secretion by ant. Pituitary gland → Inhibits testosterone secretion by Leydig cells
Disorders		
Hyper secretion		Prostate cancer
Hypo secretion		Hypogonadism , male infertility

Ovarian Hormones

Two types,

(1) Estrogens: Most important is estradiol.

(2) Progestin: Most important is progesterone.

ESTROGEN

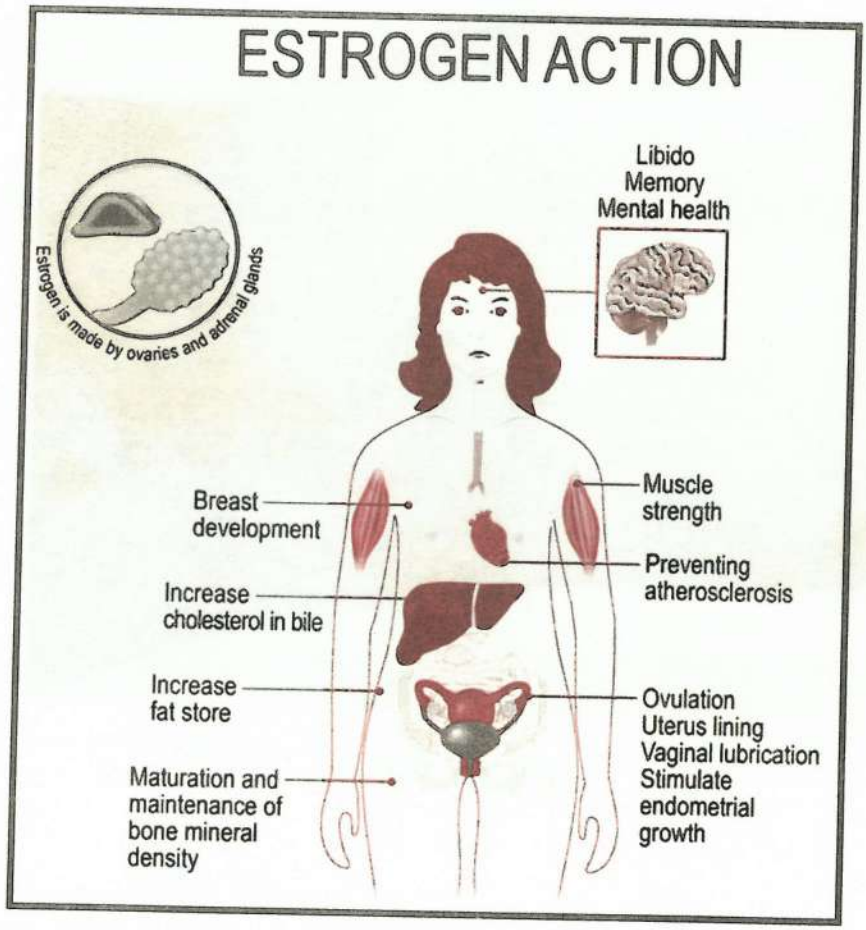
Nature		Steriod
Site of Secretion		**Sites of Secretion** (1) In non-pregnant woman: By (a) Ovaries ie by theca interna, granulosa cells and corpus luteum (b) Adrenal cortex (2) In pregnant women: By (a) Ovaries (b) Adrenal cortex (c) Placenta
Mechanism of Action Protein formation mechanism		
Other actions		• **On Vagina increase** in size and wall musculature • **On External Genitalia** ➔ Clitoris, labia minora increase in size, Increase fat deposition in mons pubis and labia majora • **On Cervix** ➔ Slight enlargement • **On Uterus** ➔ Increase in size • **On Fallopian Tubes** ➔ Proliferation of glandular tissue • **On Ovaries** ➔ Estrogen inhibits LH & FSH secretion by negative feedback mechanism So, decreases ovarian functions Used as oral contraceptive **Secondary Sex characters** • Initiates growth of breast • Not effect hairs • Skin softening • Broadens pelvis • High pitched voice • Early union of epiphysis • Increase fat deposition ' • Protein increase slightly • Estrogen is responsible for "proliferative phase" of menstrual cycle. • Decrease blood cholestrrol level
Regulation	Stimulate	FSH and LH increase the production
Disorders		
Hypo secretion		Hypogonadism

PROGESTREONE

Nature	Steriods
Site of Secretion	(1) In non-pregnant woman By (a) Corpus luteum in later half of ovarian cycle (b) Small amounts by adrenal cortex (2) In pregnant woman By (a) Corpus luteum (b) Adrenal cortex (c) Placenta

Mechanism of Action Protein formation mechanism		
Other actions		• On uterus ➔ promote secretory changes • Decrease uterine contraction • On fallopian tubes ➔ Promotes "Secretory Changes" in mucosal lining, needed for nutrition of fertilized ovum • Promote the development of lobule and alveoli in breast • Don't cause milk secretion • Inhibits ouvlation by inhibiting release of LH & FSH. During pregnancy, ovulation is inhibited by luteal and placental progesterone • Mobilizes protein during pregnancy to be used by fetus
Regulation	Stimulate	FSH and LH increase the production
Disorders		
Hypo secretion		hypogonadism

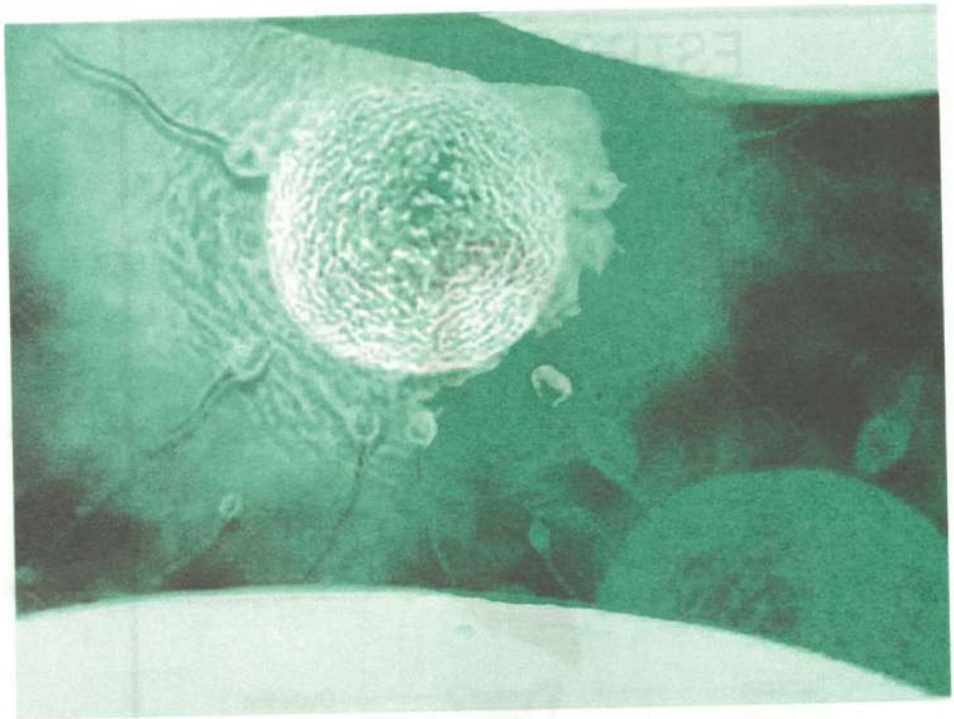
Courtesy by Guyton & Halls Physiology



Chapter # 14

Reproduction

Contents



REPRODUCTION

Male

Physiologic Anatomy of Male Sex Organs

1. TESTIS

- It is primary male sex organ located in sac like structure called scrotum
- Composed of 900 coiled tubules known as semineferous tubules in which sperms are formed.
- Sperm then enter into epididymis.
- Epididymis leads into vas deference
- The enlarged portion of vas deference is known as ampula immediately before the vas enters the prostrate gland.
- Testis is covered by 3 layers; tunica vasculosa, tunica albugenis & tunica vaginalis.

Function of Testis

1. Spermatogenesis
2. Endocrine function

- **SPERMATOGENESIS:**

The process of formation of sperms is called spermatogenesis

- **EXPLANATION:**

During formation of embryo , primodial germ cells migrate into testis & become immature germ cells called **spermatogonia,** which lie in seminiferous tubules. Spermatogonia undergo mitotic division beginning at puberty & continualy proliferate & differentiate to form sperm.

2. SEMINAL VESICLES

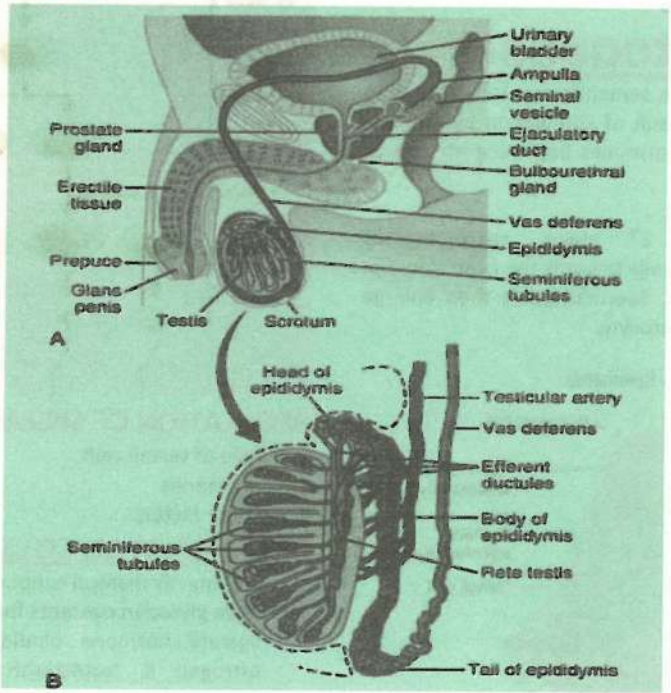
- Two seminal vesicles , one located on each side of the prostrate empty into the prostatic end of ampula.
- It is lined with the secretory epithelium that secrete a mucoid material called seminal fluid.

SEMINAL FLUID:

1. Composed of fructose in abundance,
2. Citric acid & other nutrient substances.
3. Prostaglaidins
4. Fibrinogen

Function of seminal Fluid

1. During the process of emission & ejaculation each seminal vesicle **empty its contents into the ejaculatory duct.**
2. The fructose and the other nutrients **provide nutrition for the ejaculatory sperm** until the sperm fertilize the ovum.
3. Prostaglaidin helps in fertilization by reacting with the female cervical mucus to make it **more respective to sperm**.



1. PROSTATE GLANDS

The prostatic gland *secrete a thin milky fluid called prostatic fluid.*

COMPOSITION

1. Calcium
2. Citric & phosphate ions

3.Clotting enzyme
4.Profibrinolysin

- It is alkaline in nature , it increases the bulk of semen.
- It helps to neutralize the acidity of other seminal fluid and enhances the motility and fertility of the sperm.

2. EJACULATORY DUCT

The contents from both ampula and seminal vesicle pass into ejaculatory duct.
Prostratic duct also empty from prostratic gland into ejaculatory duct.
Finally all the contents enter into the internal urethera.

3. URETHRA & PENIS

- Urethra is the last connecting link from the testis to the exterior.
- Urethra has two parts;

1.Internal urethra
2.External urethra

- Internal urethra passes through penis as external urethra
- Penis is formed of errectile tissue masses, paired corpora cavernosa & corpus spongiosum.
- The spongium surround the urethra & terminates distally to form glans penis.

Reproduction

Reproductive function of male divided into 3 subdivisions;

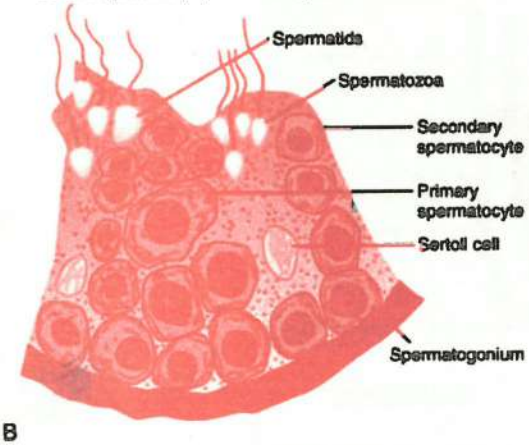
1.Spermatogenesis
2.Male sexual act
3.Regulation by hormones

1.Spermatogensis

Spermatogenesis occur in semeniferous tubules during active sexual life as a result of stimulation by anterior pituitary Gonadotropic hormones beginning at age of 13 years.

STAGE OF PROLIFERATION:

In 1st stage, spermatogonia migrate among sertoli cells towards the central lumen of seminiferoustubules. Spermatogonia then enlarge to form primary spermatocyte.



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STAGE OF GROWTH:

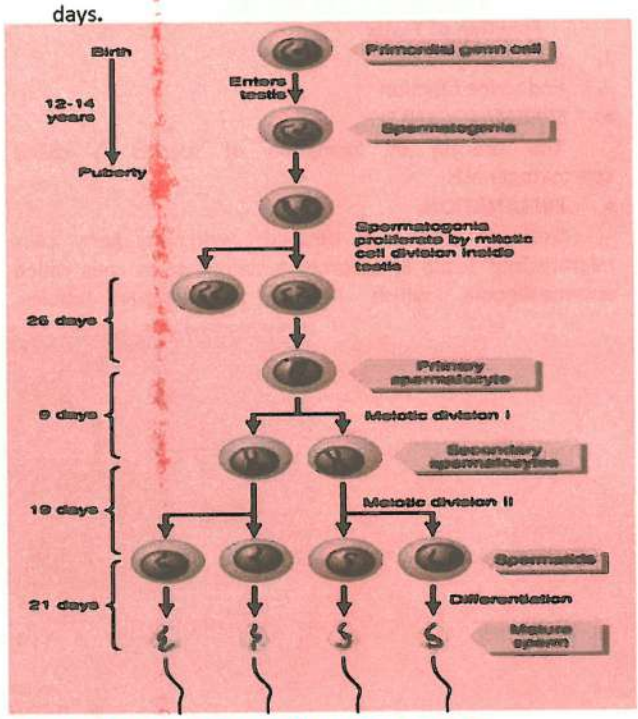
Primary spermatocyte grow into a large primary spermatocyte. There is no further change in this stage.

STAGE OF MATURATION:

- Primary spermatocyte undergo meiotic division to form 2 secondary spermatocytes.
- After another few days these 2 divides to form spermatids. Each spermatid recieves only haploid (half number of chromosomes)

STAGE OF TRANSFORMATION:

- Spermatid do not divide further. They transfer into spermatozoa (sperms). And this process is known as spermiogenesis.
- From the spermatocyte stage to spermatid stage the 46 chromosome divided into 23 chromosomes which go into each spermatid. The entire process takes about 74 days.



REGULATION OF SPERMATOGENESIS

1. Role of sertoli cells
2. Hormones
3. Other factors

ROLE OF SERTOLI CELLS:

1. Provide mechanical support for maturing gametes.
2. Have glycogen contents for energy.
3. Secrete hormone binding protein, they bind with estrogen & testosteron & make these hormones available for sperm maturation.
4. Secrete estrogen which is essential for spermatogenesis

HORMONES

- TESTOSTERONE:

1. Secereted by leyding cells of testes.
2. Essential for growth and division of germinal cells.

- LEUTINIZING HORMONE

1. Secreted by anterior pituitary gland
2. Stimulate leyding cells to secrete testosterone.

- FSH:

1. Secereted by anterior pituitary
2. Stimulate sertoli cells and cause conversion of spermatid to sperm

- ESTROGEN:

Essential for spermiogenesis.

- GROWTH HORMONE:

It promote early division of spermatogonia sperm cells

STAGES	HORMONES
PROLIFERATION	GH, TESTOSTERONE
GROWTH	GH, TESTOSTERONE
MATURATION	TESTOSTERONE
TRANSFORMATION	TESTOSTERONE, FSH, ESTROGEN

OTHER FACTORS

- TEMPERATURE

1. Increase temp decreases spermatogenesis.
2. scrotal temp is 2 degree less than body.

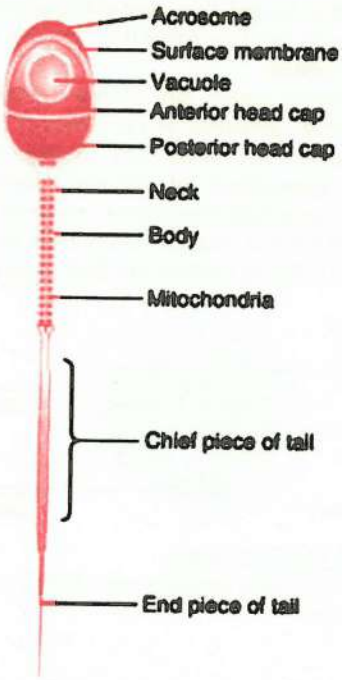
- INFECTIONS (MUMPS)

1. Cause degeneration of seminiferous tubules , so effect spermatogenesis.

SPERM

- COMPOSITION:

1. HEAD
2. TAIL



- HEAD:

It contain a thick part called acrosome. It contain high hyaluronidase and powerful proteolytic enzyme. These play role in alloying the sperm tail to enter ovum and fertilize it.

- TAIL:

Tail (flagellum) which provide motility for the sperm. The energy is supplied in the form of ATP.

CAPACITATION

- WHEN SPERM COME IN CONTACT WITH THE FEMALE GENITAL TRACT FLUID, MULTIPLE CHANGES ACCUR THAT ACTIVATE THE SPERM FOR FINAL PROCESSES OF FERTILIZATION.

1. Removal of inhibitory factors that suppress activity of sperm.
2. Entery of calcium ions into membrane of sperm to increase the whip lash movement of the sperm.
3. Calcium also responsible to release enzymes which help the sperm to cross the zona pellucida of the ovum.

ACROSOME REACTION & PENETRATION OF OVUM

- Large quantities of hyaluronidase and proteolytic enzymes are stored in the acrosome.
- When sperm reaches the zona pellucida of ovum, the anterior membrane of sperm itself binds to the specific receptors on zona pellucida, which dissolves acrosome and all enzymes are released.
- Enzymes open the penetrating pathway for passage of sperm.
- Within 30 minutes the layers fuse with each other to form a zygote, genetic material transferred and the process is called fertilization

SEMEN

- It is ejaculated during male sexual act and is composed of;
- Fluid and sperm from vas deference 10 %
- Fluid from seminal vesicle 60%
- Fluid from prostate gland 30 %

CHARACTERISTICS:

- Milky appearance
- Ph 7.5 (alkaline)
- Semen serves to wash the sperm through ejaculatory duct and urethera.
- Volume: 2-6 ml/ ejaculation
- Clotting enzyme from the prostatic fluid cause fibrinogen of seminal vesicle fluid to form a weak fibrin coagulum that hold semen into the deeper region of the vagina.
- In early few min after ejaculation, the sperm remains immobile because of viscosity of coagullum.
- As coagullum dissolved by profibrinolysin (prostatic) the sperm simulataneously become highly motile.

- Sperm can live for many week in the male genital duct but after ejaculation in the semen the life span is 24-48 hrs.

Composition of Human Semen

GENERAL COMPONANTS

- COLOR: WHITE
- SPECIFIC GRAVITY: 1.028
- PH: 7.35–7.50
- SPERM COUNT: AVERAGE ABOUT 100 MILLION/ML, WITH FEWER THAN 20% ABNORMAL FORMS

OTHER COMPONENTS

- FROM SEMINAL VESICLES (CONTRIBUTES 60% OF TOTAL VOLUME)
- FRUCTOSE (1.5-6.5 MG/ML)
- PHOSPHORYLCHOLINE
- ERGOTHIONEINE
- ASCORBIC ACID
- FLAVINS
- PROSTAGLANDINS

SPERMINE (FROM PROSTATE (CONTRIBUTES 20% OF TOTAL VOLUME)

- CITRIC ACID
- CHOLESTEROL, PHOSPHOLIPIDS
- FIBRINOLYSIN, FIBRINOGENASE
- ZINC
- ACID PHOSPHATASE
- PHOSPHATE
- BUFFERS
- BICARBONATE
- HYALURONIDASE

MATURATION & STORAGE OF SPERM

- After formation in the seminefous tubule , the sperm requires several days to pass through epididymis (6 meter long)
- Sperm removed from the semineferous tubules are non motile.
- In the epididymis after 18 to 24 hours they develop the capability of motility.
- Storage:

  2 testis form 120 million sperms / day.

  Small quantity = epididymis

  Large quantity = vas deferens
- Life expectancy of the ejaculated sperm in the female genital tract is 1-2 days.

Sperm Count

- NORMAL : 120 MILLION / ML OF SEMEN
- RANGE (35 -200 MILLION)
- AVERAGE TOTAL (400 MILLION IN SEVERAL ML OF SEMEN)
- WHEN SPERM FALLS BELOW 20 MILLION / ML PERSON BECOMES INFERTILE.
- DECREASE SPERM COUNT IS CALLED OLIGOSPERMIA.

2.MALE SEXUAL ACT

STIMULUS:

1. Massage action
2. Stimulus of anal epithelim & scrotum
3. Irritation of urethra, bladder, prostate, seminal vesicle, testis, vas deference
4. Overfilling of sex organs with secretion
5. Infection , inflammation of sex organs
6. Psychic stimulus.

STAGES OF SEXUAL ACT

1. ERRECTION
2. LUBRICATION
3. EMISSION
4. EJACULATION

(1) Erection

(Parasympathetic) Sexual stimulation (psychic or physical) → Afferent impulses thru pudendal nerve Integrated in sacral segments → Afferent impulses thru nervi erigentes (pelvic parasympathetic nerve) to penis → Dilate arteries; arterial blood build up under high pressure in erectile tissue; venous outflow occluded Erectile tissue balloon up → Penis become hard and elongated Erection.

(2) Lubrication

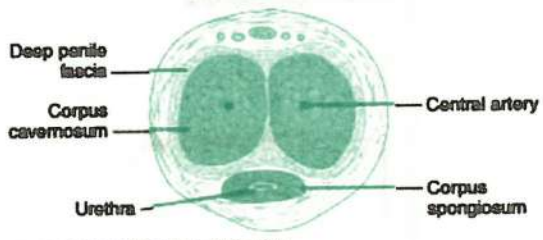
(Parasympathetic) Same parasympathetic impulses that cause erection, also stimulate urethral and bulbourethral glands to secrete mucus Lubricate during intercourse

(3) Emission

(Sympathetic) When sexual stimulation becomes extremely intense - Reflex centers of spinal cord, L_{1-2} send sympathetic impulses through hypogastric plexus Contraction of vas deferens, ampulla, prostate and lastly seminal vesicle Semen emitted into "internal urethra"

(4) Ejeculation

(Sympathetic) Semen fills internal urethra Afferent signals through pudendal nerve - Efferent signals from sacral segment of spinal cord through hypogastric plexus - Contraction of internal genital organs, ischiocavemosus bulbocavernosus - rhythmic increase in pressure of internal urethra from outside Ejaculation of semen from internal urethra into deep vagina



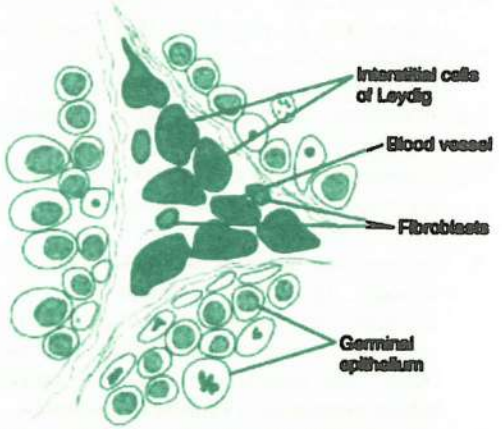
MALE ORGASM (MALE CLIMAX)

Pleasurable sensation felt during emission and ejaculation

3.HORMONES

TESTIS SECRETE MALE SEX HORMONES CALLED ANDROGEN.

1.TESTOSTERONE
2.DIHYDROTESTOSTERONE
3.ANDROSTENEDIONE



Interstitial cells of Leydig, the cells that secrete testosterone, located in the interstices between the seminiferous tubules.

(discussed in chapter "Endocrinology")

PUBERTY

Period (12 – 13 years) during which secondary sexual characters begin to develop and capability of sexual reproduction is attained

MALE CLIMACTERIC

- After puberty, gonadotropic hormones are produced by male pituitary gland for the remainder of life, and at least some spermatogenesis usually continues until death.
- Most men, however, begin to exhibit slowly decreasing sexual functions in their late 40s or 50s, and one study showed that the average age for terminating intersexual relations was 68, although the variation was great.
- This decline in sexual function is related to decrease in testosterone secretion. The decrease in male sexual function is called the MALE CLIMACTERIC.

SYMPTOMS

- HOT FLASHES
- SUFFOCATION
- PSYCHIC DISORDERS

TREATMENT

- These symptoms can be abrogated by administration of testosterone, or even estrogens that are used for treatment of menopausal symptoms in the female.

DISEASES OF MALE REPRODUCTION

1. MALE INFERTILITY

Incapability of male to produce offspring

CAUSES:

- DESTRUCTION OF SEMINEFEROUS TUBULES (MUMPS, INCREASE TEMP)
- DECREASE SPERM COUNT (LESS THAN 20 MILLION / ML)
- ABNORMAL MORPHOLOGY AND MOTILITY.

2. Erectile dysfunction

- Impotence is characterized by an inability of the man to develop or maintain an erection of sufficient rigidity for satisfactory sexual intercourse.
- Trauma to the parasympathetic nerves
- Deficient levels of testosterone
- Some drugs nicotine, alcohol, antidepressants.
- Vascular disease

3. HYPOGONADISM

Failure of leyding cells to produce androgenic hormones.

CAUSES:

- Failure of hypothalamus (GnRH)
- Failure of ant. Pituitary (LH,FSH)
- Congenital absence of testis

SYMPTOMS ACCORDING TO TYPES:

- Fetal life testes non functional ,female sexual organs are formed.
- PRE PUBERTAL: (State of Eunuchism, Voice,sex organs & sec. Sex characters are child like, bones thin, muscle weak.)
- POST PUBERTAL:(Adult Castrated male) sex organs regress, sex desire decrease, hair loss, erection accur but no ejaculation.

4. HYPERGONADISM

Excess secretion of androgenic hormones by leyding cells

CAUSE: (TESTICULAR TUMORS)

- *Interstitial Leydig cell tumors* --100 times more the normal quantities of testosterone.
- Excessive development of the male sexual organs, all skeletal muscles, and other male sexual characteristics.
- Teratoma

5. CRYPTORCHIDISM

1. Failure of testes to descent from the abdomen to the scrotum at or near the time of birth
2. In abdomen temp is higher than scrotum, so in case of cryptorchid testis spermatogenesis does not accur.

TREATMENT Surgical treatment at beginning of adult sexual life, testosterone secreted by fetal testes themselves

6. DEVELOPMENT OF ACNE:

Increase testosterone causes excessive secretion by sebaceous glands of face and this result in *acne*.

- Acne is one of the most common features of male adolescence when the body is first becoming introduced to increased testosterone.
- After several years of testosterone secretion,skin normally adapts to the testosterone in a way that allows it to overcome the acne.

7. Prostate Gland Abnormalities

- Cancer of prostate gland
- Benign prostatic fibro adenoma
- Treatment ----- testosterone and estrogen therapy

8. Adiposogenital syndrome, Fröhlich syndrome, or Hypothalamic Eunuchism.

- Genetic inability of the hypothalamus to secrete normal amounts of GnRH.
- This is often associated with a simultaneous abnormality of the feeding center of the hypothalamus, causing the person to greatly over eat.
- Consequently, obesity occurs along with eunuchism.

Sex Chromosomes and their abnormalities

- In each spermatogonium, one of the 23 pairs of chromosomes carries the genetic information that determines sex of each offspring.
- This pair is composed of one x chromosome, which is called the *female chromosome*, and one y chromosome, the *male chromosome*.
- During meiotic division,male chromosome goes to one spermatid that becomes *a male sperm*, and female chromosome goes to another spermatid that becomes a *female sperm*.
- The sex of the offspring is determined by which of these two types of sperm fertilizes the ovum
- An established defect in gametogenesis is nondisjunction, a phenomenon in which a pair of chromosomes fail to separate, so that both go to one of the daughter cells during meiosis.
- Four of the abnormal zygotes form as a result of nondisjunction of one of the x chromosomes during oogenesis.
- Individuals with xo chromosomal,gonads are rudimentary or absent, so that female external genitalia develop, stature is short, congenital anomalies, no sexual maturation at puberty.

THIS SYNDROME IS CALLED GONADAL DYSGENESIS OR OVARIAN AGENESIS OR TURNER SYNDROME.

- Individuals with the XXY pattern, the most common sex chromosome disorder, have the genitalia of a normal male.
- Testosterone secretion at puberty is often great enough for the development of male characteristics, however,seminiferous tubules are abnormal, incidence of mental retardation is higher. This syndrome is known as **seminiferous tubule dysgenesis** or **klinefelter syndrome.**
- **The xxx ("superfemale")** more common in the general population, since it does not seem to be associated with any characteristic abnormalities.
- Nondisjunction of chromosome 21 produces **trisomy 21,** the chromosomal abnormality associated with **DOWN SYNDROME**

Pineal Gland

(Vestigial remnant of third eye)

Functions in Animals

More than 13 hrs of darkness in 24 hrs (in winter season) melatonin secreted by pineal gland → Inhibits gonadotropic hormone secretion Inhibits gonads No reproduction in winter

Functions in Man

(1) Increase pineal secretion -+Hypogonadism
(2) Decreased pineal secretion Hypergonadism

Female Reproductive system

Female reproductive organs

(1) Ovaries Contains primordial follicles
(2) Fallopian tubes
(3) Uterus

Primordial Follicle

Ovum surrounded by a single layer of granulosa cells is called primordial follicle.

Development (in Fetus)

Epithelium of germinal ridges Germinal epithelium (covers outer surface of ovary) -Primordial ova Migrate into stroma Collects a layer of spindle cells around it from stroma (granulosa cells) Primordial follicle.

Number of Primordial Follicles

(1) 7 million at 30th week of gestation
(2) 2 million at birth
(3) 0.3-0.4 million at puberty

Note

Only 450 out of 0.3-0.4 million primordial follicles develop into Graafian follicles during sexual life of woman from 13 to 50 years of age; while the remainder degenerate (become atretic).

Puberty in Female

Period during which monthly sexual cycles (menstrual cycles) begin.

Age

11-15 years

Onset

At the age of 11-15 years anterior pituitary gland begins to secrete LH & FSH which causes monthly

changes in ovaries and uterus, that result in monthly sexual cycles (menstrual cycles) in female..

OVARIAN CYCLE

Rhythmic cyclic changes in ovaries and its secretions are called ovarian cycle.

Period

28 days (20 to 45 days)

Phases

Three,

(1) **Follicular (Pre-ovulatoty) Phase**

Hormones Responsible

FSH mainly and LH partly from ant. pituitary gland.

Stages of Development of Graafian Follicle

Primordial follicle Primary follicle (under influence of FSH & LH) Vesicular follicle - Mature Graafian follicle.

Structure of Graafian Follicle

(a) Theca externa Forms capsule

(b) Theca interna and granulosa cells Secrete estrogen (Estradiol)

(c) Cumulus ophorus - Surrounds ovum

(d) Antrum -, Contains follicular fluid (& estradiol)

How one follicle is selected to be the dominant follicle

- There are many **primordial follicles,**each contains immature ovum. At the start of each cycle, several of these follicles enlarge, and a cavity forms around the ovum **(antrum formation).**
- This cavity is filled with follicular fluid.Usually one of the follicles in one ovary starts to grow rapidly on about the sixth day and becomes the **dominant follicle,** while the others regress, forming **atretic follicles.**
- The atretic process involves apoptosis.

How one follicle is selected to be the dominant follicle it is related to ability of the follicle to secrete the estrogen inside it that is needed for final maturation.

Primary source of circulating estrogen is granulosa cells of ovaries.

- Spindle cells derived from the ovary interstitium collect in several layers outside the granulosa cells, giving rise to a second mass of cells **called the theca**. This is divided into two layers.
- **In the theca interna,** the cells take on epithelioid and secrete additional steroid sex hormones (estrogen and progesterone).
- **The theca externa** is the outer layer that develops into a highly vascular connective tissue capsule.

(2) ***Ovulation***

It is the process of rupture of mature Graafian follicle to set free ovum into peritoneal cavity near mouth of fallopian tube

Time

Ovulation occurs 14 days after onset of menstruation (when period is of 28 days)

Hormone Responsible

Increase LH from ant. pituitary gland

Mechanism

LH causes progesterone secretion by theca interna and granulosa cells. that causes

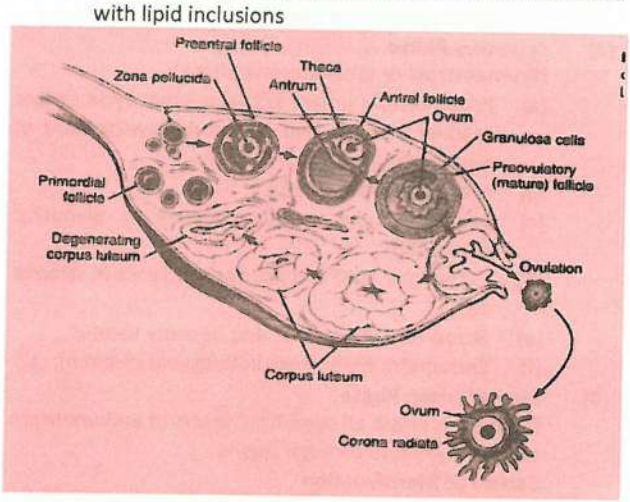
(a) Theca externa to secrete proteolytic enzymes Dissolute capsular wall

(b) Rapid growth of new blood vessels in follicle wall and secretion of prostaglandin Vasodilation.

(c) Plasma transdute into follicle Follicle swell Follicle ruptures at stigma Ovum

(3) **Luteal (Post-ovulatoiy) Phase**

After ovulation Graafian follicle converts into corpus luteum, which is a yellowish mass of Lutein cells filled with lipid inclusions



Hormone Responsible

LH (& human chorionic gonadotropin)

Structure of Corpus Luteum

(a) Lutein cells Secrete progesterone and small amounts of estrogen

(b) Strands of theca cells Secrete androgens Much of androgen is converted by granulosa cells into progesterone and estrogen

(c) Well-developed blood supply

(d) Lutein cells also secrete inhibin that inhibits FSH secretion.

Fate of Corpus Luteum

(a) If pregnancy occurs, corpus luteum inc. in size under influence of human chorionic gondotrpin of placenta - Called corpus luteum of pregnancy Secretes progesterone until end of four months.

(b) If pregnancy does not occur - Corpus luteum involute and becomes replaced by connective tissue after 12 days due to lack of LH and FSH Called corpus albicans

Menstrual Cycle

Rhythmic cyclic changes in mucous mem. (endometrium) of uterus, associated with cyclic production of estrogen and progesterone, is called menstrual cycle.

Period

28 days (20-45 days)

Phases

Three

(1) Proliferative Phase

(Post-menstrual or estrogen phase).

(a) Estrogen in first 1/2 of ovarian cycle causes rapid proliferation of stromal and epithelial cells

(b) Endometrium (that was desquamated during menstruation) is thus reepithelialized within 3-7 days

(c) Endometrium increase in thickness (3-5mm) due to inc. no. of stromal cells and endometrial glands and blood vessels.

(2) Secretory Phase

(Premenstrual or progesterone phase)

(a) Progesterone in last 1/2 of ovarian cycle causes marked swelling and secretory development of endometrium

(b) Glands become tortous

(c) Secretary substance accumulate in glandular epithelium

(d) Cytoplasm, lipid and glycogen increase in stromal cells

(e) Blood vessels increase and become tortous

(f) Endometrium increase in thickness (5-6mm)

(3) Menstruation Phase

During this phase all superficial layers of endometrium are desquamated through vagina.

Causes of Menstruation

Cessation of estrogen and progesterone secretion two days before menstruation.

Menstrual Fluid

Volume = 70 ml

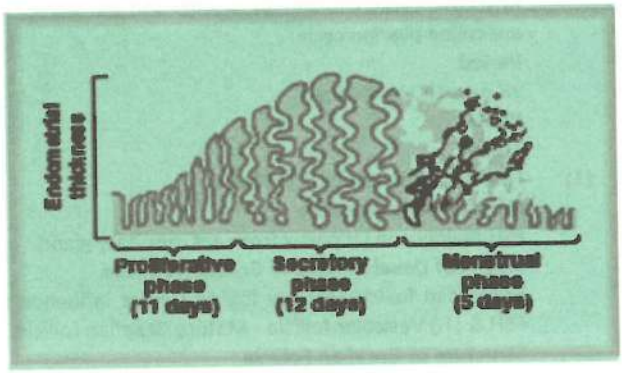
Characteristic

Does not clot due to presence of fibrinolysin.

released

LH SURGE

- **LH is necessary** for final follicular growth & ovulation.Without this hormone,even large quantities of FSH are available,follicle will not progress to stage of ovulation.
- About 2 days before ovulation rate of secretion of LH by anterior pituitary gland increases markedly,rising 6- to 10-fold and peaking about 16 hours before ovulation.
- FSH also increases about 2-fold to 3-fold at the same time, and FSH & LH cause rapid swelling of the follicle during the last few days before ovulation.
- LH also has a specific effect on granulosa & theca cells, converting them into progesterone-secreting cells.
- Therefore,rate of secretion of estrogen begins to fall about 1 day before ovulation, while increasing amounts of progesterone begin to be secreted.
- It is in this environment of
  (1) rapid growth of follicles,
  (2) diminishing estrogen secretion after a prolonged phase of excessive estrogen secretion
  (3)initiation of secretion of progesterone that ovulation occurs. Without the initial preovulatory surge of LH,ovulation will not take place..



Disorders

Anovulatory Cycles

Female sexual cycles in which ovulation does not occur, are called anovulatory cycles.

Cause by

Insufficient preovulatory LH surge.

Occur

Anovulatory cycles occur:

(1) few cycles after puberty and

(2) Several cycles before menopause.

Menarche

Onset of menstruation is called menarche. At the age of 13 Usually

Menopause

Cessation of menstruation in old age is called menopause.

Caused by

Cessation of female sex hormones secretion

Age

45-50 years

Symptoms

(1) Hot flushes

(2) Psychic sensation of dyspnea

(3) Irritability

(4) Fatigue

(5) Anxiety

Amenorrhea

Cessation of menstruation at any age is called amenorrhea.

Types

Two,

(A) False Amenorrhea

(Also called hidden menstruation or cryptomenorrhea). In this menstruation takes place but outflow of menstrual fluid is blocked at level of cervix, vagina or vulva.

(B) True Amenorrhea

In this menstrual function is suppressed so that there is no menstrual fluid.

Sub-types Two,

Physiological	Pathological
• Before puberty • During pregnancy and lactation • After menopause	**(a) Primary** It means failure of menstruation to occur at puberty. **Causes** ○ Failure of hypothalamus to secrete LHRH ○ Failure of ant. pituitary gland to secrete LH & FSH ○ Failure of ovaries to secrete estrogen and progesterone ○ Absence or disease of uterus. **(b) Secondary** It means cessation of menstruation after it has once occurred at puberty. **Causes** (i) Hypo- or hyper-thyroidism (ii) Diabetes mellitus (iii) Cushing's syndrome, etc.

Gonadal Disorders

Courtesy by Guyton & Halls Physiology

	Hypogonadism	Hypergonadism
Definition	It means low ovarian hormones secretion	It means excess secretion of ovarian hormones
Causes	(1) Poorly developed ovaries (2) Congenital absence of avaries	Tumor of granulosa cells (often after menopause).
Symptoms	• No secondary sexual characters • Sex organs are infantile • Taller height • Vagina becomes smaller • Breast atrophy and becomes pendulous • Pubic hairs become thinner	• Hypertrophy of endometrium • Irregular bleeding from hypertrophied endometrium

Female Sexual Act

- As is in male sexual act, successful female sexual act depends on both psychic stimulation & local sexual stimulation.
- Thinking sexual thoughts can lead to sexual desire & this aids greatly in performance of female sexual act.
- Desire also changes during monthly sexual cycle,reaching a peak near ovulation because high levels of estrogen secretion during preovulatory period.

Stimulation of the Female Sexual Act.

- Local ***sexual stimulation*** occurs in same manner as in men because massage & other types of stimulation of vulva, vagina & other perineal regions can create sexual sensations.
- *Clitoris is especially sensitive for initiating* sexual sensations as in male,sexual ***sensory signals*** are transmitted to sacral segments of spinal cord through pudendal nerve & sacral plexus.
- Once these signals entered spinal cord,they are ***transmitted to cerebrum***.
- ***Local reflexes integrated*** in sacral & lumbar spinal cord are at least partly responsible for some reactions in female sexual organs.

Female erection And lubrication

- Located around the introitus & extending into clitoris is erectile tissue almost identical to erectile tissue of penis.
- This ***erectile tissue like penis controlled by parasympathetic*** nerves.
- In early phases of sexual stimulation, parasympathetic signals dilate arteries of erectile tissue, probably resulting from release of acetylcholine, nitric oxide, and vasoactive intestinal polypeptide ***(VIP) at the nerve endings***.
- This allows rapid accumulation of blood in erectile tissue so that ***introitus tightens around the penis***; this aids the male greatly in his attainment of sufficient sexual stimulation for ejaculation to occur.
- Parasympathetic signals also pass to bilateral Bartholin's glands located beneath labia minora & cause them ***to secrete mucus*** immediately inside introitus.

- This mucus is ***responsible for lubrication*** during sexual intercourse,mucus secreted by the vaginal epithelium and a small amount from the male urethralglands.
- This lubrication is necessary during intercourse to establish a satisfactory ***massaging sensation*** rather than an irritative sensation,which may be provoked by a dry vagina.
- A massaging sensation constitutes the optimal stimulus for ***evoking the appropriate reflexes*** that culminate in both the male and female climaxes.

Female orgasm

- When local sexual stimulation reaches maximum intensity especially when local sensations are supported by appropriate psychic conditioning signals from cerebrum, reflexes are initiated that cause female orgasm also called the *female climax.*
- *The* ***female orgasm*** *is analogous to* emission and ejaculation in male & it help in fertilization of ovum.
- Female is more fertile when inseminated by normal sexual intercourse rather than by artificial methods thus indicating an important function of the female orgasm.

- During the orgasm perineal ***muscles of female contract*** rhythmically, which results from spinal cord reflexes similar to that cause ejaculation in male.
- It is possible that these reflexes ***increase uterine & fallopian tube motility*** during orgasm thus helping to transport sperm upward through the uterus toward ovum.
- Also, the orgasm cause **dilation of cervical canal** for up to 30 minutes allowing easy transport of sperm.

Fertile Period of Female Sexual Cycle

From one day before ovulation upto one day after ovulation.

Contraception

Prevention of pregnancy is called contraception.

Methods

(1) **Rhythm Method**

In this method, intercourse is avoided → days prior to and 3 days after calculated day of ovulation

(2) **Hormonal Methoc**

Administration of estrogen or progesterone in first 1/2 of female sexual cycle → This prevents preovulatory surge of LH -4 Prevents ovulation.

(a) Synthetic Estrogen

(i) Ethynyl estradiol Mestranol

(b) Synthetic Progesterone

(i) Norethindrone
(ii) Norethynodrel
(iii) Ethynodiol
(iv) Norgestrel

Female Sterility

It means infertility or inability to become pregnant.

Causes

(1) Failure of ovulation due to lack of FSH & LH and abnormal ovaries
(2) Endometriosis
(3) Salpingitis
(4) Abnormal secretion of mucus by cervix that plugs cervix

Pregnancy

Maturation of Ovum

(1) Shortly before ovulation, primary oocyte (22 pairs + XX) within Graafian follicle Meiosis Secondary oocyte and 1st polar body (both 22 + X)
(2) Few hours after sperm enters ovum, secondary oocyte Mature ovum and 2nd polar body.

Maturation and Fertilization of the Ovum

- In ovary ovum is in *primary oocyte stage.Before* released from ovarian follicle,its nucleus divides by meiosis & *first polar body is expelled.*
- *Primary oocyte then* becomes *secondary oocyte. In this process 23 pairs of chromosomes* loses one of its partners,which becomes incorporated in a *polar body* that is expelled.
- This leaves 23 *unpaired chromosomes in secondary oocyte.*

this time ovum in secondary oocyte stage is ovulated in abdominal cavity.

- It enters fimbriated end of one of the fallopian tubes to reach uterus cavity.

Fertilization

- After male ejaculates semen in vagina during intercourse,***few sperm are transported*** within 5-10 minutes upward through uterus to the *ampullae of* fallopian tubes ***near ovarian ends***.
- Transport of sperm is ***aided by contractions of uterus*** & fallopian tubes stimulated by prostaglandins in seminal fluid and also by oxytocin released from the posterior pituitary gland of female during her orgasm
- Almost ***half billion sperm*** deposited in vagina,few thousand succeed in reaching each ampulla.
- Fertilization of ovum normally ***takes place in ampulla*** of fallopian tubes soon after sperm & ovum enters in ampulla.
- Before a sperm can enter the ovum,it first penetrate multiple layers of granulosa cells attached outside of ovum(***corona radiata***) *and*

then bind to & penetrate ***zona pellucida*** *surrounding* the ovum itself.

- Once a sperm has entered the ovum (which is still secondary oocyte)oocyte divides again to form ***mature ovum plus a second polar body*** *that is expelled.*
- *Mature* ovum still carries in its nucleus (now ***called female pronucleus)*** *23 chromosomes.One of these chromosomes* is female chromosome known as *X chromosome.*
- In meantime, fertilizing sperm also changed.On entering the ovum, its head swells to form ***male pronucleus.***
- 23 unpaired chromosomes of male pronucleus & 23 female pronucleus align themselves to re-form complement of 46 chromosomes (23 pairs) in ***fertilized ovum.***

WHAT DETERMINES SEX OF FETUS THAT IS CREATED.

- After formation of mature sperm,half carry in their genome X chromosome (female chromosome) & half Y chromosome(male chromosome).
- if X chromosome from sperm combines with X chromosome from ovum,giving XX combination,female child will be born.
- if Y chromosome from sperm is paired with X chromosome from ovum giving XY combination,male child will be born.

Transport of Fertilized Ovum Thru Fallopian Tubes

- After fertilization 3-5 days is required for transport of fertilized ovum through fallopian tube into uterus cavity.
- This transport is effected by fluid resulting from epithelial secretion plus ciliated epithelium that lines the tube cilia always beat toward the uterus.
- Weak contractions of fallopian tube also aid the ovum passage.
- *Isthmus of fallopian tube*(2 cm before tube enters uterus) remains contracted for about first 3 days after ovulation.
- After this time increase progesterone secreted by corpus luteum first increasing progesterone receptors on fallopian tube smooth muscle then progesterone activates receptors exert tubular relaxing effect that allows entry of ovum into uterus.
- This delayed transport of the fertilized ovum through the fallopian tube allows several stages of cell division to occur before the dividing ovum.
- During this time, the fallopian tube secretory cells produce large quantities of secretions used for the nutrition of the developing blastocyst.

Implantation of Fertilized Ovum

- After reaching the uterus,developing blastocyst remains in uterine cavity an additional 1-3 days before it implants in endometrium. implantation occurs on about 5^{th} -7^{th}day after ovulation.
- Before implantation,blastocyst obtains nutrition from endometrial secretions called "uterine milk." Implantation results the action of *trophoblast cells that develop over surface of blastocyst.*
- These cells secrete proteolytic enzymes that digest & liquefy adjacent cells of endometrium.
- Fluid & nutrients released are actively transported by the same trophoblast cells into blastocyst.
- Once implantation has occur,trophoblast cells & adjacent cells proliferate form placenta & various membranes of pregnancy.

Decidua

Endometrium after implantation is called decidua. It consists of decidual cells that contains large amounts of glycogen, proteins, lipids and other nutrients.

Nutrition of Embryo

- Progesterone secreted by corpus luteum during latter half of monthly cycle has effect on endometrium,converting endometrial stromal cells into large swollen cells containing extra glycogen,proteins,lipids & minerals necessary for development of conceptus.
- These cells called *decidual cells & total mass of cells is called decidua.*trophoblast cells invade decidua,digesting & imbibing it, stored nutrients in decidua are used by embryo for growth & development.
- During 1^{st} week after implantation, this is only means by which embryo can obtain nutrients,embryo continues obtain nutrition in this way for 8 weeks, although placenta also begins to provide nutrition after 16th day beyond fertilization.

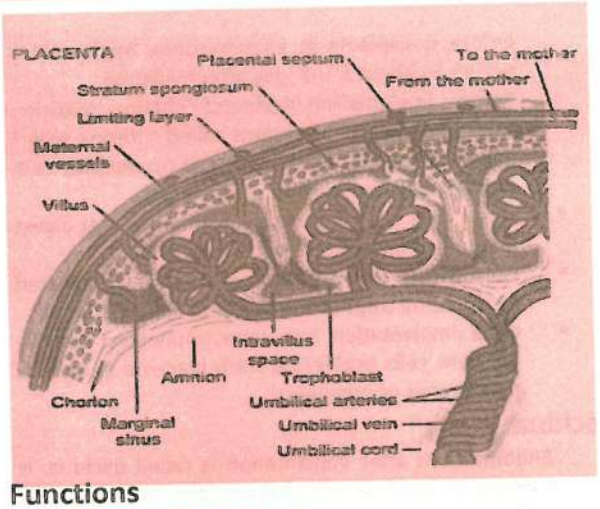
Placenta

It is a vital organ for fetus that primarily functions for exchange of:

(a) gases
(b) food and
(c) waste products b/w fetal blood and maternal blood.

Developmental & Physiologic Anatomy of Placenta

- While trophoblastic cords from blastocyst are attaching to the uterus,blood capillaries grow into the cords from the vascular system of the newly forming embryo.
- 16th day after fertilization,blood also begins to be pumped by heart of embryo itself.
- Simultaneously, *blood sinuses supplied with blood from* mother develop around trophoblastic cords.
- Trophoblast cells send out more projections, which become *placental villi into* which fetal capillaries grow.
- Villi carry fetal blood surrounded by sinuses that contain maternal blood.



Functions

(1) Respiratory Functions

(a) O_2 diffuses from maternal blood to fetal blood.

(b) CO_2 diffuses from fetal blood to maternal blood

(2) Digestive Functions

(a) Glucose is absorbed into fetal blood by facilitated diffusion

(b) Fatty acids are absorbed into fetal blood due to lipid-solubility

(c) Amino acids, PO_4, Ca^{++} and vit. C are absorbed into fetal blood by active transport.

(3) Excretory Functions

Urea, uric acid, creatinine, etc. diffuse from fetal blood into maternal blood due to conc. gradient.

(4) Protective Functions

Placental barrier prevents most of disease-causing organism from passing from maternal blood into fetal blood.

(5) Endocrine Functions

Placenta secretes → hormones

(a) Human Chorionic Gonadotropin

(i) Prevents menstruation during pregnancy

(ii) Prevents involution of corpus luteum

(iii) Causes corpus luteum to secrete more progesterone and estrogen

(iv) Causes fetal testes to secrete testosterone

(b) Human Chorionic Somatomamotropin

(i) Causes protein deposition like GH

(ii) Causes dec. glucose utilization by mother and makes this available for fetal use

(iii) Mobilizes free fatty acids from adipose tissue and provides alternate energy source for mother

(iv) In lower animals causes breast growth and lactation

(c) Estrogen

(i) Causes enlargement of uterus, and external genitalia

(ii) Causes enlargement of breast and development of duct system

(iii) Relaxes pelvic ligaments

(iv) Affects rate of cell reproduction in early embryo.

(d) Progesterone

(i) Causes development of decidual cells in endometrium

(ii) Increases secretions of fallopian tubes

(iii) Decreases contractility of gravid uterus

(iv) Prepares breast for lactation

(v) Affects cell cleavage in early embryo.

Physiological Changes During Pregnancy

Duration of Pregnancy

280 days or 40 weeks from 1st day of last menstruation.

(A) Reproductive System

i. Uterus

1. Uterus inc. in size and wt.
2. Inc. vascularity Inc. glycogen deposition
3. Weak rhythmic contractions called "Braxton-Hicks" contractions.

ii. Vagina

1. Becomes more elastic and enlarged
2. Inc. vascularity
3. Inc. glycogen deposition

iii. Cervix

1. becmoes congested
2. Glandular element inc.
3. Endocervix present honey-comb appearance

iv. Ovary

1. Corpus luteum persists
2. Ovulation does not occur

v. Breast

1. Inc. in size with tenderness
2. Brown pigmentation of areola
3. Montgomery tubercles appear on areola
4. Secretion of colostrum

(B) Blood

(1) Blood vol. Inc. by 30%

(2) Increase RBC count and Hb. Conc.

(3) Increase ESR due to inc. fibrinogen

(C) Cardio-Vascular System (CVS)

(1) Heart enlarge slightly

(2) Placental blood flow = 625 ml/min

(3) Cardiac output increase

(D) Respiration

(1) O_2 consumption increase

(2) Minute ventilation increase

(E) Urinary System

(1) Urine formation slightly increase

(2) Na+, CP and H_2O reabsorption inc.

(3) GFR increase

(F) BMR

(1) BMR increase by 15%

(2) Pregnant woman feel over-heated

(G) GIT

(1) Appetite is increased

(2) Inc. salivation

(3) Constipation

(4) Nausea and vomiting due to afferent impulses from uterus

(H) Mineral Metabolism

(1) Increase Ca++ absorption from GIT, bones and kidneys
(2) Increase Fe need
(3) Increase blood level of Na+ & Cl?

(I) Vitamin Metabolism

(1) Increase vit. D need
(2) Vit. K should be given before birth to avoid hemorrhage

(J) CNS

(1) Alteration in mood
(2) Depression, irritability, emotional instability, lethargy, apathy, etc.

(K) SKIN

(1) Pigmentation of nipple and areola
(2) Pigmentation of checks or forehead

Amniotic Fluid

Fluid present in amniotic cavity is called amniotic fluid.

Vol.

= 500 - 1000 ml

Functions

(1) Acts as a shock-absorber
(2) Regulates temperature of fetus
(3) Protects fetus from strong muscular contractions of uterus.

Pre-Eclampsia or Toxemia of Pregnancy

Pre-eclampsia is the **hypertensive** disorder of pregnancy. It is otherwise known as **toxemia of pregnancy.** About 3% to 4% of the pregnant women suffer from this. It usually occurs during last trimester of pregnancy.

Cause for hypertension

- Release of vasoconstrictor substances from placenta
- Hypersecretion of adrenal hormones and other hormones, which cause vasoconstriction
- Development of autoimmune processes induced by the presence of placenta or fetus.

Symptoms

(1) Protein deposit in basement mem. Of glomerulus → Renal blood flow decrease GFR decrease
(2) Increase salt and water retention by kidneys
(3) Weight gain
(4) Edema
(5) Arterial spasm in kidneys, liver and brain

Eclampsia

Extreme degree of preeclampsia, is called eclampsia.

Symptoms

(1) Decrease renal output
(2) Extreme vascular spasticity
(3) Extreme hypertension
(4) malfunction of liver
(5) Generalized toxic conditions of body
(6) Clonic convulsions
(7) Coma

Treatment

(1) Rapidly-acting vasodilators
(2) Immediate termination of pregnancy by cesarean section.

Pregnancy Tests

These are based on the fact that human chorionic gonadotropin begins appearing in urine of pregnant woman.

ASCHHEIM-ZONDEK TEST

- Aschheim-Zondek test was the first test invented for confirming the pregnancy. It depends upon the ovarian changes in immature mice caused by hCG.
- The immature mice do not ovulate naturally.
- Ovulation occurs only if hCG is injected. 2 mL of urine from the woman suspected for pregnancy is injected daily for 2 days into the immature mice.
- 5 days after injection of urine, the mice are killed.
- The ovaries are examined for the presence of corpora lutea (plural for corpus luteum) and hemorrhages, which indicates ovulation. Ovulation is due to the presence of hCG in urine.

FRIEDMAN TEST

In this test, 10 to 15 mL of urine is injected intravenously into rabbit and ovulation is observed by examining the ovaries after 48 hours.

Parturition (Labor)

Also Called

Child-birth or delivery

Definition

(1) Process by which baby is born
(2) Process by which product of conception is expelled from uterus thru vagina to outside world.

Stages

Three,

First Stage

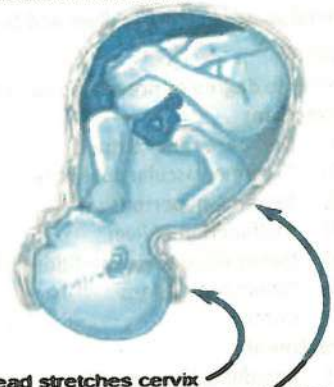
First, the strong uterine contractions called **labor contractions** commence. Labor contractions arise from fundus of uterus and move downwards so that the head of fetus is pushed against cervix. It results in dilatation of cervix and opening of vaginal canal. Exact cause for the onset of labor is not known. This stage extends for a variable period of time.

Second Stage

In this stage, the fetus is delivered out from uterus through cervix and vaginal canal. This stage lasts for about 1 hour.

Third Stage

During this stage, the placenta is detached from the decidua and is expelled out from uterus. It occurs within 10 to 15 minutes after the deliverv of the child.



1. Baby's head stretches cervix
2. Cervical stretch excites fundic contraction
3. Fundic contraction pushes baby down and stretches cervix some more
4. Cycle repeats over and over again

Onset of Labor

Through pregnancy uterus undergoes weak contractions called Braxton-Hicks's contractions. These become progressively very strong towards end of pregnancy, and are called labor contractions, which become stronger and stronger due to "positive feedback effect". They force baby thru birth canal by stretching cervix.

Factors That Increase Uterine Contractions

(1) Hormonal Factors

Hormones involved in the process of parturition:

- ***Maternal Hormones***

1. Oxytocin
2. Prostaglandins
3. Cortisol
4. Catecholamines
5. Relaxin.

- ***Fetal Hormones***

1. Oxytocin
2. Cortisol
3. Prostaglandins.

- ***Placental Hormones***

1. Estrogen
2. Progesterone
3. Prostaglandins.

(a) Estrogen to Progesterone Ratio

Estrogen excites uterine contractions, while progesterone inhibits them. After 7th month estrogen inc. while progesterone decrease, so that E/P ratio increase which increases uterine contractions

(b) Oxytocin

Irritation or stretching of cervix during labor Neurogenic reflex Posterior pituitary gland Oxytocin Increases uterine contraction

(c) Fetal Hormones

(i) Fetal posterior pituitary gland Oxytocin Increases uterine contractions

(ii) Fetal adrenal cortex Cortisol Uterine stimulant

(iii) Fetal membrane Porstaglandins increase uterine contractions

(2) Mechanical Factors

(a) Movements of fetus that stretch and excite uterine smooth muscle

(b) Irritation and stretch of cervix

(3) Contraction of Abdominal Muscles

Due to nervous reflexes initiated by pain signals from uterus, also help expel baby

Labor Pains

- With each uterine contraction,mother experiences pain.
- Cramping pain in early labor is mainly by hypoxia of uterine muscle resulting from compression of blood vessels in uterus.
- This pain is not felt when *hypogastric nerves,* which carry visceral sensory fibers leading from uterus, have been sectioned.
- During second stage of labor when fetus expelled through birth canal,more severe pain caused by cervical stretching, perineal stretching and stretching or tearing structures in vaginal canal.
- This pain is conducted to mother's spinal cord and brain by somatic nerves instead of by the visceral sensory nerves.

Involution of Uterus

Regression of uterus to small size after delivery is called involution of uterus.

Lochia

It is a fluid that is discharged through vagina during early involution of uterus. It is first bloody and then serous. It is formed by autolysis of endometrial surface at placental site.

Lactation

Lactation

Secretion of milk is called lactation

DEVELOPMENT OF BREASTS

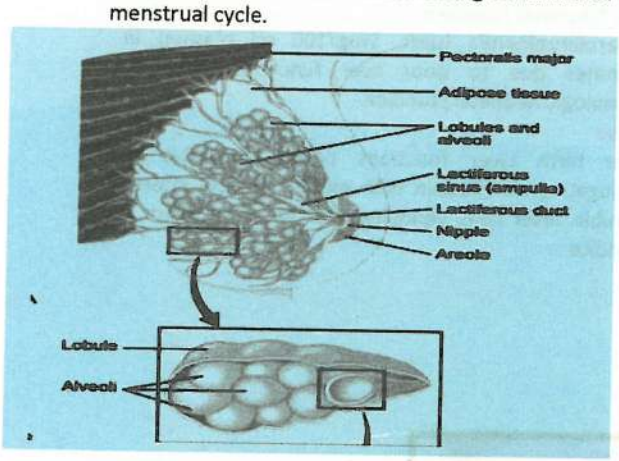
- Breasts begin to develop at puberty.This development is stimulated by estrogens of female sexual cycle.
- Estrogens cause growth of breasts *mammary glands* plus deposition of fat to give breasts mass.
- Greater growth occurs during high estrogen and then glandular tissue become completely developed for production of milk.

GROWTH OF THE DUCTAL SYSTEM—ROLE OF THE ESTROGENS.

- All through pregnancy,large quantities of estrogens secreted by placenta cause ductal system of breasts to grow and branch.
- Stroma of breasts increases in quantity and large quantities of fat are laid down in the stroma.
- Four other hormones are important *growth hormone,prolactin,adrenalglucocorticoids, insulin.*

DEVELOPMENT OF LOBULE-ALVEOLAR SYSTEM—ROLE OF PROGESTERONE.

- Final development of breasts into milk secreting organs requires *progesterone.*
- Once ductal system has developed, progesterone acting synergistically with estrogen as well as with other hormones causes additional growth of breast lobules, with budding of alveoli & development of secretory characteristics in cells of alveoli.
- These changes analogous to secretory effects of progesterone on endometrium during latter half of menstrual cycle.



Steps of Lactation

Three,

(1) Lactogenesis

Synthesis of milk by alveoli is called lactogenesis.

Hormones affecting

(a) Estrogen and Progesterone
Inhibit milk secretion

(b) Prolactin
Promotes milk secretion.

Regulation of Prolactin By,

(i) Prolactin inhibitory hormone (PIH) inhibits prolactin secretion under normal conditions.

(ii) Prolactin releasing factor (PRF) excites prolactin secretion when baby suckles nipple.

(c) Other Hormones

(i) GH Provides fatty acids

(ii) Cortisol Provides amino acid and glucose

(2) Ejection or Let-down of Milk

Flow of milk from alveoli into ducts, and then thru nipples, due to combined neurogenic and hormonal reflex, is called ejection or let-down of milk.

Mechanism

(a) Baby suckles nipples → Sensory impulses thru somatic nerves → To spinal cord Then to hypothalamus → Oxytocin and Prolactin secreted → Carried by blood to breast Contraction of myoepithelial cells around alveoli → Milk ejection or let-down.

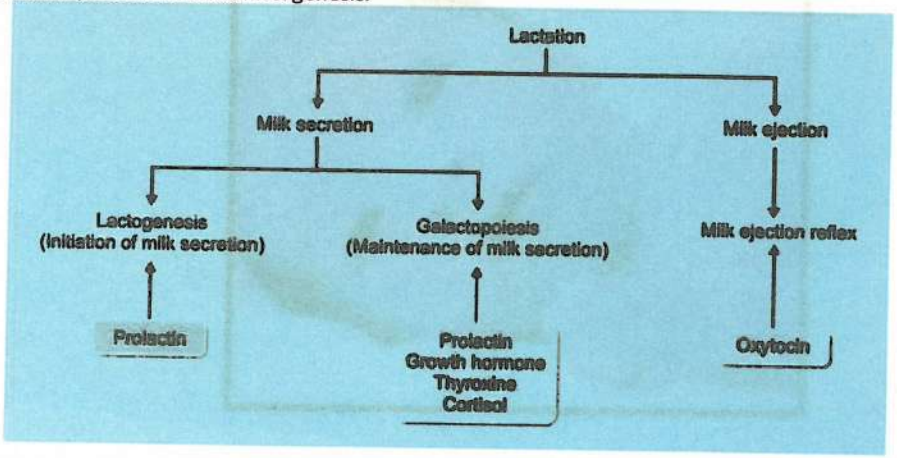
(b) Fondling the baby or hearing of baby's cry by mother Signals to hypothalamus Milk ejection or let-down.

(3) Galactopoiesis

Maintenance of lactation for a long time is called galactopoiesis.

Factors

(1) Suckling
(2) Prolactin
(3) Oxytocin
(4) GH
(5) ACTH
(6) Cortisol
(7) Thyroid hormones and
(8) Insulin.



Inhibition of Milk Ejection

(1) Psychogenic factors
(2) Generalized sympathetic stimulation

Suppression of Female Sexual Cycles During Lactation

Suckling of nipples Nervous signals To hypothalamus Suppress LHRH secretion - Suppress LH and FSH secretion Suppress ovarian cycle and ovulation (in 50% of lactating mothers).

Colostrum

It is a thin, yellow, milky fluid secreted by breast a few days before and after parturition.

Composition

Same concentration of proteins and lactose as in milk" but has no fat.

Milk

Daily Secretion

Upto 1. Lit.

Composition

(1) H_2O
(2) Fat
(3) Lactose
(4) Casein
(5) Lactalbumin
(6) Other proteins
(7) Ash.

Neonatal Physiology

Changes that Occur in Baby at Birth

(1) Onset of breathing
(2) Expansion of lungs
(3) Closure of foramen ovale
(4) Closure of ductus arteriosus
(5) Closure of ductus venosus

Characteristics of Neonates

Respiratory Rate

= 40 breaths/min.

Blood Vol.

= 300 ml

Cardiac Output

= 550 ml/min.

Arterial Pressure

(1) On first day = 70/50 mm Hg
(2) After few months = 90/60 mm Hg

RBC Count = million/mm
WBC Count = 45,000/mm3

Physiologic Neonatal Jaundice

Hyperbilirubinemia (upto 5mg/100 ml plasma) in neonates due to poor liver functions is called physiologic neonatal jaundice.

Cause

After birth Liver functions poorly Incapable of conjugating all bilirubin with glucuronic acid Plasma bilirubin level rises yellowness of skin and sclera -. Jaundice